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ORIGINAL RESEARCH

Expression of Serum LMAN2 and Sestrin2 in Septic Shock Patients and Exploration of Their Prognostic Value

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Objective: The expressions and prognostic value of serum Lectin Mannose-Binding 2 (LMAN2) and Sestrin2 were evaluated in septic shock patients, aiming to provide new biomarkers for early diagnosis and prognosis judgment of septic shock patients.

Methods: This retrospective study included 110 patients with sepsis and 50 healthy control subjects. Patients were classified into the sepsis group (SE group, 63 cases) or septic shock group (SS group, 47 cases) based on the occurrence of septic shock. Acute Physiology and Chronic Health Status II (APACHE II) scores, sequential organ failure assessment (SOFA) scores, and serum LMAN2 and Sestrin2 levels were compared between groups. The factors affecting the poor prognosis were analyzed by multivariate logistic regression. The receiver operating characteristic (ROC) curve was established to analyze the predictive value of serum LMAN2, Sestrin2, APACHE II score and SOFA score for the prognosis.

Results: The serum LMAN2 levels in the SS group and SE group were significantly increased compared with the CON group, but the serum Sestrin2 levels were decreased ($P<0.05$). The serum LMAN2 levels in the poor prognosis group were significantly higher than those in the good prognosis group, while the Sestrin2 levels were significantly decreased ($P<0.05$). Serum level of LMAN2, APACHE II scores and SOFA scores were independent risk factors, but Sestrin2 level was protective factor ($P<0.05$). Meanwhile, the AUC of serum LMAN2 and Sestrin2 combined detection was 0.894, and the specificity and sensitivity were 93.33% and 84.38%, respectively, which had high predictive value for the prognosis of septic shock patients. The AUC of serum LMAN2 and Sestrin2 combined with APACHE II score and SOFA score was 0.960, the specificity was 93.75%, and the sensitivity was 86.67%. Compared with the detection alone, the AUC of combined detection was increased ($Z = -2.166, -2.758, -2.059, -2.172$, $P<0.05$).

Conclusion: The increase of serum LMAN2 levels and the decrease of Sestrin2 levels were closely related to the severity of septic shock. The combined detection had important predictive value for the prognosis of septic shock patients. This study may have the potential to improve the management and treatment of sepsis patients.

Keywords: LMAN2, Sestrin2, sepsis, septic shock, prognosis

Introduction

Sepsis is a life-threatening disease associated with an imbalance in the host's response to infection. There are over 40 million new cases of sepsis worldwide annually, with approximately 10 million deaths, posing a serious threat to life and health.[1] Septic shock is a form of sepsis characterized by inadequate circulation and cellular hypoxia, which is a form of sepsis.[2] The mortality rate of patients with septic shock exceeds 40%, making it the leading cause of death beyond myocardial infarction.[3] Therefore, biomarkers for early diagnosis and prognostic evaluation are of great significance in improving the clinical management of septic shock.

In recent years, serum biomarkers have received increasing attention for diagnosis, disease assessment, and prognosis prediction of sepsis. Serum biomarkers are considered key factors in the development of treatment plans and monitoring their effectiveness in specific patients.[4] Serum Sestrin2 is a highly conserved protein that exerts antioxidant, anti-inflammatory, and

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antiapoptotic effects during cellular stress.[5] Previous studies have found that Sestrin2 can be downregulated in the serum of sepsis patients, which may inhibit the inflammatory response by suppressing the AMPK/NRF2 signaling pathway.[6] The AMPK/NRF2 signaling pathway is a key pathway that regulates inflammation and oxidative stress in the body. The activation of this signaling pathway enhances the antioxidant capacity of cells and reduces the injury caused by oxidative stress. It has shown potential therapeutic value in various disease models.[7] Lectin Mannose-Binding 2 (LMAN2) is an intracellular lectin. High LMAN2 expression may promote the proliferation and migration of gastric cancer, oral cancer ect., and predict the prognosis of patients.[8] However, the prognostic value of combined serum LMAN2 and Sestrin2 levels in patients with septic shock remains unclear. It is feasible and important to analyze the relationship between biomarkers and prognosis in patients with sepsis. Several studies have confirmed the value of biomarkers in predicting the prognosis of sepsis. For instance, Molano-Franco D et al[3] found that biomarkers such as procalcitonin, C-reactive protein, interleukin-6 and procalcitonin can effectively predict the mortality of patients with sepsis. In addition, when sepsis occurs, pathogens and their products (such as lipopolysaccharide, teichoic acid, etc.) are recognized by host immune cells and trigger immune responses.[9] These changes will lead to changes in the expression of various biomarkers such as C-reactive protein, procalcitonin and Presepsin, which are closely related to the prognosis of patients.

The purpose of this study was to investigate the expression levels of serum LMAN2 and Sestrin2 in septic shock patients, and to analyze the relationship between them and the prognosis of patients, to provide a theoretical basis for the early diagnosis, prognosis evaluation and treatment of septic shock.

Materials and Methods

General Materials

A total of 110 patients with postoperative sepsis treated in our hospital from January 2020 to December 2023 were retrospectively selected as the research objects. The time point of sepsis occurrence was calculated as the time when the patient had clinical manifestations that met the diagnostic criteria for sepsis and was clinically diagnosed. During the retrospective study, the clinical medical records of the patients were reviewed. The earliest time point was accurately obtained when a patient had fever, abnormal white blood cell count, or infection-related symptoms that met the diagnostic criteria for sepsis. This was used as the onset time of sepsis for subsequent analysis. All patients were treated in the intensive care unit with a routine regimen of fluid resuscitation, anti-infective therapy, administration of vasoactive substances, immunomodulation, and adjuvant therapy. General information selection was shown in Figure 1. Fifty healthy subjects (28 males and 22 females) who underwent physical examination at our hospital during the same period were included in the normal group (CON group).

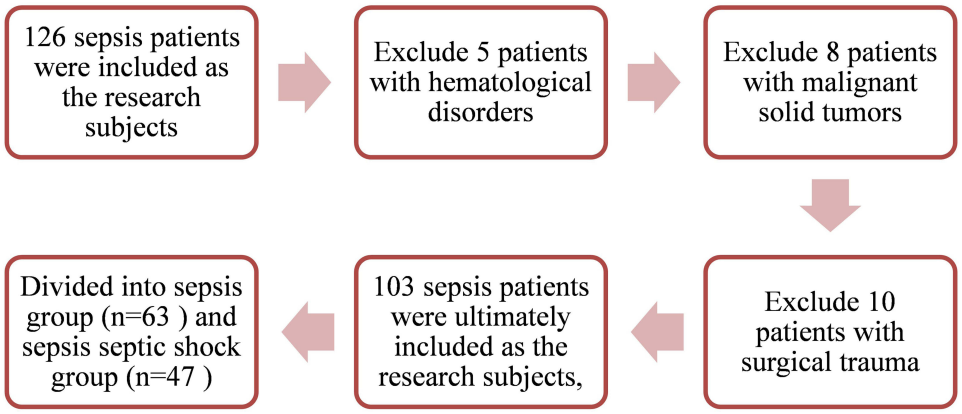

Figure 1 The inclusion process of general materials. Patients were screened according to inclusion and exclusion criteria, and 103 patients were finally included in the study.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Meet the diagnostic criteria for sepsis.[10] Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was measured by an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points. Sepsis was diagnosed when there was evidence of infection and the SOFA score increased by ≥2 points from baseline. (2) In accordance with the guidelines for diagnosis and treatment of septic shock.[10] Vasoactive agents were required after adequate fluid resuscitation to maintain a mean arterial pressure of at least 65 mmHg and a blood lactate level of more than 2 mmol per liter. (3) Age > 18 years old. (4) Complete clinical data. (5) Serum LMAN2 and Sestrin2 levels were detected. (6) Patients who developed sepsis after surgery. The exclusion criteria were as follows: (1) Participants with hematological disorders or those who used drugs that affected the hematopoietic system. (2) Participants with malignant solid tumors or those who underwent radiotherapy, chemotherapy, or immunosuppressive therapy. (3) Participants with significant liver, kidney, and heart function abnormalities. (4) Participants who experienced significant short-term blood loss, such as trauma or surgery. (5) Participants in pregnant and perinatal status.

The Acute Physiology and Chronic Health Status II (APACHE II) Scores

According to the literature, the acute physiology and chronic health evaluation II (APACHE II) score includes three main components: acute physiology score (APS), age score and chronic health status score.[11]

(1) The APS included 12 physiological indicators that were scored by the worst value within 24 hours after the patient entered the ICU. These 12 physiological indicators included body temperature, pulse rate, respiratory rate, blood pressure, blood cell count, liver and kidney function, blood gas analysis, and the Glasgow Coma Scale.

(2) The final APS score was obtained by adding the scores of all the 12 indicators. Age scores were assigned as follows: 0 points for ages <44 years, 2 points for ages 45–54, 3 points for ages 55–64, 5 points for ages 65–74, and 6 points for ages > 75 years.

(3) The chronic health condition score was based on whether the patient had a history of severe organ dysfunction or immune deficiency: 2 points for patients who underwent elective surgery and 5 points for those who had not undergone surgical treatment or emergency surgery for other conditions.

The total APACHE II score was obtained by adding the above three scores, which ranged from 0 to 71. A higher score indicated a worse condition and prognosis, and a greater risk of death.

Sequential Organ Failure Assessment (SOFA) Scores

According to the literature report, the sequential organ Failure Assessment (SOFA) score mainly covers six organ systems and was calculated as follows:[12]

(1) Respiratory system: scored based on the PaO2/FiO2 ratio (arterial oxygen partial pressure/inhaled oxygen concentration), with 1 point for values<400, 2 points for values<300, 3 points for values<200 and requiring mechanical ventilation, and 4 points for values<100 and requiring mechanical ventilation.

(2) Neurological system: According to the Glasgow Coma Scale,[13] scores of 13–14 were considered 1 point, 10–12 as 2, 6–9 as 3, and<6 as 4. The Glasgow Coma Scale was a scoring system to assess a patient's state of consciousness in three main areas: eye-opening response, verbal response, and motor response. The scores in each area were added together to create an overall score, ranging from 3 to 15 points.

(3) The cardiovascular system was scored based on the dose of vasopressors used, 1 point for MAP<70 mmHg, 2 points for the usage of dobutamine (at any dose) or dopamine ≤ 5 μg/kg/min, 3 points for the usage of dobutamine 5–15 μg/kg/min or norepinephrine ≤ 0.1 μg/kg/min, 4 points for the usage of dobutamine >15 μg/kg/min or norepinephrine >0.1 μg/kg/min.

(4) Liver system was scored based on serum bilirubin levels, with scores ranging from 20 to 32 μmol/L (1 point), 33 to 101 μmol/L (2), 102 to 204 μmol/L (3), and > 204 μmol/L (4).

(5) The coagulation system was scored based on the platelet count: < 150 $\times 10^9$/L as 1 point, below 100 $\times$ 10^9/L as 2, below 50 $\times$ 10^9/L as 3, and below 20 $\times$ 10^9/L as 4.

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(6) The renal system was scored based on creatinine levels or urine output, with creatinine levels ranging from 110 to 170 μmol/L scored as 1 point, 171–299 μmol/L scored as 2, 300–440 μmol/L or urine output less than 500 mL scored as 3, and creatinine levels exceeding 440 μmol/L or urine output less than 200 mL scored as 4. The total SOFA score was the sum of the scores from each system and ranges from 0 to 24 points. A higher score indicated a more severe condition.

Prognostic Grouping Criteria

Patients with septic shock who survived 30 days after treatment were divided into a good prognosis group (survival, n=32) and a poor prognosis group (death, n=15).

Serum LMAN2 and Sestrin2 Detection

Blood was collected for biomarker assessment within 24 hours of admission to the intensive care unit (ICU) after the diagnosis of sepsis had been made. All patients were required to draw 3 mL of fasting central cubital vein blood. After centrifugation, the upper clear liquid was collected and the levels of LMAN2 and Sestrin2 were evaluated using ELISA. First, the standard and sample wells were set. Standard samples (50 μL) at the indicated concentrations and 100 μL of test sample were added to the indicated wells. The plate was then covered with a sealing membrane and incubated at 37°C for 1 h. During each cleaning process, 350 μL of washing solution was injected into each well through an automatic or manual washing machine, soaked for 1 min, and repeated washing 5 times. Then, 0.5 μg/mL of Biotinylated detection antibody was added (100 μL/well) and incubated for 1 h. After washing, HRP avidin solution (1:5000) was added (100 μL/well) and incubated for 30 min. After washing, a substrate solution (TMB) was added (100 μL/well) and incubated in the dark for 15 min. Finally, the termination solution was added to each well. The absorbance of each well was measured at 450 nm wavelength using an ELISA reader.

Statistical Analysis

SPSS 21.0 was applied for statistical analysis. The measured data conformed to a normal distribution and were shown as ($\bar{x} \pm s$). Independent-sample t-tests and univariate analyses were performed for intergroup comparisons. The LSD-*t* test was performed for pairwise comparisons between groups. Enumeration data were represented as [cases (%)], and comparisons between groups were performed using the χ^2 test. Pearson's correlation test was used to explore the correlation between serum LMAN2 and Sestrin2 levels, and disease severity. Multivariate Logistic regression was used to analyze the influencing factors of poor prognosis in septic shock patients. The ROC curve was used to analyze the prognostic value of serum LMAN2 and Sestrin2 levels in patients with septic shock. $P<0.05$.

Results

Comparison of Baseline Characteristics Between the Two Groups

Compared with the basic data of the CON group, there was no significant difference in baseline characteristics, including age, sex, BMI, time of onset and comorbidities in SE group and SS group ($P>0.05$, Table 1).

Analysis of Severity of Disease in Each Group

Patients in the SS group had significantly higher APACHE II and SOFA scores than those in the SE group ($P<0.05$, Table 2).

Comparison of Serum LMAN2 and Sestrin2 Levels

Patients in the SE group had significantly increased serum LMAN2 levels and significantly decreased serum Sestrin2 levels compared with those in the CON group ($P<0.05$). Compared with the SE group, patients in the SS group had significantly higher serum LMAN2 levels and markedly lower serum Sestrin2 levels ($P<0.05$, Table 3).

The Correlation Between Serum LMAN2, Sestrin2 Levels and Disease Severity

Pearson correlation analysis showed that APACHE II and SOFA scores were positively correlated with serum LMAN2 levels, but negatively correlated with serum Sestrin2 levels ($P<0.05$, Figure 2).

Table 1 Comparison of Basic Data of Each Group ($\bar{x} \pm s$, %)

Group	Cases	Gender (Male/ Female	Age	BMI (kg/m^2)	Onset time (h)	Complication	
						Hypertension	Diabetes
CON group	50	28/22	49.46±6.96	21.98±2.42	/	/	/
SE group	63	39/24	50.26±6.27	21.87±1.23	3.19±1.72	33 (52.38)	30 (47.62)
SS group	47	26/21	49.74±7.39	22.10±2.18	3.40±1.81	25 (53.19)	22 (46.81)
$F/t/\chi^2$		0.615	0.20	0.19	0.619	0.007	
P		0.735	0.818	0.830	0.537	0.933	

Table 2 Analysis of Severity of Disease in Each Group ($\bar{x} \pm s$)

Groups	Cases	APACHE II Score (score)	SOFA Score (score)
SE group	63	22.35±4.11	4.81±2.53
SS group	47	26.83±4.48	8.20±2.56
t		5.442	6.917
P		<0.001	<0.001

Abbreviations: CON, normal control group; SE, sepsis group; SS, septic shock group.

Table 3 Comparison of Serum LMAN2 and Sestrin2 Levels ($\bar{x} \pm s$)

Groups	Cases	LMAN2 (ng/mL)	Sestrin2 (ng/mL)
CON group	50	0.51±0.13	15.82±3.59
SE group	63	1.31±0.22[a]	10.14±2.59[a]
SS group	47	1.86±0.30[ab]	6.36±1.44[ab]
F		442.95	152.08
P		<0.001	<0.001

Notes: [a]P<0.05 compared with the CON group, [b]P<0.05 compared with the SE group.
Abbreviations: CON, normal control group; SE, sepsis group; SS, septic shock group.

Comparison of Serum LMAN2 and Sestrin2 Levels in Septic Shock Patients With Different Prognoses

Compared to those with a good prognosis, patients with a poor prognosis had significantly higher serum LMAN22 levels and much lower serum Sestrin2 levels (P<0.05, Table 4).

Multivariate Logistic Regression Analysis was Performed to Analyze the Influencing Factors of Poor Prognosis in Septic Shock Patients

Multivariate Logistic regression analysis was performed with the prognosis of septic shock patients as dependent variables (1=poor prognosis, 0=good prognosis), and serum LMAN2 and Sestrin2 levels, APACHE II scores and SOFA scores as independent variables (all continuous variables). The results showed that serum LMAN2, APACHE II scores, and SOFA scores were independent risk factors for poor prognosis in septic shock patients, and Sestrin2 levels were protective factors (P<0.05, Table 5).

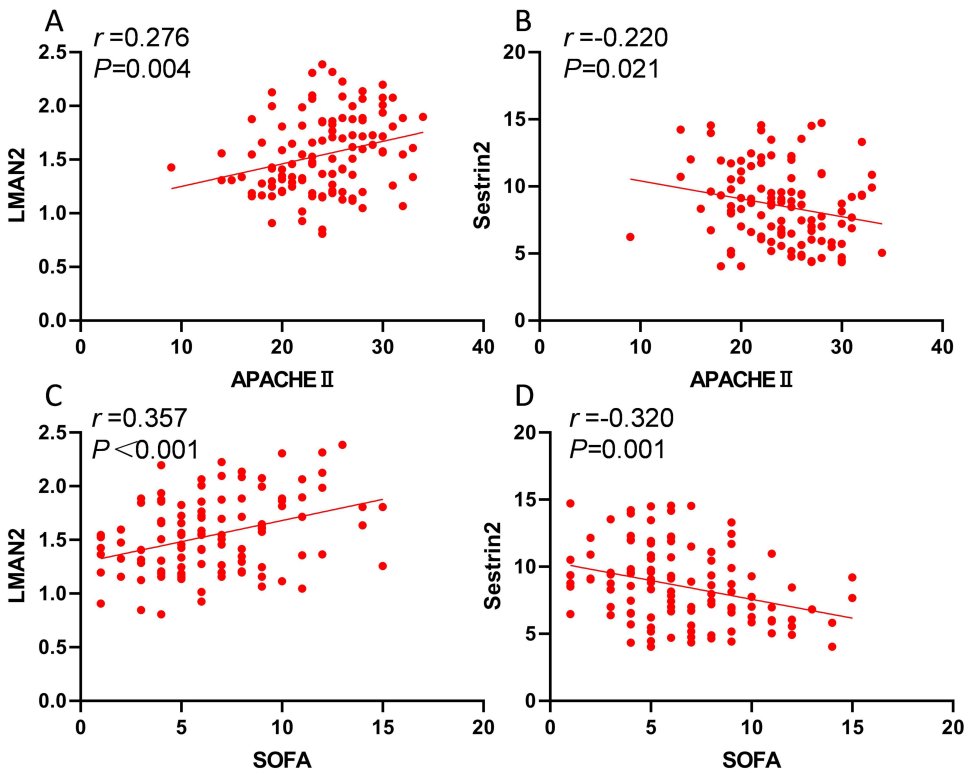

Figure 2 The correlation between serum LMAN2, Sestrin2 levels and disease severity. (**A**) APACHE II scores were positively correlated with LMAN2; (**B**) APACHE II scores were negatively correlated with Sestrin2; (**C**) SOFA score was positively correlated with LMAN2; (**D**) SOFA scores were negatively correlated with Sestrin2.

Analysis of the Prognostic Value of Serum LMAN2 and Sestrin2 in Patients with Septic Shock

ROC analysis confirmed that the AUC of serum LMAN2 and Sestrin2 combined detection was 0.894. There was no statistically significant difference in the AUC between the LMAN2 test alone and the LMAN2+Sestrin2 combined test (Z=0.758, P=0.129). The AUC of the combined test was higher than that of the Sestrin2 test alone (Z=2.5518, P=0.040), indicating that the combined detection of serum LMAN2 and Sestrin2 levels had a predictive value for the prognosis of septic shock (Table 6 and Figure 3).

Analysis of the Predictive Value of Serum LMAN2, Sestrin2 Combined with APACHE II and SOFA Scores for the Prognosis of Patients with Septic Shock by ROC Curve

Further, APACHE II score and SOFA score were included in the ROC curve analysis. The results showed that the AUC of APACHE II score alone was 0.835, and the AUC of SOFA score alone was 0.850. The AUC of serum LMAN2 and Sestrin2 combined with APACHE II score and SOFA score was 0.960, the specificity was 93.75%, and the sensitivity was 86.67%. Compared with serum LMAN2, Sestrin2, APACHE II score and SOFA score to detect biomarkers or scores

Table 4 Comparison of Serum LMAN2 and Sestrin2 Levels in Septic Shock Patients With Different Prognoses ($\bar{x} \pm s$)

Groups	Cases	LMAN2 (ng/mL)	Sestrin2 (ng/mL)
Good prognosis group	32	1.24±0.22	21.45±4.83
Poor prognosis group	15	2.03±0.45	12.47±2.27
t		8.134	6.826
P		<0.001	<0.001

Table 5 Multivariate Logistic Regression Analysis of the Factors Affecting the Poor Prognosis of Septic Shock Patients

Index	*B* value	*SE* value	*Wald* value	*P* value	OR	95% CI	
						Lower limit	Upper limit
LMAN2	1.259	0.328	14.733	<0.001	3.522	1.852	6.699
Sestrin2	−0.043	0.015	7.881	0.005	0.958	0.258	1.258
APACHE II scores	1.090	0.314	12.050	<0.001	2.974	1.608	5.501
SOFA scores	0.930	0.348	7.142	0.025	2.535	1.281	5.013

Table 6 Analysis of the Prognostic Value of Serum LMAN2 and Sestrin2 in Patients With Septic Shock

Indicators	AUC	Specificity	Sensitivity	Youden's Index	Cut-off value	*P value*	95% *CI*
LMAN2	0.845	80.00	84.38	0.644	1.39 ng/mL	<0.05	0.698–0.991
Sestrin2	0.798	93.33	59.38	0.527	16.96 ng/mL	<0.05	0.971–0.925
LMAN2+Sestrin2	0.894	93.33	84.38	0.777	——	<0.05	0.775–1.000

Abbreviations: ROC, Receiver operating characteristic; AUC, area under the curve; CI, Confidence interval.

alone, the AUC of combined detection was increased (Z =−2.166, −2.758, −2.059, −2.172, $P<0.05$), indicating that combined detection can more accurately predict the prognosis of patients with septic shock (Table 7 and Figure 4).

Discussion

The pathophysiological process of septic shock involves systemic inflammatory response, microcirculation disorder, immune disorder, and multiple organ failure. When the body is infected, the pathogen or its products trigger the immune system, release a large number of inflammatory mediators, and induce a systemic inflammatory response. This process leads to increased vascular permeability and hypoperfusion, which in turn causes tissue hypoxia and microcirculation

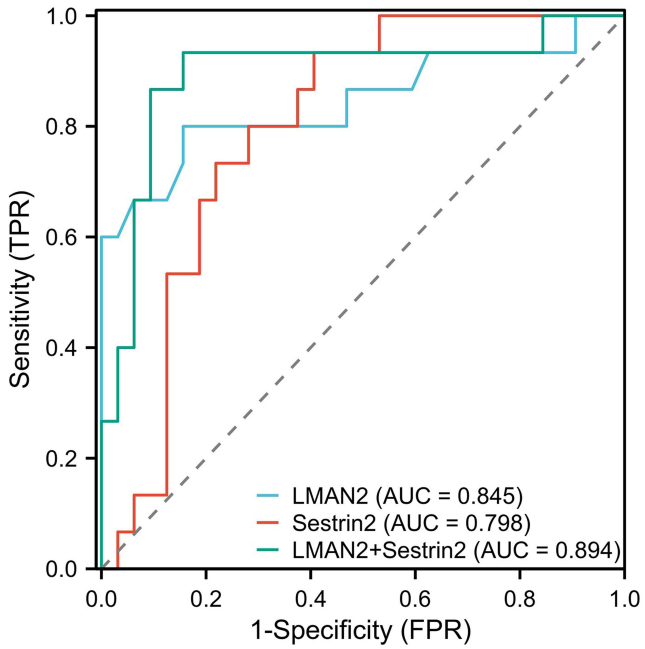

Figure 3 ROC curve analysis of serum LMAN2 and Sestrin2 for predicting the prognosis of septic shock patients. The figure showed the ROC curves of serum LMAN2 and Sestrin2 alone and in combination. The AUC of LMAN2+Sestrin2 was the highest (0.894), indicating that it had the highest prognostic value for septic shock.

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Table 7 Analysis of the Predictive Value of Serum LMAN2, Sestrin2 Combined With APACHE II and SOFA Scores for the Prognosis of Patients With Septic Shock by ROC Curve

Indicators	AUC	Specificity	Sensitivity	Youden's Index	Cut-off value	*P value*	95% CI
APACHE II score	0.835	59.38	99.25	0.586	20 score	<0.05	0.723–0.948
SOFA score	0.850	87.50	73.33	0.608	8 score	<0.05	0.732–0.968
LMAN2+Sestrin2+ APACHE II score + SOFA score	0.960	93.75	86.67	0.804	——	<0.05	0.912–1.000

disorders. At the same time, septic shock is accompanied by the disorder of the immune system, which is manifested by the over-activation or functional inhibition of immune cells. This further aggravates the process of the disease.[9,14] Although progress has been made in the treatment of septic shock in recent years, the associated mortality rate remains high. Early diagnosis and severity assessment may play an essential role in symptomatic treatment and improvement of prognosis in patients with septic shock.

Several biomarkers have been proposed for sepsis diagnosis, treatment, and prognosis. Because of the different characteristics of each marker, a single marker may have lower sensitivity and specificity for disease diagnosis.[15] This study showed that those with a severe condition and poor prognosis had lower serum Sestrin2 levels, suggesting that Sestrin2 may be involved in the progression of sepsis. Sestrin2 is a member of the Sestrin family. When subjected to oxidative stress, hypoxia, genotoxic stress, and other stimuli, the expression level of Sestrin2 significantly increases, thereby regulating cell survival and homeostasis. In addition, Sestrin2 regulates cellular energy metabolism by inhibiting the mTOR signaling pathway, promoting autophagy, and maintaining the cellular metabolic balance.[16] Sestrin2 may also reduce inflammation and ferroptosis in myocardial infarction models via LKB1-mediated AMPK activation. These results indicate that Sestrin2 can act as an important endogenous protective factor in inflammation-related diseases through antioxidant stress and inhibition of inflammatory signaling pathways.[17] At the molecular level, Sestrin2 is upregulated in response to oxidative stress and hypoxia in sepsis, indicating severe stress and tissue damage. However, Sestrin2 can inhibit ferroptosis of dendritic cells in sepsis by down-regulating ATF4-CHOP-CHAC1 signaling pathway,

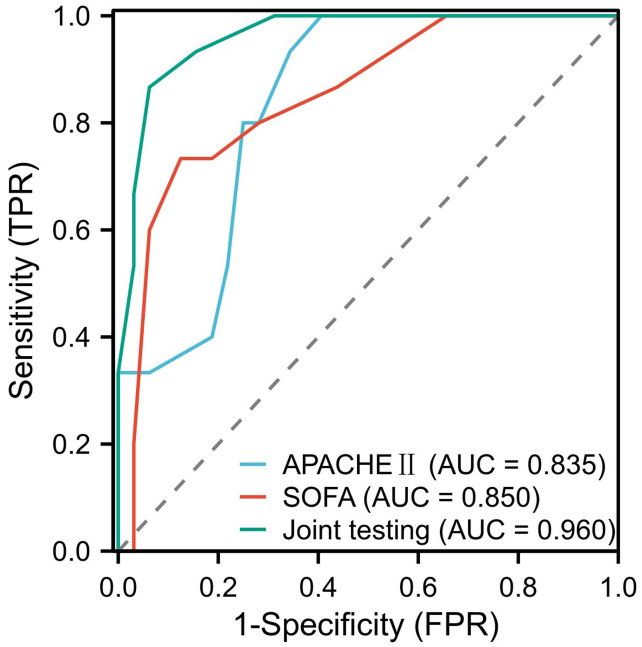

Figure 4 Analysis of the predictive value of serum LMAN2, Sestrin2 combined with APACHE II and SOFA scores for the prognosis of patients with septic shock by ROC curve.

and may play an antioxidant role.[18] It has also been confirmed that Sestrin2 can inhibit oxidative stress and inflammation. Sestrin2 is responsible for reducing cellular ROS accumulation through autophagy via AMPK activation, showing cardioprotective effects in cardiovascular diseases.[19] Sestrin2 up-regulation maybe a stress-protective response of the body, but it is not enough to combat excessive inflammation and oxidative stress damage in the severe stage of sepsis. A low basal level of Sestrin2 means that the body's initial protective ability is weak, and it is difficult to deal with the blow brought by sepsis. So, low levels of Sestrin2 are associated with poor prognosis.

In animal models of septic shock, studies have found that Sestrin2-deficient mice exhibit increased apoptosis of dendritic cells (DCs) and aggravated endoplasmic reticulum stress. This indicates that Sestrin2 is a potential regulatory factor that inhibits endoplasmic reticulum stress-induced apoptosis signal transduction and has a protective effect on DC apoptosis in sepsis,[20] in line with the conclusion of the present study. In addition, the study has revealed the protective role of Sestrin2 in sepsis, which can prevent fatal sepsis by inhibiting the pyroptosis of dendritic cells, providing a potential target for the treatment of sepsis.[21] When sepsis occurs, the body's oxidative system is unbalanced and a large number of inflammatory factors are released. Then, an inflammatory cascade occurs, resulting in multiorgan failure. In addition, tissues may experience hypoxia due to insufficient blood perfusion, which is the main cause of organ failure and death. Sestrin2 may exert a protective effect by inducing mitochondrial autophagy, reducing the phosphorylation level of ribosomal protein S6 kinase, and inhibiting inflammatory responses and endoplasmic reticulum stress.[22] In addition, Sestrin2 can block the release of inflammatory factors by inactivating the NF-κB signaling pathway, thereby alleviating damage to tissue organs.[23]

LMAN2 is a lectin in the cellular endocrine pathway and an important factor in innate immunity. LMAN2 participates in protein transport between the endoplasmic reticulum and the Golgi apparatus.[24] LMAN2 can also activate the complement system through the lectin pathway, thus enhancing phagocytosis and the adaptive immune system.[25] We found that patients with severe conditions had elevated serum LMAN2 levels, suggesting that LMAN2 may be involved in the development of sepsis. When sepsis occurs, detachment of the glycocalyx from the surface of endothelial cells affects vascular tension, leading to platelet adhesion, protein extravasation, and tissue edema. Phosphatidylinositol proteoglycan-1 (GPC-1) on the endothelial cell membrane of the glycocalyx may specifically bind to lipid rafts via glycosylphosphatidylinositol, suggesting that LMAN2 may be involved in glycocalyx detachment.[26] LMAN2 is stripped from the cell surface by lipopolysaccharide (LPS) and regulates the phagocytic activity of macrophages. Therefore, serum LMAN2 levels are speculated to be related to sepsis severity, and screening LMAN2 for serum is feasible.[27] An in-depth study of the mechanism of action of LMAN2 in septic shock will provide a new perspective for understanding the pathological and physiological processes of the disease. It can also provide a theoretical basis for developing effective diagnostic and therapeutic methods.

The expression level of LMAN2 in HR-positive breast cancer tissue was much higher than that in normal breast tissue and HR-negative breast cancer tissue.[28] In addition, high LMAN2 expression is associated with poor prognosis in HR-positive breast cancer. Serum Sestrin2 levels are closely associated with the short-term prognosis of T2DM patients complicated by acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).[29] This study found that patients with poor prognosis had significantly increased serum LMAN2 levels and decreased serum Sestrin2 levels compared to those with good prognosis. These results suggest that close monitoring of serum LMAN2 and Sestrin2 levels in patients with septic shock is of great guiding significance for the formulation of treatment plans. When the serum LMAN2 level is increased, it suggests that the patient may have more serious inflammatory reaction and tissue damage. Intensification of anti-inflammatory therapy may be considered at this time. For example, more effective antibiotics are used to control the source of infection. Also, anti-inflammatory drugs can be used to inhibit the release of inflammatory factors and reduce the damage of inflammatory cascade to the body. At the same time, because LMAN2 may be involved in the shedding of glycocalyx, it affects vascular tone. For patients with high LMAN2 levels, measures to improve microcirculation can be taken. For example, vasoactive drugs are given to regulate vascular tone and increase tissue perfusion.[30] Sestrin2 has protective effects such as anti-oxidation, anti-inflammation and anti-apoptosis. For patients with reduced serum Sestrin2 levels, attempts can be made to supplement exogenous Sestrin2 or use drugs to activate endogenous Sestrin2 expression to enhance the body's protective mechanism. For example, by activating AMPK/NRF2 signaling pathway, Sestrin2 expression is promoted, oxidative stress and inflammatory response are

reduced, and tissue and organ function is protected.[31] In addition, according to the changes in the levels of these two biomarkers, the intensity and direction of immunomodulatory therapy can also be adjusted. For patients with immune overactivation, the immune response can be appropriately suppressed. For patients with immunosuppression, immune function should be enhanced to maintain the body's immune balance and improve the prognosis of patients. It is worth noting that the results of this study were similar to the study published by Bao J et al,[32] which also points out the importance of serum LMAN2 level in patients with sepsis and septic shock, and explores its predictive value for prognosis. In addition, the study by Baspınar O et al[33] evaluated the role of Sestrin2 as a sepsis marker and a predictor of disease severity and similarly found that Sestrin2 was associated with the severity of sepsis. However, this study not only analyzed the expressions of serum LMAN2 and Sestrin2 levels separately in patients with septic shock, but also further explored the prognostic value of the combined detection of the two in patients with septic shock. By constructing the receiver operating characteristic (ROC) curve, we found that the area under the curve (AUC) of the combined detection of serum LMAN2 and Sestrin2 was higher than that of the single detection, indicating that the combined detection had higher prediction accuracy. In this study, the serum LMAN2 and Sestrin2 levels were not only considered in assessing the prognosis of patients. Clinical indicators such as APACHE II scores and SOFA scores were also combined to provide a more comprehensive assessment system. Using LMAN2 and Sestrin2 as biomarkers has many potential benefits in clinical practice. On the one hand, they can be used as early diagnostic indicators. In the early stage of septic shock, by detecting serum LMAN2 and Sestrin2 levels, they can help doctors identify high-risk patients more quickly and buy time for early intervention. When the serum LMAN2 level increases rapidly and the Sestrin2 level decreases significantly, it suggests that the patient may be in the early stage of septic shock, and intensive treatment measures need to be taken in time. On the other hand, these two biomarkers can be used to monitor the therapeutic effect. During the treatment, if the patient's serum LMAN2 level gradually decreases and Sestrin2 level gradually rises, it indicates that the treatment plan may be effective and the disease is controlled. Otherwise, doctors need to re-evaluate the treatment plan and adjust the treatment strategy. In addition, by monitoring these two biomarkers, the prognosis of patients can also be stratified. For patients with poor prognosis, closer monitoring and more aggressive treatment can be given, and medical resources can be rationally allocated to improve the overall treatment effect.

Based on the results of this study, we recommend the following to improve diagnosis and treatment strategies in the intensive care setting: Early detection of biomarkers: Monitoring serum LMAN2 and Sestrin2 levels enables early diagnosis and assessment of septic shock. This helps doctors to intervene in time to prevent further progression of the disease. Develop a personalized treatment plan: A personalized treatment plan is developed based on the patient's biomarker level and the severity of the condition. For example, for patients with elevated serum LMAN2 levels, treatment strategies targeting their pathophysiological mechanisms can be considered, including inhibiting inflammatory responses or improving microcirculation. Strengthen the management of the intensive care unit: optimize the environment and resource allocation of the intensive care unit, and improve the professional quality and emergency response ability of medical staff. By strengthening teamwork and interdisciplinary collaboration, the success rate of treating septic shock patients can be improved. Explore new therapeutic strategies: Explore new therapeutic strategies and methods for the complex pathophysiological process of septic shock. By regulating the function of the immune system, improving microcirculation disorder, or alleviating systemic inflammatory response, the mortality of patients can be reduced.

Conclusion

In summary, the serum LMAN2 levels and Sestrin2 levels were significantly increased and decreased in patients with septic shock with poor prognosis. The combined detection of the two indexes had a high predictive value for the prognosis of septic shock. The results of this study had an expected impact on clinical practice, provided a new basis for early clinical diagnosis and prognosis assessment, and helped to improve the clinical management level of septic shock patients.

However, the sample size of this study was relatively small and it was a single-center study with data from only one hospital, which might have certain regional and medical practice biases. Future multi-center and cross-regional studies would help verify and expand the findings of this study. In addition, the study included patient data from January 2020 to December 2023. Although the period covered data in recent years, future studies could further extend the observation period to assess long-term trends in biomarker levels. This study only discussed the prediction of serum LMAN2 and

Sestrin2 on the prognosis of patients 30 days after surgery, and the time was still short. The sample size can be increased and the time extended for further verification in the later stage. This study mainly focused on the expressions of serum LMAN2 and Sestrin2 biomarkers in patients with septic shock and their relationship with prognosis. In subsequent studies, we plan to include more biomarkers related to the pathogenesis and prognosis of sepsis for analysis, to more comprehensively reveal the pathophysiological process of sepsis. It also provides a more accurate and reliable basis for clinical diagnosis and treatment.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki Declaration and its later amendments or comparable ethical standards.

This study was approved by The Ethics Committee of Suzhou municipal hospital.

Consent to Participate

Informed consent was obtained from all the participants, and the patients participating in the study agreed to publish the research results.

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Disclosure

The authors declare that they have no competing interests.

References

1. Lyu QQ, Zheng RQ, Chen QH, et al. Early administration of hydrocortisone, vitamin C, and thiamine in adult patients with septic shock: a randomized controlled clinical trial. *Crit Care*. 2022;26(1):295. doi:10.1186/s13054-022-04175-x
2. Payen D, Dupuis C, Deckert V, et al. Endotoxin mass concentration in plasma is associated with mortality in a multicentric cohort of peritonitis-induced shock. *Front Med Lausanne*. 2021;8(1):749405. doi:10.3389/fmed.2021.749405
3. Molano-Franco D, Arevalo-Rodriguez I, Muriel A, et al. Basal procalcitonin, C-reactive protein, interleukin-6, and presepsin for prediction of mortality in critically ill septic patients: a systematic review and meta-analysis. *Diagn Progn Res*. 2023;7(1):15. doi:10.1186/s41512-023-00152-2
4. Rello J, van Engelen TSR, Alp E, et al. Towards precision medicine in sepsis: a position paper from the European society of clinical microbiology and infectious diseases. *Clin Microbiol Infect*. 2018;24(12):1264–1272. doi:10.1016/j.cmi.2018.03.011
5. Ala M. Sestrin2 in cancer: a foe or a friend?. *Biomark Res*. 2022;10(1):29. doi:10.1186/s40364-022-00380-6
6. Liu W, Xu C, Zou Z, et al. Sestrin2 suppresses ferroptosis to alleviate septic intestinal inflammation and barrier dysfunction. *Immunopharmacol Immunotoxicol*. 2023;45(2):123–132. doi:10.1080/08923973.2022.2121927
7. Wang P, Guo X, Wang H, et al. Neuregulin-4 protects cardiomyocytes against high-glucose-induced ferroptosis via the AMPK/NRF2 signalling pathway. *Biol Direct*. 2024;19(1):62. doi:10.1186/s13062-024-00505-x
8. Chu HW, Chang KP, Yen WC, et al. Identification of salivary autoantibodies as biomarkers of oral cancer with immunoglobulin A enrichment combined with affinity mass spectrometry. *Proteomics*. 2023;23(9):e2200321. doi:10.1002/pmic.202200321
9. Velissaris D, Zareifopoulos N, Karamouzos V, et al. Presepsin as a diagnostic and prognostic biomarker in sepsis. *Cureus*. 2021;13(5):e15019. doi:10.7759/cureus.15019
10. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
11. Han D, Zhang L, Zheng S, et al. Prognostic Value of blood urea nitrogen/creatinine ratio for septic shock: an analysis of the mimic-III clinical database. *Biomed Res Int*. 2021;2021(1):5595042. doi:10.1155/2021/5595042
12. Dusaj N, Papoutsi E, Hoffman KL, et al. Lost in a number: concealed heterogeneity within the sequential organ failure assessment (SOFA) score. *Crit Care*. 2024;28(1):6. doi:10.1186/s13054-023-04782-2
13. Teasdale G, Maas A, Lecky F, et al. The Glasgow coma scale at 40 years: standing the test of time. *Lancet Neurol*. 2014;13(8):844–854. doi:10.1016/S1474-4422(14)70120-6
14. Marques A, Torre C, Pinto R, et al. Treatment advances in sepsis and septic shock: modulating pro- and anti-inflammatory mechanisms. *J Clin Med*. 2023;12(8):2892. doi:10.3390/jcm12082892

15. Gong L, Wang Z, Wang Z, et al. Sestrin2 as a potential target for regulating metabolic-related diseases. *Front Endocrinol*. 2021;12(1):751020. doi:10.3389/fendo.2021.751020
16. Hu H, Lu X, He Y, et al. Sestrin2 in POMC neurons modulates energy balance and obesity related metabolic disorders via mTOR signaling. *J Nutr Biochem*. 2024;133:109703. doi:10.1016/j.jnutbio.2024.109703
17. Qian Y, Chen L, Gao B, et al. Sestrin2 levels in patients with anxiety and depression myocardial infarction was up-regulated and suppressed inflammation and ferroptosis by LKB1-mediated AMPK activation. *Clin Exp Hypertens*. 2023;45(1):2205049. doi:10.1080/10641963.2023.2205049
18. Li JY, Ren C, Wang LX, et al. Sestrin2 protects dendrite cells against ferroptosis induced by sepsis. *Cell Death Dis*. 2021;12(9):834. doi:10.1038/s41419-021-04122-8
19. Gao A, Li F, Zhou Q, et al. Sestrin2 as a potential therapeutic target for cardiovascular diseases. *Pharmacol Res*. 2020;159:104990. doi:10.1016/j.phrs.2020.104990
20. Wang LX, Zhu XM, Luo YN, et al. Sestrin2 protects dendritic cells against endoplasmic reticulum stress-related apoptosis induced by high mobility group box-1 protein. *Cell Death Dis*. 2020;11(2):125. doi:10.1038/s41419-020-2324-4
21. Wang LX, Ren C, Yao RQ, et al. Sestrin2 protects against lethal sepsis by suppressing the pyroptosis of dendritic cells. *Cell mol Life Sci*. 2021;78(24):8209–8227. doi:10.1007/s00018-021-03970-z
22. Pan C, Ai C, Liang L, et al. Sestrin2 protects against hypoxic nerve injury by regulating mitophagy through SESN2/AMPK pathway. *Front Mol Biosci*. 2023;10:1266243. doi:10.3389/fmolb.2023.1266243
23. Hsieh YH, Chao AC, Lin YC, et al. The p53/NF-kappaB-dependent induction of sestrin2 by amyloid-beta peptides exerts antioxidative actions in neurons. *Free Radic Biol Med*. 2021;169:36–61. doi:10.1016/j.freeradbiomed.2021.04.004
24. Jacobson S, Larsson P, Åberg AM, et al. Levels of mannose-binding lectin (MBL) associates with sepsis-related in-hospital mortality in women. *J Inflamm*. 2020;17(1):28. doi:10.1186/s12950-020-00257-1
25. Behairy MY, Abdelrahman AA, Abdallah HY, et al. Role of MBL2 polymorphisms in sepsis and survival: a pilot study and in silico analysis. *Diagnostics*. 2022;12(2):460. doi:10.3390/diagnostics12020460
26. Iba T, Maier CL, Helms J, et al. Managing sepsis and septic shock in an endothelial glycocalyx-friendly way: from the viewpoint of surviving sepsis campaign guidelines. *Ann Intensive Care*. 2024;14(1):64. doi:10.1186/s13613-024-01301-6
27. Shirakabe K, Hattori S, Seiki M, et al. VIP36 protein is a target of ectodomain shedding and regulates phagocytosis in macrophage Raw 264.7 cells. *J Biol Chem*. 2011;286(50):43154–43163. doi:10.1074/jbc.M111.275586
28. Zhang D, Ye L, Hu S, et al. Comprehensive analysis of the expression and prognostic value of LMAN2 in HER2+ breast cancer. *J Immunol Res*. 2022;2022:7623654. doi:10.1155/2022/7623654
29. Wang J, Du H, Sun Q, et al. The promotion of sestrin2/AMPK signaling by HIF-1α overexpression enhances the damage caused by acute myocardial infarction. *BMC Cardiovasc Disord*. 2023;23(1):571. doi:10.1186/s12872-023-03604-1
30. Feng C, Li P, Liu P, et al. LMAN2 promotes breast cancer tumorigenesis and drug resistance by interacting with MAPK9 via activation of the MAPK Pathway. *Cancer Med*. 2024;13(23):e70448. doi:10.1002/cam4.70448
31. Zhang N, Liao HH, Feng H, et al. Knockout of AMPKα2 blocked the protection of sestrin2 overexpression against cardiac hypertrophy induced by pressure overload. *Front Pharmacol*. 2021;12:716884. doi:10.3389/fphar.2021.716884
32. Bao J, Zha Y, Chen S, et al. The importance of serum LMAN2 level in septic shock and prognosis prediction in sepsis patients. *Heliyon*. 2022;8(11):e11409. doi:10.1016/j.heliyon.2022.e11409
33. Baspınar O, Kocer D, Aydın K, et al. Assessment of sestrin 2 as a sepsis marker and predictor of disease severity. *Aging Male*. 2024;27(1):2424300. doi:10.1080/13685538.2024.2424300