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The Relationship between Thioredoxin-2, Systemic Immune-inflammatory Index, and Short-term Adverse Cardiovascular Events in Septic Cardiomyopathy

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ABSTRACT

To explore the relationship between thioredoxins (Trx) -2, systemic-immune inflammatory index (SII), and short-term major adverse cardiac events (MACE) in septic cardiomyopathy (SCM).

A retrospective study was conducted on 98 SCM patients admitted to Affiliated Jinling Hospital, Medical School of Nanjing University Emergency Intensive Care Unit (EICU) from July 2022 to June 2024. Patients underwent routine blood tests and data assessment upon admission. Based on the occurrence of MACE by day 28, patients were divided into the MACE group and the non-MACE (N-MACE) group. Clinical data were collected, and logistic regression, along with restricted cubic spline models, analyzed the relationships between SII, Trx-2, and MACE risk in SCM patients.

Among the 98 SCM patients included, there were 35 (35.71%) in the MACE group and 63 (64.29%) in the N-MACE group. Logistic regression analysis showed that elevated SII and serum Trx-2 levels correlated with an increased risk of MACE within 28 days post-admission for SCM patients. Restricted cubic spline analysis revealed a linear dose-response relationship between both SII and Trx-2 levels with short-term MACE risk in SCM. The ROC curve showed AUC values of 0.869 for LVEF, 0.881 for SII, while combining SII + Trx-2 yielded 0.926 (95% CI: 0.862-0.989), with specificity at 83.98% and sensitivity at 98.80%.

The abnormal increase of serum SII and Trx-2 levels in SCM patients is related to the occurrence of MACE within 28 days after admission. The risk of MACE increases with the increase of serum SII and Trx-2 levels.

Keywords: Cardiovascular diseases; Cardiomyopathy; Neutrophils; Septic; Thioredoxins

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INTRODUCTION

Sepsis is a severe inflammatory response resulting from the host's dysfunctional response to infection. Although the treatment of sepsis has developed rapidly in the past few years, the incidence and mortality of sepsis in clinical treatment are still rising. Sepsis can lead to organ dysfunction affecting various systems, including the lungs, liver, kidneys, and heart; It may also result in impairment among critically ill patients.[1-3] When cardiac involvement occurs during this process, it can precipitate varying degrees of myocardial injury known as sepsis cardiomyopathy (SCM) or sepsis-induced myocardial injury (SIMI).[4] Surveys indicate that among patients admitted to hospitals in the United States due to sepsis, between 20% and 65% of them develop cardiomyopathy. Cardiac dysfunction leads to a mortality rate of 11.9 % within the emergency intensive care unit (EICU) and an overall in-hospital mortality rate of about 18.9%. Major adverse cardiac events (MACE) are identified as a primary cause of death among these.[5-6] In 2022, SCM diagnosis and treatment also proposed that effective protection of the heart and reduction of cardiovascular events can help improve the prognosis of patients with sepsis and reduce their mortality.[7] Therefore, how to reduce MACE in patients with septic cardiomyopathy is an urgent problem to be solved.

Thioredoxins (Trx), as an antioxidant molecule, play an important role in many physiological processes such as redox regulation.[8] Among them, thioredoxin-2 (Trx-2) is an important member of the thioredoxin family, and its role in myocardial diseases has attracted increasing attention.[9-10] Studies[11] have shown that cardiovascular diseases such as congestive heart failure may aggravate symptoms by inhibiting the activity of Trx and reducing oxidative stress. By inhibiting the activity of Trx-2, thioredoxin-interacting proteins interfere with its ability to bind other signaling molecules, affect glucose uptake in cells, and thus hinder its physiological functions. Wang et al[12] found that the mortality of TRX-2 can significantly reduce the mortality of sepsis model in mice, which is related to the decrease of inflammatory cytokines and the decrease of organ damage. The systemic immune inflammatory index (SII) is a scoring system used to evaluate the function of the immune system. At present, its role in predicting the survival of patients with cardiovascular disease, malignant tumors, and acute kidney injury has been reported.[13-15] Related studies have reported that there may be a certain correlation between SII and the occurrence and development of sepsis.[16,17] However, there are few reports on the relationship between Trx-2, SII, and SCM short-term MACE. The purpose of this study is to explore the relationship between Trx-2, SII, and the occurrence of short-term MACE in SCM, in order to provide new ideas and methods for the prevention and treatment of SCM.

MATERIALS AND METHODS

Participants

A total of 98 patients with septic cardiomyopathy admitted to Affiliated Jinling Hospital, Medical School of Nanjing University, emergency intensive care unit (EICU) from July 2022 to June 2024 were retrospectively included in the study. Inclusion criteria: (1) meet the diagnostic criteria for sepsis.[18] (2) SCM meets the diagnostic criteria proposed by Parker et al[19] in 1984, and echocardiography within 48 hours of admission indicates SCM; (3) 18-78 years old; (4) Clinically relevant case data are complete. Exclusion criteria: (1) congenital heart disease; (2) no previous history of heart failure and coronary heart disease (coronary atherosclerotic heart disease); (3) with malignant tumors, connective tissue disease, autoimmune diseases involving cardiac function; (4) end-stage of chronic kidney disease; (5) viral myocarditis, infective endocarditis; (6) Patients who were diagnosed with sepsis in other hospitals for more than 24 hours; (7) Acute cardiovascular events occurred within 48 hours of admission; (9) Female patients during pregnancy and lactation. This study was approved by Affiliated Jinling Hospital, Medical School of Nanjing University (2023DKKY-053-01).

Project Check

After the patient was admitted to the hospital, about 5 mL of peripheral blood was routinely collected and centrifuged at 4000*g* for 5 minutes using a Microfuge 20 desktop high-speed centrifuge (Beckman Coulter) to obtain serum or plasma. The whole blood cell analyzer was used to analyze the blood routine of the patients, and the blood cell-related values were obtained. The SII value was calculated by the formula SII = (peripheral platelet value × neutrophil count/lymphocyte count).[20] Serum creatine kinase (CK) and creatine kinase isoenzymes-MB (CK-MB) were detected by enzyme enzyme-coupling method. Serum cardiac troponin

(cTnl), lactate dehydrogenase (LDH), and interleukin 6 (IL-6) were detected by chemiluminescence.[21] Serum Trx-2, N-terminal pro B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and procalcitonin (PCT) were detected by ELISA. Serum creatinine (Scr) was detected by colorimetry. Blood urea nitrogen (BUN) was detected by the urease method.

Clinically Relevant Information

Relevant clinical data of patients were collected. Including gender, age, source of infection, body temperature, past history, acute physiology and chronic health evaluation (APACHE II),[22] sequential organ failure score (SOFA),[23] arterial blood lactate, 24h lactate clearance rate, left ventricular ejection fraction (LVEF), continuous renal replacement therapy (CRRT), vasoactive inotropic score (VIS).

MACE Definition

Acute cardiovascular events occurred within 28 days of admission, including acute heart failure, acute myocardial infarction, cardiogenic shock, cardiogenic stroke, and cardiogenic death. Ninety-eight patients with septic cardiomyopathy who developed MACE within 28 days of admission were divided into the MACE group and the non-MACE (N-MACE) group.

Statistical Methods

Project data processing using statistical software (SPSS version 29.0); the measurement data conforming to the normal distribution were expressed as (mean± SD), and the *t* test was used for comparison. The enumeration data were described by n (%), and the χ^2 test was used for comparison. Logistic regression was used to analyze the relationship between serum Trx-2, SII, and MACE in the short term of SCM. The dose-response relationship between Trx-2, SII, and SCM short-term MACE risk was analyzed by the restricted cubic spline method. Two-sided test level α=0.05.

RESULTS

Basic Information

In this study, 116 patients with SCM were included, and 98 patients were finally included after screening (Figure 1). According to the occurrence of MACE within 28 days after admission, the patients were divided into the MACE group (n=35) and N-MACE group (n=63). Figure 1. The difference in body temperature between the two groups was statistically significant (p>0.05) (Table 1).

Comparison of Laboratory Indexes between the Two Groups

There were significant differences in SII and Trx-2 between the MACE group and the N-MACE group (p<0.05). There was no significant difference in other laboratory indices between the two groups (p>0.05), Table 2.

Analysis of the Influencing Factors of MACE in the Short Term of SCM

Logistic analysis was performed on the indicators with p<0.05 in Table 1 and Table 2 as independent variables, and MACE (0=No, 1=Yes) in SCM patients within 28 days of admission as dependent variables. The assignment of each variable is shown in Table 3. Logistic regression analysis showed that elevated levels of SII and Trx-2 were associated with an increased risk of MACE within 28 days of admission in SCM patients (p<0.05) Table 4.

Table 1. Comparison of baseline data between the two groups of patients

Project	MACE group (n=35)	N-MACE group (n=63)	t/χ^2	*P*
Sex			0.436	0.509
Male	21 (60.00)	42 (66.67)		
Female	14 (40.00)	21 (33.33)		
*Age (years)	48.26 ± 9.36	47.19 ± 10.09	0.514	0.608
Body temperature (°C)			3.993	0.046
<36	11 (31.43)	33 (52.38)		
>38.3	24 (68.57)	30 (47.62)		
Source of infection			2.017	0.569
Pulmonary infection	21 (60.00)	32 (50.78)		
Urinary tract infection	8 (22.86)	12 (19.05)		
Peritonitis	3 (8.57)	10 (15.87)		
Burn infection	3 (8.57)	9 (9.52)		
*APACHE II score (points)	25.14 ± 4.15	24.57 ± 4.18	0.650	0.517
*SOFA score (points)	10.23 ± 2.33	9.68 ± 2.19	1.156	0.251
Hypertension	7 (20.00)	15 (23.81)	0.188	0.665
Diabetes	8 (22.86)	17 (26.98)	0.202	0.653
Chronic obstructive pulmonary disease	2 (5.71)	4 (6.35)	0.016	0.900
Chronic kidney disease	8 (12.70)	7 (11.11)	2.395	0.122
CRRT treatment (%)			0.048	0.826
Yes	12 (34.29)	23 (36.51)		
No	23 (65.71)	40 (63.49)		

MACE: Major Adverse Cardiac Events; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Score; CRRT: continuous renal replacement therapy; * mean±standard deviation.

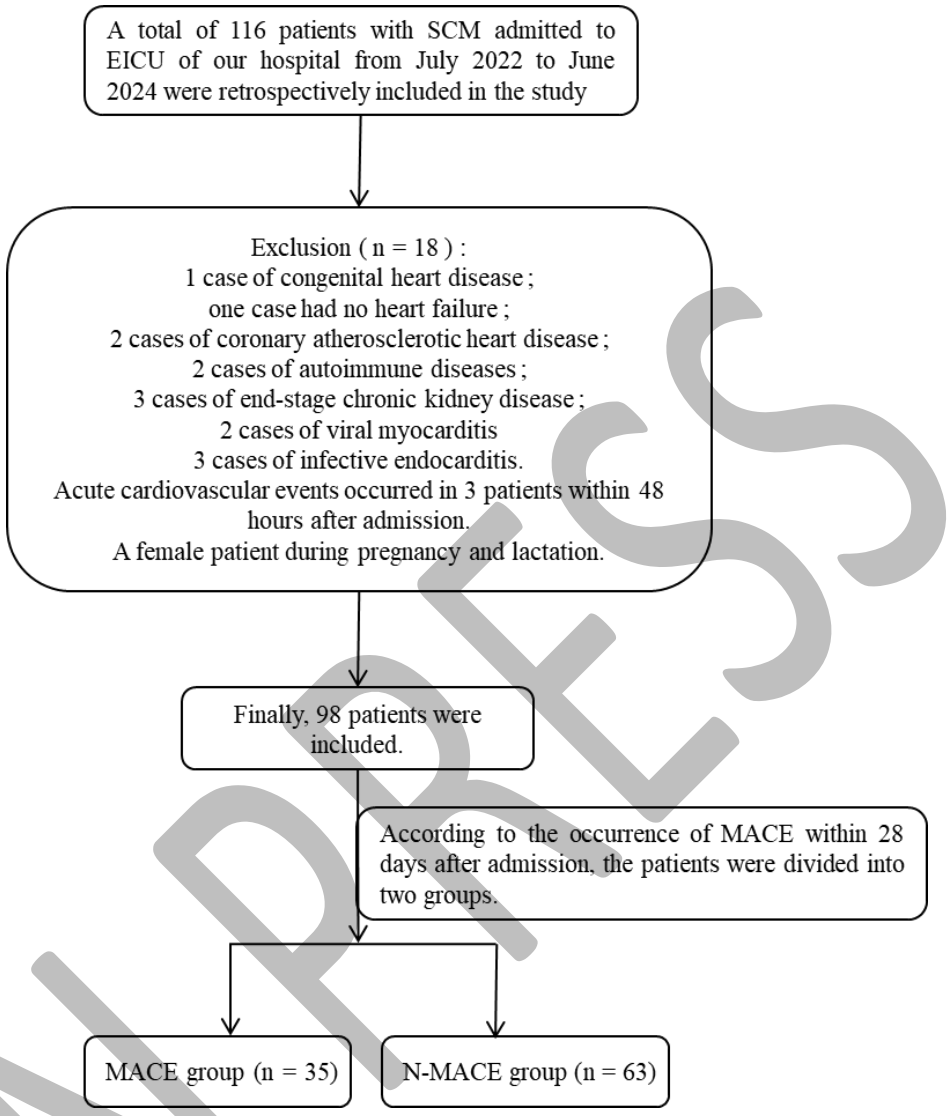

Figure 1. Patient screening flow chart. MACE: Major Adverse Cardiac Events; SCM: sepsis cardiomyopathy.

Table 2. Comparison of laboratory indicators between the two groups

Projects	MACE group(n=35)	N-MACE group(n=63)	*T/U*	*P*
*Blood lactic acid (mmol/L)	6.80 ± 1.90	6.38 ± 1.82	1.075	0.285
*24h lactic acid clearance (%)	48.63 ± 6.90	49.32 ± 7.11	−0.465	0.643
*LVEF (%)	35.54 ± 3.19	36.85 ± 3.10	−1.984	0.050
*VIS (points)	48.60 ± 8.49	47.92 ± 8.51	−0.218	0.828
*cTnI (μg/L)	0.32 ± 0.09	0.30 ± 0.09	0.997	0.321
*CK (U/L)	168.50 ± 25.35	166.85 ± 24.55	0.315	0.753
*CK-MB (U/L)	18.30 ± 4.40	17.68 ± 4.78	0.623	0.535
*LDH (U/L)	261.38 ± 35.40	258.64 ± 33.20	0.384	0.702
*NT-proBNP(pg/mL)	794.55 ± 91.50	788.95 ± 89.44	0.294	0.769
*CRP (mg/L)	192.30 ± 21.35	189.89 ± 22.58	0.516	0.607
*PCT (ng/mL)	36.28 ± 5.22	35.22 ± 5.87	0.883	0.380
*IL-6 (pg/mL)	353.30 ± 52.42	351.88 ± 51.34	0.131	0.896
SII	412.48(340.27, 515.61)	319.75(253.02, 396.69)	−3.503	<0.001
*Scr (μmol/L)	112.30 ± 18.55	110.44 ± 16.85	0.505	0.615
*BUN (mmol/L)	11.60 ± 3.35	10.82 ± 3.17	1.160	0.249
*Trx-2 (ng/mL)	368.29 ± 31.79	277.29 ± 44.63	−10.646	<0.001

MACE: Major Adverse Cardiac Events; LVEF: left ventricular ejection fraction; VIS: vasoactive inotropic score; CK: creatine kinase; CK-MB: creatine kinase isoenzymes-MB; cTnl: cardiac troponin; LDH: lactate dehydrogenase; IL-6: interleukin-6; Trx-2: Thioredoxins-2; NT-proBNP: Nterminal pro B type natriuretic peptide; CRP: C reactive protein; PCT: procalcitonin; Scr: serum creatinine; BUN: blood urea nitrogen; SII: systemic immune inflammatory index; * mean ± standard deviation

Table 3. Assignment

Factors	Variables	Assignment
Body temperature (°C)	X1	1≤36, 2≤36
SII	X3	Original value entry
Trx-2 (ng/mL)	X4	Original value entry

SII: systemic immune-inflammation index; Trx-2: Thioredoxin-2.

Table 4. Multivariate Logistic regression analysis of MACE in the short term of SCM

Index	β	SE	Wald χ^2	*p*	OR	95% CI
Body temperature (°C)	1.253	0.722	3.008	0.083	3.501	0.850–14.422
SII	0.010	0.003	10.655	0.001	1.010	1.004–1.016
Trx-2(ng/mL)	0.024	0.007	13.261	<0.001	1.025	1.001–1.038
Constant value	−13.320	2.562	27.800	<0.001	-	-

Dose-response Relationship between SII, Trx-2, and Short-term MACE Occurrence in SCM Patients

According to the results of multivariate Logistic regression, after adjusting the related confounding factors, the results of restricted cubic spline analysis showed that there was a linear dose-response relationship between SII and SCM short-term MACE risk ($P_{total\ trend}$=0.006, $P_{non\text{-}linearity}$=0.495); there was a linear dose-response relationship between Trx-2 and the short-term MACE risk of SCM ($P_{total\ trend}$=0.001, $P_{non\text{-}linearity}$=0.090), as shown in Figure 2. That is, the risk of MACE in SCM patients within 28 days of admission increased with the increase of serum SII and Trx-2 levels.

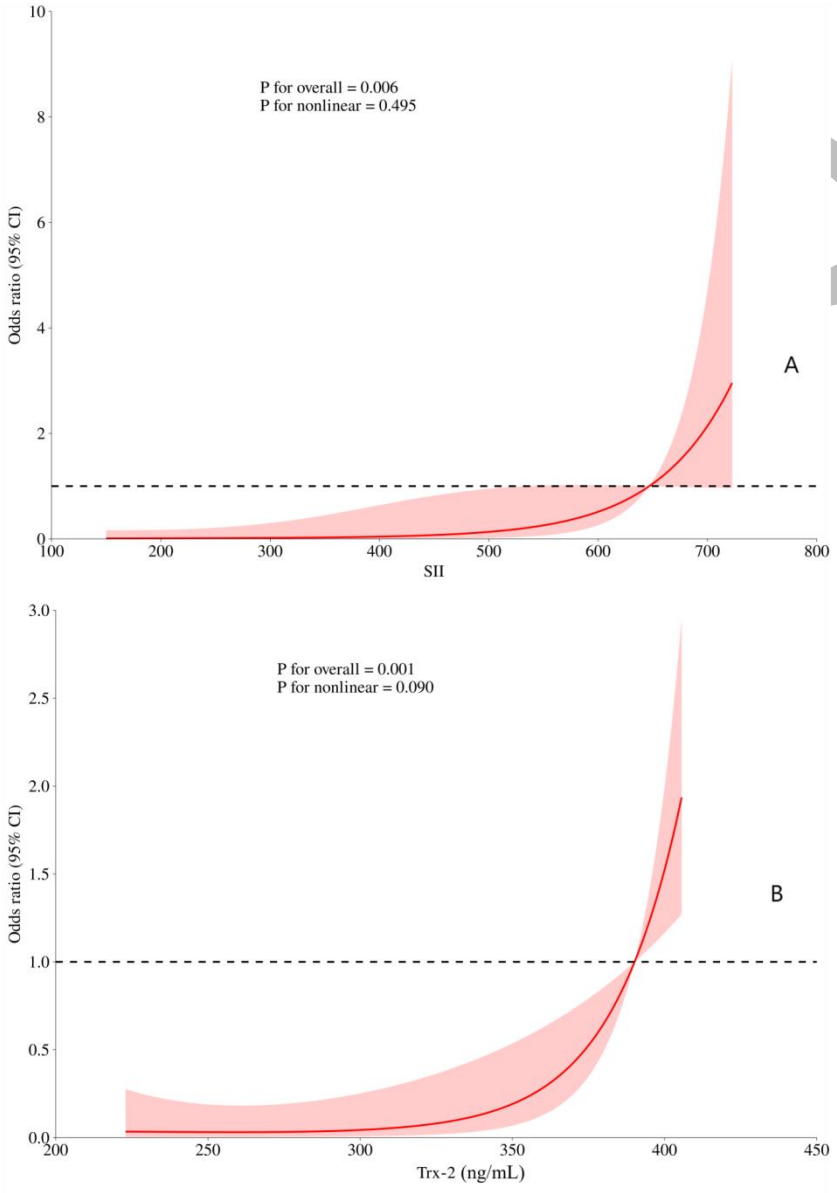

Figure 2. A. SII and MACE in SCM patients in the short term; B. the dose-response relationship between Trx-2 and MACE in SCM patients in the short term; MACE: major adverse cardiac events; Trx-2: Thioredoxin-2; SII: Systemic immune inflammatory index; SCM: sepsis cardiomyopathy.

The Predictive Effect of Combined SII and Trx-2 on Short-term MACE in SCM Patients

ROC curve showed that the AUC of SII and Trx-2 in predicting MACE in SCM patients in the short term was 0.869 and 0.881, respectively. The AUC of the ROC curve of the combined SII + Trx-2 model was 0.926 (95% CI: 0.862-0.989), and the specificity and sensitivity were 83.98% and 98.80%, respectively, suggesting that the area under the ROC curve of the combined SII + Trx-2> the area of each index alone, and can effectively improve the predictive validity of MACE in SCM patients in the short term. As shown in Table 5, Figure 3.

Table 5. The predictive effect of combined SII and Trx-2 on short-term MACE in SCM patients

Index	AUC	95% CI	Sensitivity	Specificity	*p*
SII	0.869	0.791–0.947	85.70%	84.13%	＜0.001
Trx-2	0.881	0.802–0.960	82.90%	80.95%	＜0.001
SII+Trx-2	0.926	0.862–0.989	82.90%	96.83%	＜0.001

AUC: area under the curve; CI: confidence interval; MACE: Major Adverse Cardiovascular Events; SCM: stress cardiomyopathy; SII: systemic immune-inflammation index; Trx-2: Thioredoxin-2.

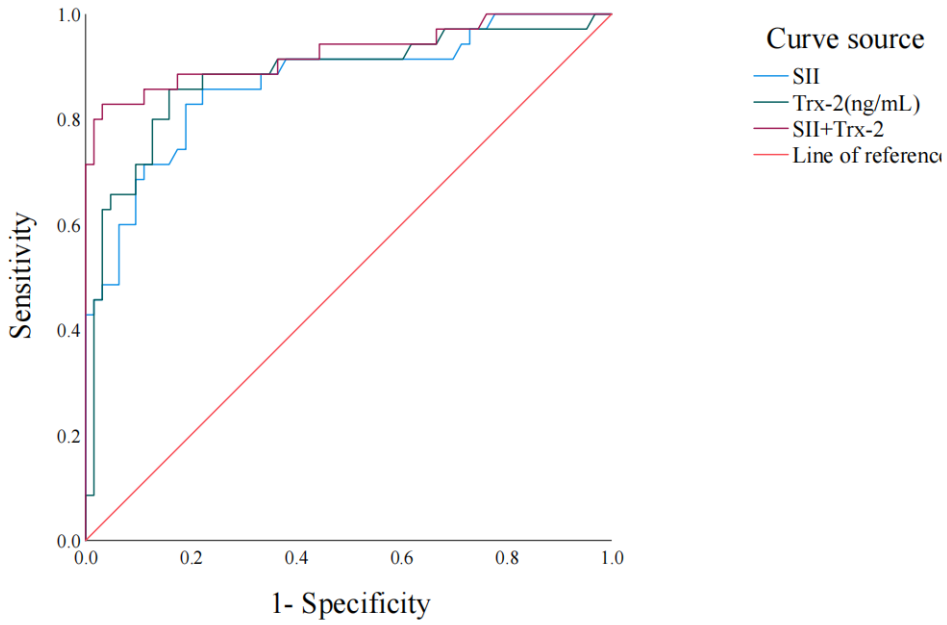

Figure 3. ROC curve of SII and Trx-2 in predicting MACE in SCM patients in the short term. MACE: Major Adverse Cardiac Events; Trx-2: Thioredoxin-2; SII: systemic immune inflammatory index

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DISCUSSION

The heart is one of the target organs frequently affected by sepsis. Myocardial inhibition resulting from sepsis poses a greater risk than dysfunction in other organs. Patients may develop refractory shock within a short period, significantly increasing the likelihood of sudden death.[24] A clinical cohort study showed that patients with sepsis in the intensive care unit had a 32.8 % probability of myocardial depression, and 30% to 70 % of patients with myocardial depression had MACE during treatment. If the heart function of these patients could not be restored, they would eventually go to cardiac pump failure.[4] In this study, 35.71 % of SCM patients had MACE within 28 days of admission, of which 15 patients had sudden cardiac death, which meant that SCM was the main cause of in-hospital death in MACE patients. Therefore, it is of great significance for clinical management strategies to improve the prognosis of MACE patients by paying attention to the in-hospital situation of MACE patients, accurately judging the risk of SCM, and effectively predicting it.

In this study, the levels of serum SII and Trx-2 in the MACE group were abnormally increased. Logistic regression data also indicated that the abnormal increase of serum SII and Trx-2 levels was related to the occurrence of MACE in the short term of SCM (p<0.05). Neutrophils and lymphocytes play crucial roles as components of both the innate immune system and the adaptive immune system. Their derived indicators, NLR and PLR, can also reflect the level of inflammatory response and have been widely used in clinical practice. Platelets constitute an essential component of blood. When there is inflammation in the body, it can induce the activation of the coagulation pathway. Thrombin can bind to the protease-activated receptor on the surface of platelets to initiate platelet activation and aggregation, and release pro-inflammatory factors and chemokines to participate in the inflammatory response process.[25,26] NI et al[27] studied 174 patients with sepsis and found that the change of NLR can evaluate the prognosis of patients with sepsis. The initial NLR measured at emergency admission was independently correlated with 28-day mortality, which was consistent with the results of this study. At the same time, systemic inflammatory response activation, endothelial cell damage, pathogenic microorganisms, and other factors can activate platelets in sepsis. Activated platelets can further release inflammatory factors, activate immune cells and endothelial cells, aggravate vascular endothelial injury, and interact with coagulation and immunity, forming a vicious circle, leading to further deterioration of the patient's condition.[28,29] Mangalesh et al[30] found that SII performed better than single cell count, platelet/lymphocyte ratio, or neutrophil/lymphocyte ratio in the independent prediction of sepsis mortality. Li et al[31] pointed out that Trx-2 can protect ischemia-reperfusion injury by inhibiting the apoptosis of H9c2 cardiomyocytes. Studies have found that when the body has oxidative stress, Trx is released from cells, and Tnc in serum or plasma is increased, which is a sign of oxidative stress.[32,33] Studies have shown that the release of inflammatory factors induced by oxidative stress is an important mechanism affecting the prognosis of sepsis.[34] The abnormal increase of Trx-2 level indicates that the body is in an oxidative stress state, [35] which also explains the increase of MACE risk in SCM patients caused by the abnormal increase of Trx-2 level in this study. Therefore, clinical monitoring of SII and Trx-2 levels can predict the risk of MACE in patients and provide a key basis for disease assessment.

Body temperature management has always been an important part of sepsis treatment. Mild hypothermia management has gradually become a key research direction of sepsis treatment in recent years. Studies have shown that mild hypothermia has a positive inotropic effect. When hypothermia occurs, myocardial metabolic needs decrease and heart rate slows down, but myocardial contractility increases, which helps to alleviate myocardial effects.[36] In addition, hypothermia can inhibit the release of inflammatory cytokines, and its mechanism may be related to the change of anti-inflammatory hormone levels.[37] Therefore, body temperature>38.3°C in patients with septic cardiomyopathy affects myocardial metabolism and is not conducive to anti-inflammatory treatment. Paying attention to body temperature management is the key to improving the prognosis of patients' cardiac function. However, there is no significant difference in the multivariate analysis of this study. It may be related to the small sample size of this study, and the sample size can be increased in the future to further explore.

In this study, the risk of MACE in SCM patients increased with the increase of serum SII and Trx-2 levels within 28 days after admission, suggesting that the detection of serum SII and Trx-2 levels is helpful to evaluate the risk of MACE. The ROC curve drawn in

this study showed that serum SII and Trx-2 alone and combined prediction of MACE risk in SCM patients had certain predictive value, and the combined predictive value was higher than that of SII and Trx-2 alone. It was further confirmed that the expression of serum SII and Trx-2 was related to the risk of MACE in SCM patients within 28 days of admission, and they could be used to predict the short-term MACE risk of SCM patients. Therefore, the detection of serum SII and Trx-2 levels can be incorporated into the clinical process, and SCM patients can be hierarchically managed according to the test results, and active intervention strategies can be formulated for high-risk patients to reduce the risk of MACE and improve the clinical outcome of patients. There are some shortcomings in this study: 1. The sample size is relatively small, which may affect the statistical efficiency. In the future, the sample size needs to be expanded to verify the results. 2. Only single-center patients were included, and the extrapolation of research results should be cautious; multicenter studies can be carried out in the future. This study only explored the relationship between SIIS, Trx-2, and short-term MACE in SCM patients, but its internal mechanism is still unclear, and further in vivo and in vitro studies are needed to elucidate the mechanism. The above limitations may affect the reliability of the research results to a certain extent, which needs to be improved in future research.

In summary, the abnormal increase of serum SIIS and Trx-2 levels in SCM patients is related to the occurrence of MACE within 28 days of admission, and the risk of MACE increases with the increase of serum SII and Trx-2 levels.

STATEMENT OF ETHICS

This study was approved by Affiliated Jinling Hospital, Medical School of Nanjing University. (2023DKKY-053-01).

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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