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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 sepsisinduced 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 Studies11 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 al¹² 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 al¹⁹ 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 connective malignant tumors, 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 4000g 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 (NTproBNP), 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.

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Project	MACE group	N-MACE group	t/χ^2	Р
	(n=35)	(n=63)		
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	25.14 ± 4.15	24.57 ± 4.18	0.650	0.517
(points)				
*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	2 (5.71)	4 (6.35)	0.016	0.900
pulmonary disease				
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)		

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

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.

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

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Projects	MACE	N-MACE	T/U	Р
U U	group(n=35)	group(n=63)		
*Blood lactic acid	6.80 ± 1.90	6.38 ± 1.82	1.075	0.285
(mmol/L)				
*24h lactic acid	48.63 ± 6.90	49.32 ± 7.11	-0.465	0.643
clearance (%)				
*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-	794.55 ± 91.50	788.95 ± 89.44	0.294	0.769
proBNP(pg/mL)				
*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,	319.75(253.02,	-3.503	< 0.001
	515.61)	396.69)		
*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

Table 2	. Con	narison	of labo	oratory	indicators	between	the two	groups
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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

Index	β	SE	Wald $\chi^2$	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	-	-

SII: Systemic immune-inflammation index; Trx-2: Thioredoxin-2

## 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 ( $P_{total trend}=0.006$ ,  $P_{non-linearity}=0.495$ ); there was a linear dose-response relationship between Trx-2 and the short-term MACE risk of SCM ( $P_{total trend}=0.001$ ,  $P_{non-linearity}=0.090$ ), 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 SIT and TTX-2 on short-term MACE in SCW patient	Table	5. The	e predictive	effect of c	combined S	II and Trx-	-2 on short-	-term MAC	E in SCM	patients
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Index	AUC	95% CI	Sensitivity	Specificity	р
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 al²⁷ 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 al³⁰ 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 al³¹ pointed out that Trx-2 can protect ischemiareperfusion 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 antiinflammatory 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 singlecenter 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.

## REFERENCES

- Liu D, Huang SY, Sun JH, Zhang HC, Cai QL, Gao C, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. Mil Med Res. 2022;9(1):56.
- Srzić I, Nesek Adam V, Tunjić Pejak D. SEPSIS DEFINITION: WHAT'S NEW IN THE TREATMENT GUIDELINES. Acta Clin Croat. 2022;61(Suppl 1):67-72.
- Jacobi J. The pathophysiology of sepsis 2021 update: Part
  organ dysfunction and assessment. Am J Health Syst Pharm. 2022;79(6):424-36.
- 4. Narváez I, Canabal A, Martín C, Sánchez M, Moron A, Alcalá J, et al. Incidence and evolution of sepsis-induced cardiomyopathy in a cohort of patients with sepsis and septic shock. Med Intensiva (Engl Ed). 2018;42(5):283-291.
- Jayaprakash N, Gajic O, Frank RD, Smischney N. Elevated modified shock index in early sepsis is associated with myocardial dysfunction and mortality. J Crit Care. 2018;43(8):30-35.
- 6. Boissier F, Aissaoui N. Septic cardiomyopathy: Diagnosis and management. J Intensive Med. 2021;2(1):8-16.
- Carbone F, Liberale L, Preda A, Schindler TH, Montecucco F. Septic Cardiomyopathy: From Pathophysiology to the Clinical Setting. Cells. 2022;11(18):2833.
- Yang B, Lin Y, Huang Y, Shen YQ, Chen Q. Thioredoxin (Trx): A redox target and modulator of cellular senescence and aging-related diseases. Redox Biol. 2024;70(5):103032.
- 9. Kundumani-Sridharan V, Subramani J, Owens C, Das KC. Nrg1β Released in Remote Ischemic Preconditioning Improves Myocardial Perfusion and Decreases Ischemia/Reperfusion Injury via ErbB2-Mediated Rescue of Endothelial Nitric Oxide Synthase and Abrogation of

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Trx2 Autophagy. Arterioscler Thromb Vasc Biol. 2021;41(8):2293-14.

- Wei ZX, Cai XX, Fei YD, Wang Q, Hu XL, Li C, et al. Zbtb16 increases susceptibility of atrial fibrillation in type 2 diabetic mice via Txnip-Trx2 signaling. Cell Mol Life Sci. 2024;81(1):88.
- Chen Z, Feng Y, Zhang RB, Li X, Xu JB. Effect of grelin on TRX expression in chronic heart failure tissue: A protocol of systematic review and meta-analysis. Medicine (Baltimore). 2020;99(21):e20294.
- Wang X, Xing Y, Tang Z, Tang Y, Shen J, Zhang F. Thioredoxin-2 impacts the inflammatory response via suppression of NF-κB and MAPK signaling in sepsis shock. Biochem Biophys Res Commun. 2020;524(4):876-82.
- 13. Xia Y, Xia C, Wu L, Li Z, Li H, Zhang J. Systemic Immune Inflammation Index (SII), System Inflammation Response Index (SIRI) and Risk of All-Cause Mortality and Cardiovascular Mortality: A 20-Year Follow-Up Cohort Study of 42,875 US Adults. J Clin Med. 2023;12(3):1128.
- 14. Ding P, Guo H, Sun C, Yang P, Kim NH, Tian Y, et al. Combined systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI) predicts chemotherapy response and prognosis in locally advanced gastric cancer patients receiving neoadjuvant chemotherapy with PD-1 antibody sintilimab and XELOX: a prospective study. BMC Gastroenterol. 2022;22(1):121.
- 15. Sun J, Qi Y, Wang W, Meng P, Han C, Chen B. Systemic Immune-Inflammation Index (SII) as a Predictor of Short-Term Mortality Risk in Sepsis-Associated Acute Kidney Injury: A Retrospective Cohort Study. Med Sci Monit. 2024;30:e943414.
- 16. Jiang D, Bian T, Shen Y, Huang Z. Association between admission systemic immune-inflammation index and mortality in critically ill patients with sepsis: a retrospective cohort study based on MIMIC-IV database. Clin Exp Med. 2023;23(7):3641-50.
- 17. Liu C, Wu X, Deng R, Xu X, Chen C, Wu L, et al. Systemic immune-inflammation index combined with quick sequential organ failure assessment score for predicting mortality in sepsis patients. Heliyon. 2023;9(9):e19526.
- Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181-1247.
- Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med. 1984;100(4):483-90.

- Ye C, Yuan L, Wu K, Shen B, Zhu C. Association between systemic immune-inflammation index and chronic obstructive pulmonary disease: a population-based study. BMC Pulm Med. 2023;23(1):295.
- 21. Zhang S, Wei Y, Liu J, Zhuang Y. MiR-940 Serves as a Diagnostic Biomarker in Patients with Sepsis and Regulates Sepsis-Induced Inflammation and Myocardial Dysfunction. J Inflamm Res. 2021;14(4):4567-4574.
- Zimmerman JE, Kramer AA. Outcome prediction in critical care: the Acute Physiology and Chronic Health Evaluation models. Curr Opin Crit Care. 2008;14(5):491-7.
- 23. Balamuth F, Scott HF, Weiss SL, Webb M, Chamberlain JM, Bajaj L, et al. Validation of the Pediatric Sequential Organ Failure Assessment Score and Evaluation of Third International Consensus Definitions for Sepsis and Septic Shock Definitions in the Pediatric Emergency Department. JAMA Pediatr. 2022;176(7):672-8.
- 24. Lin YM, Lee MC, Toh HS, Chang WT, Chen SY, Kuo FH, et al. Association of sepsis-induced cardiomyopathy and mortality: a systematic review and meta-analysis. Ann Intensive Care. 2022;12(1):112.
- 25. Yang J, Ran T, Lin X, Xu J, Zhou S, Chen C, et al. Association between preoperative systemic immune inflammation index and postoperative sepsis in patients with intestinal obstruction: A retrospective observational cohort study. Immun Inflamm Dis. 2024;12(2):e1187.
- 26. Pricop M, Ancusa O, Talpos S, Urechescu H, Bumbu BA. The Predictive Value of Systemic Immune-Inflammation Index and Symptom Severity Score for Sepsis and Systemic Inflammatory Response Syndrome in Odontogenic Infections. J Pers Med. 2022;12(12):2026.
- 27. Ni J, Wang H, Li Y, Shu Y, Liu Y. Neutrophil to lymphocyte ratio (NLR) as a prognostic marker for inhospital mortality of patients with sepsis: A secondary analysis based on a single-center, retrospective, cohort study. Medicine (Baltimore). 2019;98(46):e18029.
- Su M, Chen C, Li S, Li M, Zeng Z, Zhang Y, et al. Gasdermin D-dependent platelet pyroptosis exacerbates NET formation and inflammation in severe sepsis. Nat Cardiovasc Res. 2022;1(8):732-47.
- Russell NJ, Stöhr W, Plakkal N, Cook A, Berkley JA, Adhisivam B, et al. Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: A global neonatal sepsis observational cohort study (NeoOBS). PLoS Med. 2023;20(6):e1004179.
- Mangalesh S, Dudani S, Malik A. The systemic immuneinflammation index in predicting sepsis mortality. Postgrad Med. 2023;135(4):345-51.

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- 31. Li YY, Xiang Y, Zhang S, Wang Y, Yang J, Liu W, et al. Thioredoxin-2 protects against oxygen-glucose deprivation/reperfusion injury by inhibiting autophagy and apoptosis in H9c2 cardiomyocytes. Am J Transl Res. 2017;9(3):1471-82.
- Matsuo Y. Introducing Thioredoxin-Related Transmembrane Proteins: Emerging Roles of Human TMX and Clinical Implications. Antioxid Redox Signal. 2022;36(13-15):984-1000.
- 33. Lu H, Li S, Zhong X, Huang S, Jiao X, He G, et al. Immediate outcome prognostic value of plasma factors in patients with acute ischemic stroke after intravenous thrombolytic treatment. BMC Neurol. 2022;22(1):359.
- 34. Zhang W, Chen H, Xu Z, Zhang X, Tan X, He N, et al. Liensinine pretreatment reduces inflammation, oxidative stress, apoptosis, and autophagy to alleviate sepsis acute kidney injury. Int Immunopharmacol. 2023;122(8):110563.
- 35. Liu AB, Li SJ, Yu YY, Zhang JF, Ma L. Current insight on the mechanisms of programmed cell death in sepsisinduced myocardial dysfunction. Front Cell Dev Biol. 2023;11(9):1309719.
- Qin Z, Shen S, Qu K, Nie Y, Zhang H. Mild hypothermia in rat with acute myocardial ischaemia-reperfusion injury complicating severe sepsis. J Cell Mol Med. 2021;25(13):6448–54.
- 37. Levy B, Girerd N, Amour J, Besnier E, Nesseler N, Helms J, et al. Effect of Moderate Hypothermia vs Normothermia on 30-Day Mortality in Patients With Cardiogenic Shock Receiving Venoarterial Extracorporeal Membrane Oxygenation: A Randomized Clinical Trial. JAMA. 2022;327(5):442-53.