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ORIGINAL RESEARCH

Construction of a Risk Prediction Model for Stroke Occurrence in Septic Shock Patients: A Combined Analysis Using LASSO and Multivariate Logistic Regression

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Background: This study aimed to develop and validate a risk prediction model for stroke within 90 days in patients with septic shock and to identify independent risk factors.

Methods: A retrospective, single-center study was performed, including 2127 septic shock patients admitted to Dongyang City People's Hospital from June 2016 to December 2024. Clinical variables were selected using LASSO regression, and the prediction model was established by multivariate logistic regression. Internal validation was conducted using nomogram, calibration curves, ROC curves, and decision curve analysis (DCA).

Results: Seven variables (age, hypertension, ALB, TC, Cr, TBIL, and WBC) were screened by LASSO regression. Multivariate analysis confirmed that age, hypertension, ALB, TC, and TBIL were independent risk factors. These factors may reflect age-related vascular vulnerability, chronic hypertension-related cerebrovascular damage, and metabolic or hepatic dysfunction associated with stroke risk in septic shock. The model showed good predictive performance, with AUCs of 0.754 and 0.76 in the modeling and testing cohorts, respectively. Calibration and DCA curves confirmed satisfactory discrimination, calibration, and clinical utility.

Conclusion: This prediction model demonstrates favorable performance for stroke risk stratification in septic shock patients. It may allow early identification of high-risk individuals, enabling timely intervention to reduce stroke-related mortality and disability.

Keywords: stroke, LASSO, sepsis

Introduction

Sepsis, defined as life-threatening organ dysfunction triggered by infection, remains a critical challenge in critical care medicine, affecting millions of patients globally each year. With a mortality rate of 25%-30% and long-term cognitive impairment common among survivors, sepsis imposes immense clinical and societal burdens.[1,2] Global estimates indicate that, in 2017 alone, there were 48.9 million sepsis cases, resulting in 11 million deaths—accounting for nearly one-fifth of all global deaths that year.[3] In China, sepsis contributes to approximately 1 million deaths annually, with a standardized mortality rate of 66.7 per 100,000 people.[4] A multicenter study across 44 Chinese ICUs further highlighted the severity of the issue, reporting that sepsis affects one-fifth of ICU admissions, with a 90-day mortality rate of 35.5%.[5] These figures underscore sepsis as not only a medical priority but also a pressing public health concern.

Stroke, characterized by acute neurological dysfunction due to cerebrovascular damage, shares similar daunting epidemiological profiles. As the second leading cause of death worldwide,[6] it is the primary cause of adult mortality and disability in China. However, barriers to timely care persist, making risk stratification and targeted intervention crucial for reducing stroke-related morbidity, mortality, and socioeconomic costs.[7]

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Emerging evidence has revealed a strong bidirectional link between sepsis and stroke. Notably, this study focuses specifically on post-discharge stroke, which differs from in-hospital stroke in terms of pathophysiological mechanisms and clinical management priorities. Stroke incidence tends to decrease with age, and traditional cardiovascular risk factors fail to fully explain this shift.[8] Mechanistically, both inflammatory and metabolic pathways bridge these conditions: inflammatory markers such as interleukin-6 (IL-6) and troponin T (TNT) are key mediators. IL-6 is an independent predictor of stroke recurrence and poor outcomes,[9] whereas elevated TNT levels in sepsis patients correlate with disease severity and adverse stroke prognosis.[10,11] Beyond inflammation, metabolic dysregulation plays a pivotal role in vascular injury and subsequent stroke risk. Sepsis induced systemic metabolic reprogramming includes dysregulated lipid metabolism, altered amino acid pathways, and accumulation of oxidative stress-related metabolites.[12,13] These metabolic alterations impair vascular endothelial function, promote oxidative stress and thrombosis, and exacerbate neurovascular damage, collectively increasing stroke vulnerability. Clinically, sepsis increases the risk of ischemic stroke by 3-fold and hemorrhagic stroke by 7-fold,[14] and septic shock survivors face a 1.64-fold greater risk of stroke within 5 years post-discharge than does the general population.[15]

To date, existing research on sepsis-related complications has focused primarily on generalized analyses of post-infection outcomes,[16,17] with limited attention to stroke as a specific endpoint. Few studies have constructed targeted risk prediction models for post-discharge stroke in septic shock patients, and those available lack comprehensive integration of clinical variables and metabolic correlates. Additionally, prior models often fail to distinguish post-discharge stroke from in-hospital events, limiting their clinical utility for long-term follow-up and intervention. Therefore, this study intends to incorporate more comprehensive clinical variables based on the hospital data platform and adopt LASSO regression (suitable for high-dimensional data screening and dimensionality reduction) to develop a risk prediction model for stroke within 90 days after septic shock. By identifying independent risk factors, this study aimed to provide a practical risk assessment tool for clinical practice, facilitate early intervention in high-risk patients reduce stroke-related mortality and disability, and alleviate the economic burden on families and society and thus holding significant clinical and public health significance.

Materials and Methods

Study Population and Data Collection

A retrospective, single-center study was conducted. Clinical data were collected from patients with septic shock admitted to Dongyang City Peaple's Hospital from June 2016 to December 2024 using the hospital's data platform. All information was verified, corrected, and supplemented via electronic medical records. The diagnosis of septic shock was based on the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) issued by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Inclusion criteria: (a) suspected or confirmed infection with a Sequential Organ Failure Assessment (SOFA) score $\geq$ 2; (b) circulatory failure with blood lactic acid (lac) level > 2 mmol/L; (c) requirement for vasoactive agents to maintain a mean arterial pressure (MAP) $\geq$ 65 mmHg. Exclusion criteria: (a) age < 18; (b) in-hospital death; (c) a history of stroke or cerebral infarction; (d) long-term chronic inflammatory diseases. This study was approved by the Institutional Ethics Committee of Dongyang City Peaple's Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. All patients were followed up by reviewing hospitalization records and telephone interviews to determine whether stroke occurred within 90 days after the diagnosis of septic shock.

Ascertainment of Stroke

Stroke was defined as acute neurological dysfunction consistent with either ischemic or hemorrhagic stroke, and all events were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. The endpoint was stroke occurrence within 90 days after discharge.

Observation Indicators

Upon hospitalization, patient demographic data, including sex, age, smoking history, and hypertension history, were collected. The following laboratory test indicators were recorded at admission: cholinesterase (CHE), albumin (ALB), pro-brain natriuretic peptide (pro-BNP), total cholesterol (TC), triglyceride (TG), high-sensitivity C-reactive protein (hs-

CRP), creatinine (Cr), D-dimer (DD), total bilirubin (TBIL), and white blood cell (WBC) count. Patients were divided into a stroke group and a control group according to whether stroke occurred within 90 days after discharge.

Handling of Missing Data

Variables or cases with >20% missing values were excluded. For remaining missing values, random forest imputation (missForest package) was used to minimize bias and retain sample size.

Statistical Methods

All the statistical analyses were performed via R software. Continuous variables with a normal distribution are expressed as the means ± standard deviations, and intergroup differences were analyzed via t tests. Continuous variables that did not follow a normal distribution are presented as medians (minimum - maximum), and intergroup differences were assessed via the Wilcoxon rank-sum test. Categorical variables are described as percentages, and intergroup comparisons were conducted via the chi-square test.

The dataset were randomly split into a modeling group and a testing group at a 7:3 ratio. Given that the study focused on binary stroke occurrence within a fixed 90-day period rather than time-to-event analysis, logistic regression was appropriate for the study design and objective. LASSO regression (glmnet package) was used for variable selection, with continuous variables standardized. Variables were selected using the minimum λ value. Selected variables were entered into multivariate logistic regression to construct the prediction model. A nomogram was established using the rms package. Model performance was evaluated using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results

Patient Characteristics

A total of 2127 patients with septic shock were enrolled in this study, including 608 patients in the stroke group (28.6%) and 1519 patients in the control group (71.4%). In the stroke group, there were 358 male patients, accounting for 58.88%, with a mean age of 76.89 ± 10.79 years. In the control group, 890 patients were male (58.59%), and the average age was 64.00 ± 20.35 years.

Statistically significant differences were observed between the two groups in terms of age, hypertension status, cholinesterase level, ALB level, pro-BNP level, TC level, TG level, hs-CRP level, and Cr level (all $P < 0.05$, 95% CIs are provided in Table 1). However, no significant differences were found in smoking status, DD level, TBIL level, or WBC count between the two groups (all $P > 0.05$) (see Table 1).

Table 1 Clinical Baseline Characteristics of Patients with Septic Shock

	Stroke (n=608)	**Control (n=1519)**	**(χ^2/Z)**	**P value**
Male (%)	358 (58.88%)	890 (58.59%)	χ^2=0.02	0.90
Age (Mean ± SD)	76.89 ± 10.79	64.00 ± 20.35	t=−18.92	**<0.01**
Hypertension (%)	432 (71.05%)	564 (37.13)	χ^2=200.68	**<0.01**
Smoke (%)	178 (29.28)	442 (29.10)	χ^2=0.01	0.93
Cholinesterase (U/L)	3324.00 (1647.50, 4490.25)	3710.00 (1713.50, 5014.50)	Z=−3.75	**<0.01**
ALB (g/L)	16.10 (14.10, 18.50)	17.10 (14.30, 19.60)	Z=−4.81	**<0.01**
Pro-BNP (pmol/L)	3983.50 (1117.00, 11,144.75)	3117.44 (1102.80, 8238.50)	Z=−3.24	**<0.01**
TC (mmol/L)	4.89 (4.11, 5.69)	4.54 (3.61, 5.41)	Z=−6.35	<0.01
TG (mmol/L)	1.59 (1.19, 1.91)	1.50 (1.13, 1.91)	Z=−3.62	<0.01
HSCRP (mg/dL)	146.13 (111.40, 174.67)	139.50 (106.24, 171.67)	Z=−2.57	<0.01
Cr (μmol/L)	115.00 (91.00, 167.25)	106.00 (75.00, 154.00)	Z=−5.99	<0.01
D-Dimer (mg/dL)	5.88 (1.77, 10.00)	5.37 (1.75, 10.00)	Z=−1.76	0.08
TBIL (μmol/L)	16.75 (13.10, 35.50)	16.60 (11.85, 41.05)	Z=−0.26	0.79
WBC (×10^9/L)	13.88 (10.62, 17.34)	13.56 (10.54, 17.14)	Z=−1.18	0.24

Note: P values less than 0.05 are indicated in bold.

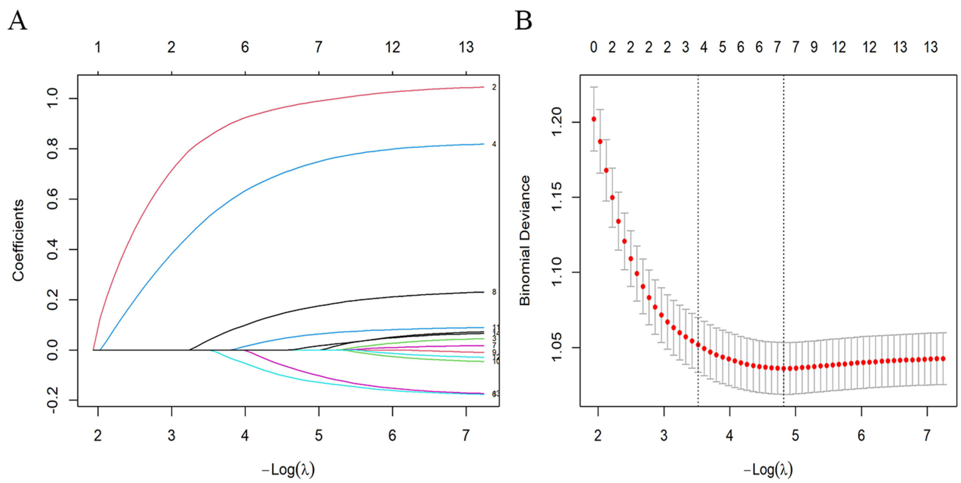

Figure 1 Distribution plot of LASSO regression coefficients and cross-validation curve plot. (**A**) Distribution plot of regression coefficients; (**B**) Cross-validation curve plot.

Variable Selection via LASSO Regression

In this study, LASSO regression was employed for variable selection to eliminate multicollinearity among variables, which in turn helps improve the predictive accuracy of the model. With the minimum lambda value set as the screening criterion, the cross-validation results indicated that when λ was 0.0080, there were 7 variables with nonzero coefficients, including age, hypertension, ALB, TC, Cr, TBIL and WBC, and these variables were selected as key variables that contributed significantly to the model (Figure 1A and B).

Multivariate Logistic Regression Analysis of Stroke in Patients with Septic Shock

With the occurrence of stroke in patients with septic shock as the dependent variable and age, hypertension, ALB, TC, Cr, TBIL and WBC count as independent variables, multivariate logistic regression analysis was performed. The results (Table 2) revealed that among the 7 independent variables screened by LASSO regression, Cr and WBC were not associated with the occurrence of stroke ($P>0.05$), whereas the other five factors were associated with an increased risk of stroke (all $P < 0.05$, 95% CIs are provided in Table 2).

Visualization and Efficacy Validation of the Risk Prediction Model for Stroke in Patients with Septic Shock

The nomogram was plotted via the “rms” package with the five independent variables that showed statistical significance in the multivariate logistic regression analysis. The weights of each independent variable were visualized to achieve a quantitative assessment of the individual risk of death (Figure 2A). In addition, all septic patients in this study were

Table 2 Multivariate Logistic Regression Analysis of Stroke in Patients with Septic Shock

	β	SE	P	OR	95% CI
Age	0.0454	0.0054	**0**	1.0464	0.0029–0.0376
Hypertension	1.0357	0.134	**0**	2.8171	1.0356–1.0578
ALB	−0.0384	0.0153	**0.0122**	0.9624	2.1701–3.6705
TC	0.1488	0.0427	**0.0005**	1.1604	0.9338–0.9916
Cr	0.0005	0.0003	0.1201	1.0005	1.0679–1.2628
TBIL	−0.0025	0.0011	**0.0284**	0.9975	0.9999–1.0011
WBC	0.0049	0.0057	0.3938	1.0049	0.9952–0.9996

Note: P values less than 0.05 are indicated in bold.

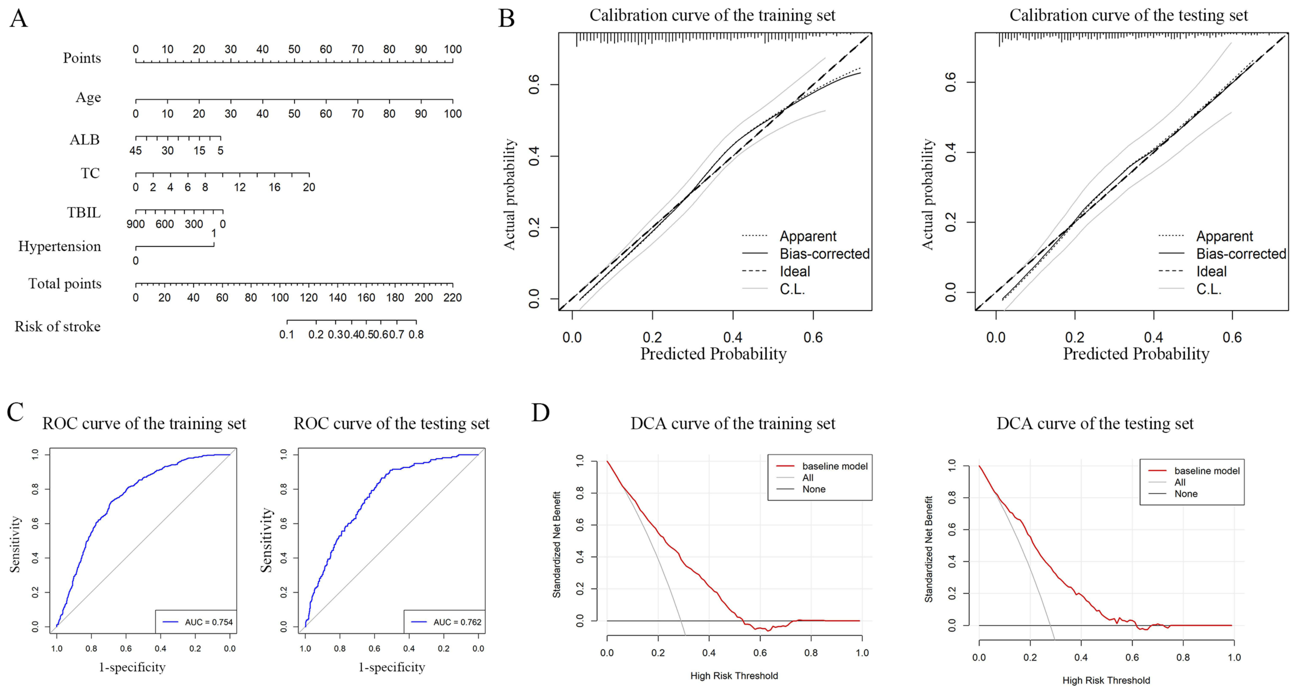

Figure 2 Visualization and efficacy validation of the risk prediction model for stroke in patients with septic shock. (**A**) Nomogram model; (**B**) Calibration curve; (**C**) ROC curve; (**D**) DCA curve.

randomly divided into a modeling group and a testing group, and calibration curves, ROC curves, and DCA curves were used to comprehensively evaluate the predictive performance of the model. The results (Figure 2B) revealed that both the internal validation curves (Apparent) and bias-corrected curves of the calibration curves in the modeling group and the testing group were close to the ideal reference line (Ideal), suggesting that the predicted probabilities of the model were highly consistent with the actual event rates. ROC curve analysis (Figure 2C) revealed that the areas under the curve (AUCs) of the model for predicting the risk of stroke in the modeling group and the testing group were 0.754 and 0.76, respectively, which indicated that the model had high discriminative ability. The DCA decision curve (Figure 2D) further verified its clinical utility, and the application of this model significantly improved the clinical net benefit rate (net benefit) in both groups. The above multidimensional validation results indicated that the model had good calibration, discrimination, and clinical transformation values.

Discussion

Septic shock, a severe condition characterized by widespread organ dysfunction, is associated with persistently high mortality rates. Notably, survivors of septic shock who are discharged from the hospital face a significantly elevated risk of subsequent cardiovascular and cerebrovascular diseases. In the present study, among 2127 patients with septic shock, 608 (28.6%) developed stroke during follow-up. These findings underscore the critical need to identify factors associated with stroke in this patient population, as such insights would facilitate rapid and accurate risk stratification during clinical management, ultimately playing a pivotal role in preventing stroke and improving patient outcomes.

LASSO regression enables efficient variable selection through L1 regularization, demonstrating significant advantages in multivariate logistic regression analysis. It can not only shrink the coefficients of redundant variables to effectively address multicollinearity but also reduce the subjective bias of traditional stepwise regression by selecting the optimal penalty parameter via cross-validation. This approach enhances the generalization ability of the model and maintains predictive performance while reducing the dimensionality of variables.[18,19] In this study, LASSO regression was used to analyze the factors associated with stroke in patients with septic shock. The results revealed that age, hypertension, ALB, TC, Cr, TBIL and WBC count were associated with the occurrence of stroke. Further multivariate

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logistic regression analysis of the above factors revealed that age, hypertension, ALB, TC and TBIL were independently associated with stroke risk. The lack of significance of Cr and WBC in multivariate analysis may be attributed to their potential collinearity with other variables.

Age is an important risk factor for stroke in patients with septic shock. Studies have shown that vascular aging can exacerbate postseptic endothelial dysfunction and arterial stiffness.[20] Elderly individuals exhibit increased oxidative stress and impaired autophagy, increasing the susceptibility of cerebrovascular vessels to sepsis-induced microvascular thrombosis.[21] Furthermore, immunosenescence during the aging process may prolong the systemic inflammatory state, as evidenced by the persistently elevated levels of IL-6 and TNF-α even one year after the onset of sepsis, which are associated with increased carotid intima–media thickness.[22] Notably, aging-related metabolic decline may synergize with sepsis-induced metabolic stress, further amplifying the risk of cerebrovascular injury. For instance, elderly patients have lower baseline albumin synthesis and reduced ability to compensate for sepsis-induced protein catabolism, exacerbating hypoalbuminemia-related vascular dysfunction.[13]

The results of this study revealed that hypertension significantly increased the risk of stroke after septic shock. Hypertension is prevalent in the stroke-prone population. It not only increases the risk of stroke but also deteriorates the outcome of stroke.[23] In patients with septic shock, hypertension can activate the renin–angiotensin–aldosterone system, thereby disrupting the autoregulatory function of the brain and leading to the occurrence of stroke. Taking active blood pressure control measures during sepsis and long-term antihypertensive treatment can reduce the risk of stroke. Metabolically, hypertension exacerbates sepsis-induced lipid metabolism disorders and impairs endothelial nitric oxide metabolism, promoting vascular inflammation and thrombosis. This synergistic effect of hypertension and metabolic dysfunction may explain its strong association with post-sepsis stroke.

Mounting evidence from metabolomic studies has highlighted that systemic metabolic dysregulation is a critical mechanistic link between septic shock and subsequent stroke.[24,25] Sepsis triggers profound metabolic reprogramming characterized by disrupted lipid metabolism, imbalanced amino acid pathways, impaired protein synthesis, and diminished antioxidant metabolite production, all of which compromise vascular endothelial integrity, enhance oxidative stress, and promote a prothrombotic state. Disturbances in lipid and amino acid metabolism have been consistently associated with vascular dysfunction and poor outcomes in patients with sepsis. Moreover, metabolic failure in sepsis impairs cerebrovascular homeostasis and increases vulnerability to ischemic or hemorrhagic injury long after discharge.

ALB is a protein with anti-inflammatory, nutritional, and hemorheological properties that can inhibit platelet activation and aggregation. Recent studies have shown that hypoalbuminemia is associated with poor prognosis in septic patients.[26] This study also revealed that low ALB levels are an independent risk factor for stroke, which is consistent with previous research results. Mechanistically, ALB maintains endothelial integrity by stabilizing the glycocalyx and inhibiting platelet aggregation.[27] In sepsis, the level of albumin decreases due to increased capillary leakage and inhibited hepatic synthesis, leading to reduced nitric oxide bioavailability and increased procoagulant activity.[28,29] Therefore, albumin supplementation during sepsis may provide long-term cerebrovascular benefits.

Both TBIL and WBC count have emerged as factors associated with stroke in septic shock patients. Previous research has revealed the antioxidative and anti-inflammatory properties of TBIL. A study revealed that low TBIL levels were associated with an increased risk of early neurological deterioration in acute ischemic stroke patients.[28] In septic shock, a reduced TBIL level might reflect an impaired antioxidant defense system, potentially increasing the vulnerability of cerebral vessels to oxidative stress and inflammation, thus contributing to stroke development.

WBCs play a crucial role in the inflammatory response in the context of sepsis. A historical cohort study revealed that in septic shock patients, a rising WBC trajectory was independently associated with increased mortality.[30] During sepsis, an elevated WBC count may indicate a robust but dysregulated immune response. Excessive leukocyte infiltration can lead to microvascular obstruction in the brain, the release of cytotoxic substances, and increased inflammation, all of which could precipitate stroke.

This study identified modifiable risk factors for postsepsis stroke, suggesting the need for comprehensive follow-up programs, including blood pressure management, nutritional support, lipid control, and antioxidant strategies. However, limitations of this study include: (1) its single-center design, which may limit the generalizability of findings to other populations or healthcare settings; (2) only internal validation was performed, and external validation using multicenter data is lacking; (3) missing data on key confounders such as atrial fibrillation, diabetes, and medications, which may influence stroke risk but were not fully captured due to incomplete documentation in early electronic medical records; (4) the lack of long-term inflammation markers and genetic predisposition data; and (5) the focus on clinical variables without integration of omics data, which may limit the depth of mechanistic insights.

Conclusion

Age, hypertension, ALB, TC, and TBIL independently predictors stroke in septic shock patients, supporting the utility of these variables for risk stratification rather than proving causal mechanisms. These findings highlight the importance of integrating metabolic considerations into post-sepsis care and emphasize the need for multidisciplinary management focused on vascular health and metabolic homeostasis to improve long-term outcomes.

Abbreviations

IL-6, interleukin-6; TNT, troponin T; SCCM, Society of Critical Care Medicine; ESICM, European Society of Intensive Care Medicine; SOFA, Sequential Organ Failure Assessment; CHE, cholinesterase; ALB, albumin; pro-BNP, pro-brain natriuretic peptide; TC, total cholesterol; TG, triglyceride; hs-CRP, high-sensitivity C-reactive protein; Cr, D-, creatinine; DD, dimer; TBIL, total bilirubin; WBC, white blood cell.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. This research project was initially approved by the Institutional Ethics Committee of Dongyang City People's Hospital (Approval No.: 2023-YX-056) prior to the commencement of the study, confirming the compliance of the research protocol with ethical guidelines. Given that this study is a retrospective analysis utilizing fully de-identified clinical data retrieved from the hospital's information system—with all patient-specific identifiers removed to ensure strict protection of individual privacy—the Institutional Ethics Committee of Dongyang City People's Hospital further issued a formal decision to waive the requirement for individual informed consent (Approval No.: 2025-YX-198) during the manuscript preparation phase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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