

The value of right ventricular ultrasound assessment and cardiac biomarkers in the prognosis of sepsis

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Abstract. – OBJECTIVE: The aim of this study was to explore the risk factors affecting the prognosis of patients with sepsis using a prospective design.

PATIENTS AND METHODS: From January 2022 to March 2023, a prospective study was conducted in the Intensive Care Unit (ICU) of Cangzhou Central Hospital, including 58 patients who met the diagnostic criteria for sepsis. Patients were divided into a survival group (39 cases) and a death group (19 cases) based on outcome. Within 24 hours, the following indicators were collected: gender, age, underlying diseases, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, cardiac troponin I (cTnI), B-type natriuretic peptide (BNP), lactate, procalcitonin, ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), systolic velocity (S'), and global longitudinal strain/strain rate (GLS/GLSr) and global circumferential strain/strain rate (GCS/GCSr) by speckle tracking. Logistic regression analysis was used to evaluate the risk factors for mortality in septic patients, and receiver operating characteristic (ROC) curves were used to evaluate the predictive value of various risk factors for sepsis-related death.

RESULTS: There was no significant difference in gender, age, underlying diseases, BNP, procalcitonin, EF, TAPSE, S', GLSr, GCS, or GCSr between the two groups ($p>0.05$). There were statistically significant differences in APACHE II score, SOFA score, cTnI, lactate, and GLS between the two groups ($p<0.05$). Logistic regression analysis showed that SOFA score (OR=2.32, 95% CI: 1.067-5.289, $p<0.05$), cTnI (OR=1.19, 95% CI: 1.001-1.312, $p<0.05$), and GLS (OR=1.58, 95% CI: 1.012-2.721, $p<0.05$) were risk factors for sepsis-related death ($p<0.05$). The areas under the ROC curves for SOFA score, cTnI, and GLS were 0.769, 0.757, and 0.846, respectively.

CONCLUSIONS: SOFA score, cTnI, and GLS are independent risk factors for mortality in patients with sepsis. Among these factors, GLS

has the highest predictive value for patient prognosis. Therefore, when predicting the prognosis of patients with sepsis, the assessment of right ventricular ultrasound can be used in clinical practice.

Key Words:

Right ventricular ultrasound, Cardiac biomarkers, Sepsis, Prognosis, Significance, Logistic regression, Receiver operating characteristic curve.

Introduction

Sepsis is a serious disease caused by a systemic inflammatory response to infection, often accompanied by multiple organ dysfunction, and is one of the most common diseases in the intensive care unit (ICU)¹. In recent years, with the advancement of medical technology, the treatment methods for sepsis have also been further improved, enhancing the prognosis of sepsis patients to a certain extent². However, the mortality rate of sepsis remains high. Therefore, the search for effective prognostic indicators for sepsis has become a hot topic in current clinical research.

There are many clinical methods and indicators for assessing the prognosis of sepsis, including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, left ventricular ejection fraction (EF), etc.³. In addition, several polymorphisms in antigen recognition genes and inflammatory pathway genes have been demonstrated. Recently, a GWAS study identified a gene strongly associated with sepsis survival. Homozygotes for the C allele of the tyrosine protein kinase Fer gene had a 44% lower sepsis mortality rate. Given the high frequency of this allele, it is likely that a large population benefits from

this protective effect. The exact role of FER or its interacting partners in septic response remains elusive, and further biochemical discovery and translational studies are required.

Encouragingly, recent studies^{4,5} have pointed to the potential value of echocardiography in assessing the prognosis of patients with sepsis⁴. Echocardiography is a non-invasive, convenient, and reproducible tool for the assessment of cardiac function⁵. However, to date, there is still a lack of large-scale clinical studies exploring the role of echocardiography in sepsis prognosis. Therefore, this study aims to investigate the value of echocardiography in the prognosis of sepsis, with a view to providing a more accurate and reliable index for the treatment and prognostic assessment of sepsis patients.

Patients and Methods

Baseline Data

From January 2022 to March 2023, a prospective study was conducted on 58 patients with sepsis admitted to the intensive care unit (ICU) of Cangzhou Central Hospital. Patients were diagnosed based on sepsis diagnostic criteria. According to their outcomes, patients were divided into a survival group (39 cases) and a death group (19 cases). This study complied with medical ethics guidelines and was approved by the hospital ethics committee.

Inclusion and Exclusion Criteria

(1) Inclusion criteria: 1. Patients aged 18 years or older; 2. patients diagnosed with sepsis or septic shock according to the 2018 Guidelines for the Treatment of Sepsis and Septic Shock; 3. patients with successful fluid resuscitation after diagnosis; 4. patients with complete ultrasound evaluation and cardiac biomarker data; 5. patients and their families are informed about the study and have signed relevant consent forms.

(2) Exclusion criteria: 1. Patients with acute coronary syndrome, history of cardiac surgery, liver or kidney failure, malignant tumors, or autoimmune diseases; 2. patients with incomplete ultrasound evaluation or cardiac biomarker data; 3. patients with unclear ultrasound images; 4. patients with psychiatric or communication disorders.

Methods

According to the protocols⁶, patients are given interventions such as antibiotics and fluid resuscitation and, if necessary, treated with va-

sopressors and mechanical ventilation. Within 24 hours following admission, a transthoracic echocardiography (GE Healthcare, Illinois, Chicago, USA) and 2D-STE (Mindray Medical International Limited, Nanshan, Shenzhen, China) examination are performed, and the patient's gender, age, underlying diseases, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, cardiac troponin I (cTnI), B-type natriuretic peptide (BNP), lactate, pro-BNP, left ventricular ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), longitudinal strain are measured by speckle tracking analysis [global longitudinal strain/strain rate (GLS/GLSr)], and global circumferential strain/strain rate (GCS/GCSr) are calculated.

Statistical Analysis

GraphPad Software Corporation (Los Angeles, CA, USA) was used for graphic software, and SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. For measurement data, the mean and standard deviation were used, and statistical analysis was performed using a *t*-test or analysis of variance to compare differences between the two groups. For categorical data, frequency and percentage were used, and the comparison was performed using Chi-square tests or Fisher's exact tests. Multivariate logistic regression analysis was used to analyze the correlation between multiple factors, and receiver operating characteristic (ROC) curves were plotted to determine the area under the curve (AUC) of risk factors. $p < 0.05$ was considered the threshold of statistical significance.

Results

Baseline Characteristics of the Two Groups of Patients

There was no statistically significant difference in the comparison of gender, age, underlying diseases, BNP, pro-BNP, EF, TAPSE, S', GLSr, GCS, and GCSr ($p > 0.05$). However, there was a statistically significant difference in the comparison of APACHE II score, SOFA score, cTnI, lactate, and GLS ($p < 0.05$) (Table I).

Logistic Regression Analysis of Risk Factors for Mortality in Sepsis Patients

The variables with statistical significance in the comparison of baseline data (APACHE II

Table I. Comparison of general data between the two groups of patients.

	Survival group (n=39)	Death group (n=19)	t/ χ^2	p
Gender			0.009	0.923
Male	20	10		
Female	19	9		
(Age)	59.3±11.4	60.2±11.1	0.284	0.777
Combined underlying disease				
Hypertension	21	10	0.007	0.930
Diabetes	23	11	0.006	0.937
Hyperlipidemia	19	10	0.078	0.779
APACHE II score	18.7±4.3	23.9±3.5	4.577	<0.001
SOFA score	16.2±3.1	19.7±2.6	4.242	<0.001
cTnI (mg/L)	0.35±0.16	0.68±0.11	8.089	<0.001
BNP (ng/L)	1843±769	2007±976	0.696	0.488
Lactic acid (mmol/L)	2.9±2.1	5.4±2.7	3.868	<0.001
Procalcitonin (mg/L)	56±41	78±39	1.948	0.056
EF (%)	55±4	56±4	0.893	0.375
TAPSE (mm)	22.86±3.24	21.39±3.72	1.544	0.128
S' (cm/s)	7.47±0.62	7.11±0.76	1.925	0.059
GLS (%)	-20.7±2.2	-18.4±1.5	4.106	<0.001
GLSr (s-1)	-1.32±0.21	-1.30±0.18	0.355	0.723
GCS (%)	-20.6±2.1	-19.4±2.3	1.980	0.052
GCSr (s-1)	-1.46±0.22	-1.43±0.23	0.480	0.632

APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Assessment score; cTnI: cardiac Troponin I; BNP: B-type Natriuretic Peptide; EF: Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; S': systolic velocity; GLS: Global Longitudinal Strain; GLSr: Global Longitudinal Strain rate; GCS: Global Circumferential Strain; GCSr: Global Circumferential Strain rate.

score, SOFA score, cTnI, lactate, GLS) were included in the logistic regression analysis.

The results showed that SOFA score [OR=2.32, 95% CI: 1.067-5.289, $p<0.05$], cTnI [OR=1.19, 95% CI: 1.001-1.312, $p<0.05$], and GLS [OR=1.58, 95% CI: 1.012-2.721, $p<0.05$] were risk factors affecting mortality in sepsis patients ($p<0.05$) (Table II and Figure 1).

ROC Curves for Various Risk Factors in Septic Patients

Receiver operating characteristic (ROC) curve analysis was performed for the risk factors (SOFA score, cTnI, GLS) identified in the logistic regression analysis. The results showed that the area under the ROC curve (AUC) for SOFA score (Figure 2A), cTnI (Figure 2B), and GLS (Figure 2C)

Table II. Logistic regression analysis of risk factors for mortality in sepsis patients.

Factor	β	SE	Wald	p	Exp (β)	95% CI
APACHE II score	0.345	0.219	2.54	0.111	1.43	0.923-2.174
SOFA score	0.865	0.403	4.52	0.033	2.39	1.067-5.289
cTnI	0.135	0.067	3.99	0.043	1.17	1.001-1.312
Lactic acid	0.414	0.278	2.27	0.135	1.52	0.882-2.585
GLS	0.612	0.207	8.61	0.002	1.63	1.012-2.721

APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Assessment score; cTnI: cardiac Troponin I; GLS: Global Longitudinal Strain.

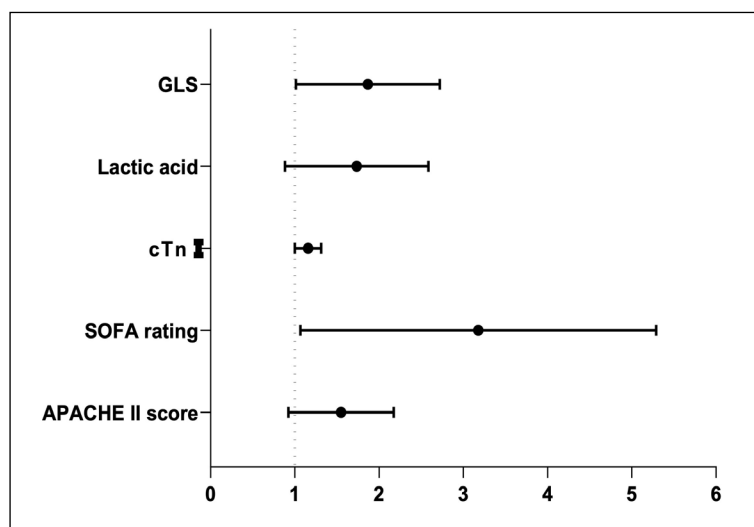


Figure 1. Forest plot of logistic regression analysis for risk factors of mortality in septic patients.

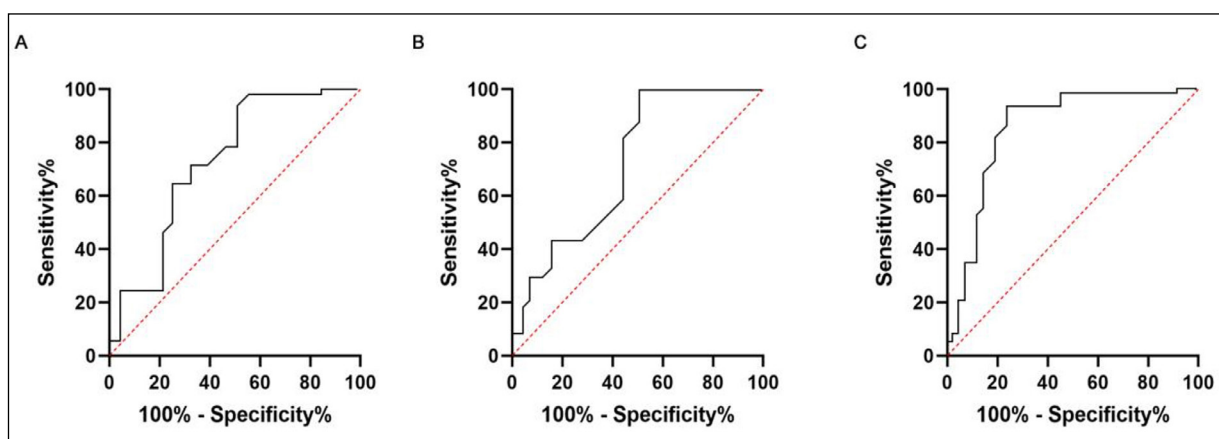


Figure 2. Receiver operating characteristic (ROC) curves of various risk factors in septic patients. A, The area under the ROC curve (AUC) for SOFA score, (B) the area under the ROC curve (AUC) for cTnI, (C) the area under the ROC curve (AUC) for GLS.

were 0.769, 0.757, and 0.846, respectively. These findings indicate that SOFA score, cTnI, and GLS have high predictive value for the prognosis of septic patients (Table III and Figure 2).

Discussion

Sepsis is one of the leading causes of death in critically ill patients and often leads to multi-organ dysfunction syndromes. The heart is one of the organs most frequently affected by sepsis, with a prevalence ranging from 9.7% to 66.4%^{7,8}. Sepsis-induced cardiac dysfunction is an intrinsic abnormality of myocardial contraction and/or diastole, typically manifested by ventricular dilatation, reduced myocardial compliance, and

reduced responsiveness to fluid resuscitation and catecholamine stimulation⁹. Cardiac insufficiency has been found to exacerbate disease progression and increase the risk of multi-organ failure and death, with mortality rates of up to 70% to 90% in patients with cardiac insufficiency, compared to approximately 20% in patients without cardiac insufficiency^{10,11}. Therefore, assessment of myocardial function in patients with sepsis is crucial in determining their prognosis.

cTnI and lactate are commonly used biochemical markers for clinical assessment of myocardial injury. cTnI is an isoform of cardiac troponin, which is released from cardiomyocytes into the bloodstream when they are damaged¹². Therefore, measurement of serum cTnI levels can determine the extent of myocardial damage. Lactate is a waste product

Table III. ROC curves for various risk factors in septic patients.

Project	AUC	Standard Deviation	<i>p</i>	95% CI
SOFA score	0.769	0.22	<0.05	0.664-0.869
cTnI	0.757	0.61	<0.05	0.633-0.882
GLS	0.846	0.53	<0.05	0.742-0.958

SOFA score: Sequential Organ Failure Assessment score; cTnI: cardiac Troponin I; GLS: Global Longitudinal Strain.

produced during energy metabolism and is rapidly removed under normal conditions. However, when cardiomyocytes are damaged due to ischemia and hypoxia, energy metabolism is affected, and there is an imbalance between lactate production and clearance¹³. However, several studies^{14,15} have shown that elevated lactate levels do not necessarily imply the severity of myocardial injury because lactate production is influenced by a variety of factors, such as myocardial ischemia, hypoxia, and acidosis. The results of this study showed significant differences in cTnI and lactate levels between the two groups of patients. However, in logistic regression analysis, lactate was not an independent risk factor for death in sepsis patients, and the reason for this phenomenon may be related to the fact that this study did not dynamically observe the 4-hour lactate clearance rate of the patients, etc. cTnI was an independent risk factor for death in sepsis patients, and the reason for this phenomenon may be related to the fact that sepsis patients have impaired microcirculatory blood flow, which leads to myocardial cell ischemia, hypoxia and even necrosis.

A recent study on sepsis by Wang et al¹⁵ has also clearly indicated that the risk of death in patients with significantly elevated cardiac troponin levels is much higher than that in patients with stable levels. There is a consensus that the SOFA score and APACHE II score have become clinical predictors of sepsis prognosis^{16,17}, and that both scoring systems are clinically less difficult to obtain and easy to use. In this study, there were significant differences in the levels of SOFA score and APACHE II score between the two groups of patients. However, in logistic regression analysis, APACHE II score did not emerge as an independent risk factor for death in patients with sepsis, the reason for which may be related to the small sample size of the present study. SOFA score was an independent risk factor for death in patients with sepsis, a finding similar to that reported in a previous study¹⁸. In addition, based on the predictions of the cardiac biomarkers and scoring systems described above, this study also assessed patients' right ventricular function using echocardiography and 2D-STE techniques. The

results showed that a decrease in GLS was associated with an increased risk of sepsis-related death. To date, the exact mechanism of myocardial depression in sepsis patients is unknown. However, a study¹⁹ found that the associated myocardial depression in sepsis patients is not limited to the left ventricle; the right ventricle is often affected as well. A related study²⁰ showed that about 9.1% of sepsis patients had isolated systolic dysfunction, 14.3% had both systolic and diastolic dysfunction, and 37.4% had isolated diastolic dysfunction. This study showed that decreased right ventricular systolic function is also associated with sepsis-related mortality. On the one hand, decreased peripheral vascular resistance in sepsis patients can lead to decreased left ventricular afterload, and on the other hand, acute lung injury can increase pulmonary vascular resistance, leading to increased right ventricular afterload²¹.

Unlike the left ventricle, the right ventricle, because of its own anatomical characteristics, cannot effectively compensate for sudden increases in load. Therefore, right ventricular dysfunction may be more prominent than left ventricular dysfunction in patients with septic myocardial injury. The results of this study showed that the difference in EF levels between the two groups was not significant, while the difference in GLS levels was significant. This result suggests that right ventricular dysfunction may manifest more prominently when septic myocardial injury occurs. The use of echocardiography in ICU hemodynamic assessment is now becoming increasingly important. However, in septic patients, the assessment of myocardial function by conventional echocardiographic parameters (e.g., EF) is largely influenced by persistent changes in preload and afterload conditions²².

2D-STE is a method of ventricular function evaluation that does not rely on Doppler and angle measurements. It is a novel cardiac function monitoring method based on a semiautomatic algorithm that measures changes in myocardial segment length by tracking the displacement of acoustic "speckles" in the myocardium. Compared with EF, 2D-STE is much less affected by changes in ventricular load-

ing conditions, myocardial compliance, and after-load characteristics²³. The most common unit of measurement for 2D STE is strain, which is defined as the change in the original length of end-systolic myocardial fibers relative to the original length of end-diastolic myocardial fibers²³. Strain can be measured in both longitudinal and circumferential directions²⁴. Strain can be measured in the longitudinal, radial, and circumferential directions. GLS measures the average longitudinal strain of 17 myocardial segments and has been shown to be the most reproducible measurement²⁵. The results of the study showed that the GLS in the death group was significantly lower than that in the survival group. Logistic regression analysis showed that GLS was an independent risk factor affecting the mortality of sepsis patients. Meanwhile, ROC analysis showed that the area under the ROC curve of GLS was 0.846, indicating its high clinical predictive value for the prognosis of sepsis patients.

Our study has several strengths. Firstly, independent risk factors for death in septic patients have been investigated, and it would be interesting to scrutinize the relationship between the methods of assessment. Several biomechanical parameters were assessed. The results of this study make it possible to examine whether these parameters can predict their prognosis. Secondly, based on new scientific insights and a previous study by our research group, a more complex treatment regimen was able to extend the therapeutic effect.

Limitations

However, there are some limitations to consider. Due to the large differences between experimental and control therapies, it is not feasible to blind therapists and patients. Therefore, to our knowledge, the specificity of these parameters yet concerns the prognosis of sepsis.

Conclusions

The SOFA score, cTnI, and GLS were independent risk factors for mortality in patients with sepsis. Among them, GLS had the highest predictive value for patient prognosis. Therefore, in predicting the prognosis of patients with sepsis, clinicians can assess the right ventricular ultrasound to evaluate GLS.

Data analysis must consider the clinical impact of different sepsis cases. Understanding the underlying causes and prognostic indices of sepsis events from healthcare will help to find drivers

of infection prevention. Designing trials that contribute to the development of predictive models, multi-analytic diagnostic aids, targeted drug discovery, and repositioning strategies will help to stratify and treat high-risk patients and improve prognosis.

Ethics Approval

This study has obtained ethical approval from Cangzhou Central Hospital (Approval No.: 82574368). The research will adhere to relevant ethical guidelines, including the Helsinki Declaration, to protect the rights and privacy of participants and ensure the security and integrity of research data.

Informed Consent

Written Informed consent was obtained from patients involved in the study.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

No funds were received for this study.

Authors' Contributions

All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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