

# The prognostic value of left ventricular systolic function and cardiac biomarkers in pediatric severe sepsis

Juanzhen Li, MM, Botao Ning, MD, PhD\*, Ying Wang, MB\*, Biru Li, MB, Juan Qian, MD, PhD, Hong Ren, MM, Jian Zhang, MM, Xiaowei Hu, MD, PhD

## Abstract

Echocardiography and cardiac biomarkers, such as cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) are useful tools to evaluate cardiac dysfunction. Left ventricular systolic dysfunction (LVSD) is common in pediatric severe sepsis. The aim of this study is to evaluate the prognostic value of LVSD, cTnI, and NT-pro BNP for pediatric severe sepsis.

A prospective, single center, observational study was conducted. Severe sepsis children were enrolled in the study from December 2015 to December 2016 in pediatric intensive care unit of Shanghai Children's Medical Center. Recorded general information, transthoracic echocardiography were performed at day 1, 2, 3, 7, and 10, using Simpson to measure left ventricular end-diastolic dimension and left ventricular end-systolic dimension, obtained echocardiography parameters: left ventricular ejection fraction (LVEF), left ventricular fractional shortening, left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke volume, cardiac output. At the same time collecting the blood sample to measure cTnI, NT-pro BNP. The definition of LVSD was LVEF <50%. According to the prognosis of 28 days, children with severe sepsis were divided into survived group and nonsurvived group.

Total of 50 pediatric patients who were diagnosed with severe sepsis (including septic shock) were enrolled, the incidence of LVSD was 52%. The 28-day mortality rate of severe sepsis was 34%. Multivariate logistic regression analyses for predictors of death in pediatric severe sepsis revealed that the 28-day mortality of severe sepsis was associated with mechanical ventilation (MV) within the first 6 hours of admission (odds ratio [OR], 0.01; 95% confidence interval [CI], 0.00–0.07) and total MV time (OR, 0.81; 95% CI, 0.68–0.97). The receiver operating characteristic curves LVEF (area under curve=0.526), cTnI (area under curve=0.480), and NT-pro BNP (area under curve=0.624) were used to predict the 28-day mortality in pediatric severe sepsis. Follow-up echocardiography parameters for survived group and nonsurvived group showed no significant changes in LVEF, LVFS, stroke volume index, cardiac index (CI), left ventricular end-diastolic volume index and left ventricular end-systolic volume index at day 1, 2, 3, 7, and 10, except for CI at day 1 and 2. Kaplan–Meier plot of 28-day mortality and LVSD in pediatric severe sepsis showed there were no statistical differences ( $\chi^2=0.042$ ,  $P=.837$ ).

LVSD occurs frequently in pediatric with severe sepsis. The 28-day mortality rate of severe sepsis was also high. In this study, none of LVSD, cTnI, and NT-proBNP was associated with the prognosis of pediatric severe sepsis.

**Abbreviations:** ARDS = acute respiratory distress syndrome, AUC = area under curve, CI = cardiac index, cTnI = cardiac troponin I, ICU = intensive care unit, LVEF = left ventricular ejection fraction, LVFS = left ventricular fractional shortening, LVSD = left ventricular systolic dysfunction, MV = mechanical ventilation, NT-pro BNP = N-terminal pro-B-type natriuretic peptide, PCIS = pediatric critical illness score, PICU = pediatric intensive care unit, ROC = receiver operating characteristic, SIRS = systemic inflammatory response syndrome, TTE = transthoracic echocardiography.

**Keywords:** cTnI, left ventricular systolic dysfunction, NT-pro BNP, prognosis, severe sepsis

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Department of Pediatric Intensive Care Unit, Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, Shanghai, China.

\* Correspondence: Ying Wang, and Botao Ning, Department of Pediatric Intensive Care Unit, Shanghai Children's Medical Center, 1678 Dongfang Road, Pudong District, Shanghai 200127, China (e-mails: ywang\_picu@shsmu.edu.cn, ningbotao@126.com).

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## 1. Introduction

Sepsis is the systemic inflammatory response syndrome (SIRS) induced by infection, severe sepsis is the organ dysfunction or tissue hypoperfusion caused by sepsis, septic shock is tissue hypoperfusion, and cardiac dysfunction caused by sepsis.<sup>[1]</sup> With high morbidity, high mortality, and hospitalization cost, sepsis remains the main cause of mortality in critically ill patients in pediatric intensive care unit (PICU).

Myocardial dysfunction is one of the common organ dysfunction of severe sepsis. Septic myocardial dysfunction was first reported in 1984 by Parker et al.<sup>[2]</sup> Previous studies found that the incidence of left ventricular systolic dysfunction (LVSD) in severe sepsis was 20% to 60%.<sup>[3–7]</sup> There were many studies on myocardial function of adult sepsis, especially in LVSD, but few studies in pediatric sepsis. We have more known for myocardial function in severe sepsis with the use of echocardiography in intensive care unit (ICU). Among the echocardiography parameters, left ventricular ejection fraction (LVEF) is most commonly used to evaluate LVSD. The definition of LVSD was LVEF <50%.<sup>[4,8,9]</sup> LVSD maybe contribute to unfavorable outcomes in pediatric severe sepsis.

Previously, there were studies about association between cardiac biomarkers or cardiac dysfunction and prognosis of sepsis in adults. In this study, we use echocardiography and cardiac biomarkers, such as cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) to evaluate cardiac dysfunction. The aim of this study was to evaluate the incidence of LVSD in pediatric severe sepsis in PICU and the prognostic value of LVSD, cTnI, and NT-pro BNP in pediatric severe sepsis.

## 2. Methods

A prospective, single center, observational study was carried out at the PICU of Shanghai Children's Medical Center, from December 2015 to December 2016. Informed consent was obtained. The study was approved by the institutional review board of Shanghai Children's Medical Center affiliated Shanghai Jiaotong University School of Medicine (SCMCIRB-K2016017).

After complying with inclusion and exclusion criteria, a total of 50 children with severe sepsis were enrolled. Inclusion criteria were listed as below: sepsis was the SIRS induced by infection, severe sepsis was the organ dysfunction or tissue hypoperfusion caused by sepsis, septic shock was tissue hypoperfusion and cardiac dysfunction caused by sepsis, SIRS was the presence of at least 2 of the following 4 criteria: tachycardia, tachypnea, temperature change, leukocytosis, or leukopenia, organ dysfunction criteria were according to Goldstein et al,<sup>[11]</sup> with the age greater than 28 days and younger than 18 years old. Exclusion criteria were listed as: congenital heart disease, congenital heart disease postoperative, cardiomyopathy, myocarditis, chronic cardiac dysfunction, heart failure, coronary artery disease, chronic renal insufficiency, immunosuppression, there were chest trauma, cardiopulmonary resuscitation, defibrillation, and cardioversion within 1 week.

Transthoracic echocardiography (TTE) was performed with SonoSite M-Turbo Ultrasound Machine System with a 5-1 MHz transducer, in all enrolled children at study within the first 24 hours of admission (D1), D2, D3, D7, and D10 after recruitment. Left ventricular end-diastolic dimension and left ventricular end-systolic dimension were measured in the left ventricular long-axis view, recording echocardiography parameters: LVEF, left ventricular fractional shortening (LVFS), left ventricular end-

diastolic volume, left ventricular end-systolic volume, stroke volume and cardiac output. Each examination had 3 measurements to minimize variation. All the above parameters were standardized by patient's body surface area. The definition of LVSD was LVEF <50%.<sup>[8,10]</sup>

Cardiac biomarkers including cTnI and NT-proBNP were collected in this study, which were measured within the first 24 hours of admission (D1), D2, D3, D7, and D10 after recruitment. Baseline clinical variables were collected including age, gender, pediatric critical illness score (PCIS), acute respiratory distress syndrome (ARDS), vasoactive drugs and mechanical ventilation (MV) within the first 6 hours of admission.

Our outcomes were the incidence of LVSD, the 28-day mortality, the prognostic value of LVSD, cTnI, and NT-pro BNP in pediatric severe sepsis. The prognostic markers in this study were: total MV time, hospital stay time, PICU stay time, and the 28-day mortality.

All the enrolled severe sepsis were grouped to survivors group and nonsurvivors group according to the 28-day mortality, and grouped to LVSD (LVEF <50%) and non-LVSD (LVEF >50%) on the first day after admission to PICU according to the value of LVEF.

Statistical analyses were performed using SPSS version 19.0.  $P < .05$  was statistically significant. Descriptive statistical analysis was listed as following: quantitative variables are expressed as mean  $\pm$  standard deviations (SD) or median (interquartile range) according to the Gaussian distribution; qualitative variables are expressed as absolute number (percentage). For comparison between groups, quantitative variables were compared using Student unpaired *t* test for variables with normal distribution and Mann-Whitney *U* test for variables with non-normal distribution. Qualitative variables were tested using the Chi-square test. In this study, the variables for which  $P < .05$  in univariate analysis were included in the multivariate logistic regression. The mortality risk factors among pediatric severe sepsis were identified by multivariate logistic regression model. Receiver operating characteristic (ROC) curve analysis was performed to predict the association of LVEF, cTnI, and NT-pro BNP with 28-day mortality in pediatric severe sepsis. Kaplan-Meier analysis was used to evaluate the influence of LVSD on 28-day mortality in pediatric severe sepsis. Log-rank was used to examine the differences in survival rates.

## 3. Results

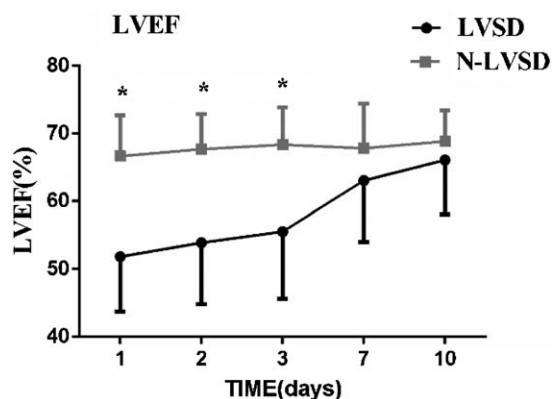
There were 50 pediatric patients (35 boys and 15 girls) who were diagnosed with severe sepsis (including septic shock) were enrolled. The mean age was found to be  $91.56 \pm 60.96$  months. The total incidence of LVSD in pediatric severe sepsis was 26 (52%). The 28-day mortality rate of severe sepsis was 34%, among them 52.9% patients had LVEF <50%. Critical score of PCIS showed significant difference among the survivors and nonsurvivors (mean and SD:  $78.24 \pm 8.53$  vs  $69.18 \pm 10.66$ ;  $P = .02$ ). Accompanied with ARDS or not and used vasoactive drugs did not differ between the survived group and nonsurvived group. Compared with survivors (9/33 [27.3]), nonsurvivors (6/17 [94.1]) exhibited significantly higher number of MV within the first 6 hours of admission ( $P = .00$ ), and higher total MV time (median day, 2 [1–7] vs 0 [0–4.50] day;  $P = .00$ ). PICU stay time and the hospital stay time for survived group and nonsurvived group also showed no statistical difference ( $P = .22$ ,  $P = .28$ , respectively). The comparisons between the survivor group and the nonsurvivor group are depicted in (Table 1).

**Table 1**  
**Baseline characteristics of patients.**

	Survivors (n=33)	Non survivors (n=17)	t/ $\chi^2$ /Z	P-value
Age, mo	106.33±61.83	62.88±49.09	t=2.51	.15
Male, n (%)	23 (69.7)	12 (70.6)	$\chi^2=0.00$	.95
LVSD (LVEF <50%), n (%)	17 (51.5)	9 (52.9)	$\chi^2=0.00$	.92
Critical score				
PCIS	78.24±8.53	69.18±10.66	t=3.27	.02
ARDS, n (%)	8 (24.2)	8 (47.1)	$\chi^2=2.68$	.10
Vasoactive drugs, n (%)	23 (69.7)	11 (64.7)	$\chi^2=0.13$	.72
MV in 6 h, n (%)	9 (27.3)	16 (94.1)	$\chi^2=20.05$	.00
Total MV time, d	0 (0–4.50)	2 (1–7)	Z=−3.08	.00
PICU stay time, d	7 (7–12)	5 (2.50–15.50)	Z=−1.22	.22
Hospital stay time, d	26.15±21.60	19.06±22.27	t=1.09	.28
Echocardiographic parameters				
LVEF (%)	59.24±10.54	58.38±10.16	t=0.28	.78
LVFS (%)	31.12±7.17	30.44±6.80	t=0.32	.75
SVI, ml/m <sup>2</sup>	38.20±10.29	45.74±18.70	t=−1.55	.14
CI, L/min/m <sup>2</sup>	4.74±1.33	6.62±2.87	t=−2.56	.02
LVEDVI, ml/m <sup>2</sup>	66.35±18.20	81.51±40.48	t=−1.47	.16
LVESVI, ml/m <sup>2</sup>	28.16±11.91	35.77±23.75	t=−1.25	.23
Cardiac biomarkers				
cTnI, ng/ml	0.07 (0.05–0.19)	0.05 (0.05–0.33)	Z=−0.24	.81
NT-pro BNP, pg/ml	748 (181.50–7674.50)	6361 (482–12412.50)	Z=−1.42	.16

ARDS=acute respiratory distress syndrome, CI=cardiac index, cTnI=cardiac troponin I, LVEDVI=left ventricular end-diastolic volume index, LVEF=left ventricular ejection fraction, LVESVI=left ventricular end-systolic volume index, LVFS=left ventricular fractional shortening, LVSD=left ventricular systolic dysfunction, MV=mechanical ventilation, NT-pro BNP=N-terminal pro-B-type natriuretic peptide, PCIS=pediatric critical illness score, PICU=pediatric intensive care unit, SVI=stroke volume index.

TTE were performed at day 1, 2, 3, 7 and 10 among the enrolled patients. LVEF was significantly lower in patients with LVSD than in those with non-LVSD on day 1, 2, and 3 ( $P=.00$ ,  $P=.00$ , and  $P=.00$ , respectively), there was no significant difference at the time of day 7 and day 10 ( $P=.05$  and  $P=.16$ , respectively) (Fig. 1). Echocardiography parameters for survived group and nonsurvived group showed no significant difference in LVEF, LVFS, stroke volume index, left ventricular end-diastolic volume index, and left ventricular end-systolic volume index, except for cardiac index (CI) at day 1 and day 2 ( $P=.19$ ,  $P=.039$ , respectively) (Fig. 2). At the same time, cTnI and NT-pro BNP between survived group and nonsurvived group showed no significant difference. The comparisons between survivors and nonsurvivors pediatrics with severe sepsis were shown in Table 1.



**Figure 1.** Comparison of LVEF between LVSD and N-LVSD in d1 to d3, d7, d10,  $P < .05$ . LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction.

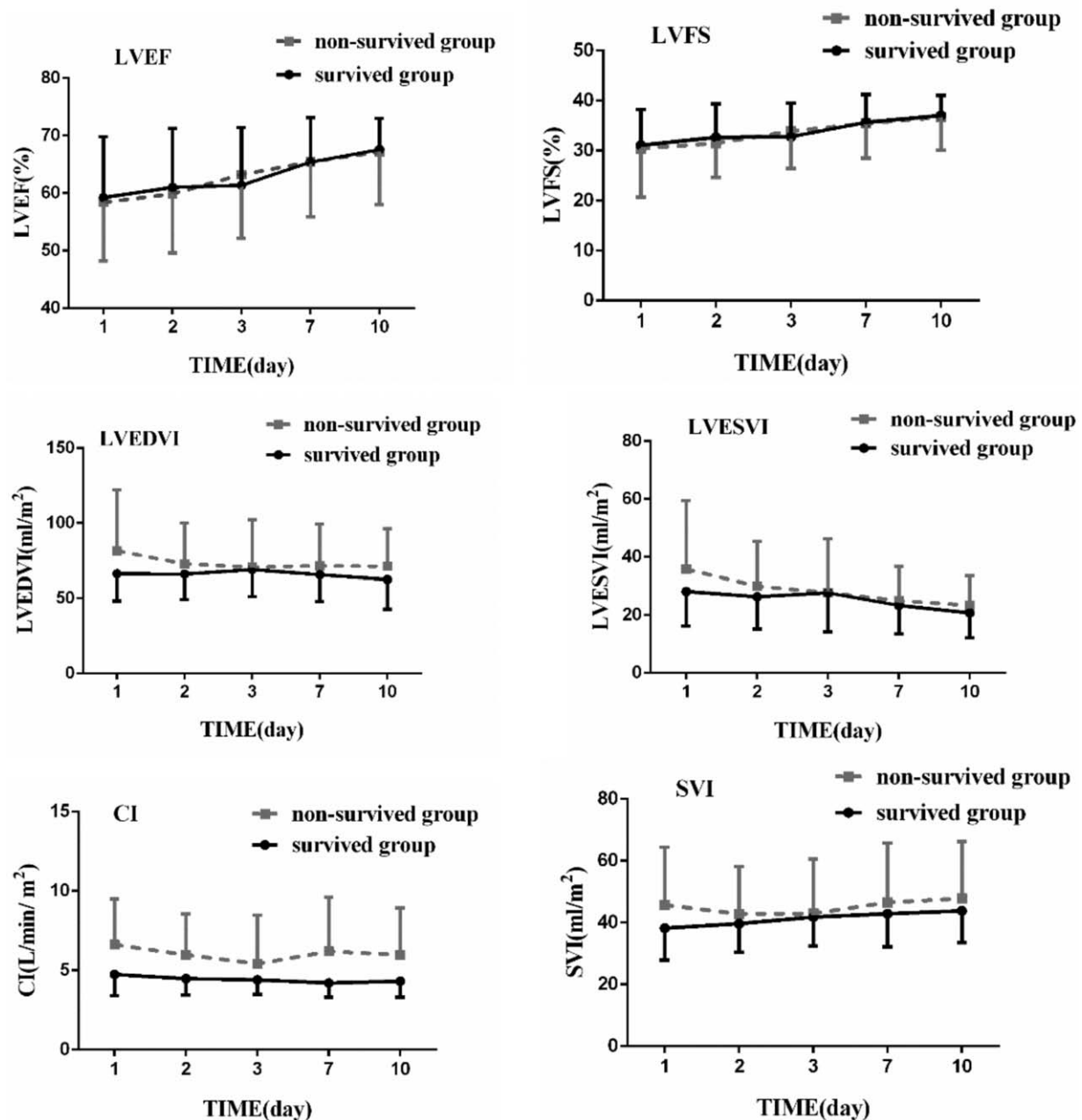
In this study, the variables of PCIS, MV within the first 6 hours of admission, total MV time and CI for which  $P < .05$  among the survivors and nonsurvivors were included. In the multivariate logistic regression analyses, the 28-day mortality of severe sepsis was associated with MV within the first 6 hours of admission (odds ratio [OR], 0.01; 95% confidence interval [CI], 0.00–0.07) and total MV time (OR, 0.81; 95% CI, 0.68–0.97) (Table 2).

The ability of LVEF, cTnI, and NT-pro BNP to predict the 28-day mortality in pediatric severe sepsis according to ROC was shown in Table 3. The area under the curve (AUC) for LVEF, cTnI, NT-pro BNP were found to be 0.526, 0.480, and 0.624, respectively.

Kaplan–Meier survival analysis of 28-day mortality demonstrated no difference between the patients with LVSD and without LVSD ( $\chi^2=0.042$ ,  $P=.837$ ) (Fig. 3).

#### 4. Discussion

Sepsis was defined as a SIRS caused by infection, and further developed to severe sepsis or septic shock, which was one of the most common causes of death among children worldwide.<sup>[11]</sup> LVSD induced by sepsis was a reversible organ dysfunction that occurs in the early stages of severe sepsis or septic shock and first described by Parker et al in 1984.<sup>[2,12]</sup> Left ventricular dysfunction was common in severe sepsis or septic shock. With the application of bedside echocardiography in ICU, people have a widely known about cardiac dysfunction induced by sepsis. Vieillard-Baron et al<sup>[3]</sup> and Post et al<sup>[13]</sup> have reported that the LVSD in adult septic shock were 59% to 60%. Additionally, Charpentier et al<sup>[14]</sup> described that LVSD was present in 44% of adult patients with severe sepsis or septic shock. In the study of children with septic shock, Williams<sup>[6]</sup> and Raj<sup>[7]</sup> found that the incidence of LVSD were 44% and 37%, respectively. In this study, LVEF was significantly lower in patients with LVSD within



**Figure 2.** Follow-up echocardiography data for survivors and nonsurvivors. Data presented for LVEF, LVFS, LVESVI, LVEDVI, CI, and SVI. CI = cardiac index, LVEF = left ventricular ejection fraction, LVFS = left ventricular fractional shortening, LVEDVI = left ventricular end-diastolic volume index, LVESVI = left ventricular end-systolic volume index, SVI = stroke volume index.

the first 3 days of admission, and return to normal gradually. The incidence of LVSD in pediatric severe sepsis was 52%, which was consistent with previous studies. The multivariate logistic regression analyses suggested that the 28-day mortality of severe sepsis was associated with MV within the first 6 hours of admission and the total MV time. LVEF, cTnI, and NT-pro BNP were not the independent mortality risk factors in pediatric severe sepsis.

The mortality rate of severe sepsis was 28% to 52%.<sup>[15]</sup> Patients with LVSD could be as high as 47%.<sup>[14]</sup> In our study, the 28-day mortality rate of severe sepsis was found to be 34%, among them 52.9% patients had ejection fraction <50%. Although people have a widely known about sepsis-induced

myocardial dysfunction, some study found that lower LVEF with better prognosis, but its association with the prognostic was still in controversial.<sup>[2,3,16]</sup> Prabhu<sup>[5]</sup> suggested that LVSD was associated with the mortality of septic shock in adults, Weng<sup>[17]</sup> found similar results. Conversely, a meta-analysis by Sevilla Berrios<sup>[18]</sup> showed that LVSD which defined by LVEF <50% was not correlated with the prognosis of severe sepsis or septic shock in adults. Studies of Raj<sup>[7]</sup> and Williams<sup>[6]</sup> have similar findings on pediatric septic shock. Our study was consistent with some results. Generally, children will more sensitive for drug, with stronger recovery ability, positive noninvasive hemodynamic monitoring, and positive treatment, all of them could make cardiac dysfunction have no influence on prognosis.

**Table 2**

**Multivariate logistic regression model of mortality risk in pediatric severe sepsis.**

Variables	B	S.E.	Wald $\chi^2$	P	OR	OR 95% CI	
						Lower	Upper
MV in 6 h	-5.32	1.33	16.07	.00	0.01	0.00	0.07
Total MV time, d	-0.21	0.09	5.45	.02	0.81	0.68	0.97

MV = mechanical ventilation.

**Table 3**

**ROC for predicting 28-d mortality by LVEF, cTnl, NT-pro BNP.**

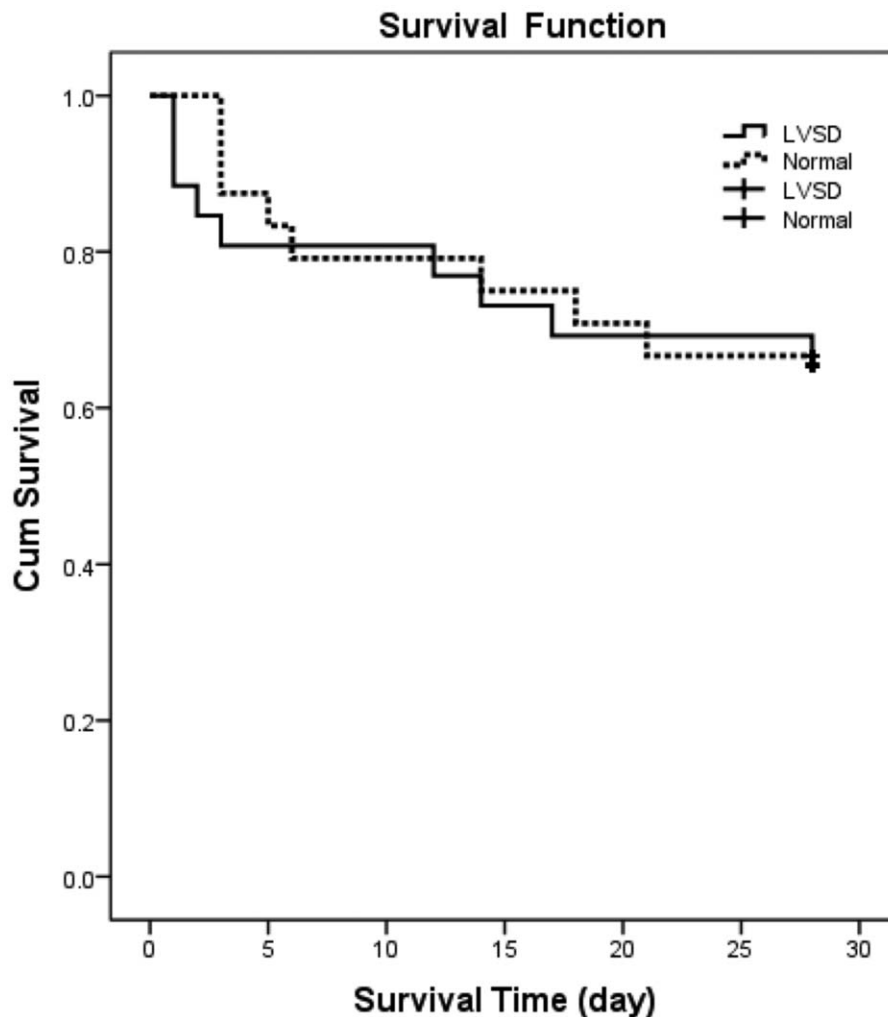
	AUC	SE	95% CI	P
LVEF	0.526	0.088	0.354–0.698	.767
cTnl	0.480	0.094	0.297–0.664	.822
NT-pro BNP	0.624	0.084	0.460–0.788	.155

cTnl = cardiac troponin I, LVEF = left ventricular ejection fraction, NT-pro BNP = N-terminal pro-B-type natriuretic peptide.

Generally, LVEF accepted as a tool for determining LVSD.<sup>[4]</sup> In our study, survived group and nonsurvived group showed no significant changes in follow-up echocardiography parameters, except for CI at day 1 and day2. Suggested that cardiac

dysfunction may have no influence on 28-day mortality rate. Similar to the findings of Sturgess et al<sup>[19]</sup> in cardiac dysfunction with septic shock. The difference in CI maybe was associated with positive fluid resuscitation in pediatric severe sepsis or septic shock. In this study, ROC curve for predicting 28-day mortality by using LVEF, AUC was 0.526 (less than 0.7). That mean LVEF could not predict the 28-day mortality in pediatric severe sepsis with LVSD. In another similar study by Prabhu et al,<sup>[5]</sup> AUC was 0.656.

NT-pro BNP was a common cardiac biomarker synthesized by myocardial cells, the increase of ventricular wall tension, end-diastolic pressure, and volume was the main reason for elevated serum level.<sup>[20]</sup> The results of studies between NT-proBNP and prognosis of sepsis patients with LVSD were inconsistent. A



**Figure 3.** Kaplan–Meier plot of 28-d mortality and left ventricular systolic dysfunction in pediatric severe sepsis ( $\chi^2=0.042$ ,  $P=.837$ ).



number of studies have found that the rising of NT-proBNP levels was associated with the LVSD in adult sepsis, elevated NT-proBNP levels can be used to predict mortality.<sup>[13,20,21]</sup> A study in pediatric septic shock, also found the increase of NT-proBNP level was related to the LVSD and disease severity.<sup>[22]</sup> There was no significant correlation between NT-proBNP and mortality in the studies of septic shock with LVSD by Weng et al<sup>[17]</sup> and Williams et al.<sup>[6]</sup> In our study, NT-proBNP for survived group and nonsurvived group showed no significant changes. The ability of NT-proBNP to predict the 28-day mortality in pediatric severe sepsis according to ROC curve was low (AUC=0.624).

cTnI only exists in the heart muscle, which was a specific antigen of heart with highly sensitive and specific. Small damage to myocardial cells can cause a rise in cTnI. cTnI was one of common cardiac biomarkers. Multiple studies have shown that changes in the structure of myocardial cells in severe sepsis were shown to be increase of in serum cTnI levels. The changes of myocardial cell membrane permeability, refractory hypotension, shock, apoptosis, and the application of vasoactive drugs were all related to the increase of cTnI level in sepsis.<sup>[23]</sup> The correlation between cTnI and LVSD is controversial. Some studies have shown that the increase of cTnI was related to LVSD in sepsis.<sup>[24,25]</sup> There are also some studies showing that cTnI levels were not related to LVSD in sepsis. Klouche et al found that no significant difference in cTnI levels in sepsis with or without LVSD.<sup>[20]</sup> In this study, cTnI has no statistically significant differences between survived group and nonsurvived group, the increase of cTnI may have no correlation with 28-day mortality, which was consistent with studies by Weng<sup>[17]</sup> and Charpentier.<sup>[14]</sup> The ability of cTnI to predict the 28-day mortality in pediatric severe sepsis according to ROC curve was low (AUC=0.480), also suggested there was no correlation between cTnI and prognosis.

In this study, Kaplan–Meier survival analysis of 28-day mortality suggested no differences among the pediatrics severe sepsis with or without LVSD ( $\chi^2=0.042$ ,  $P=.837$ ).

## 5. Study limitations

There were some limitations in this study. First, this study did not include the study of left ventricular diastolic function and right ventricular function. The second, due to the critical condition, the application of vasoactive drugs in most pediatric patients may lead to an underestimate of the incidence of LVSD. Finally, this study was single-center, with small sample size and need to further study.

## 6. Conclusion

In our study, LVSD occurs frequently in pediatric with severe sepsis. The 28-day mortality rate of severe sepsis was also high. None of LVSD, cTnI and NT-proBNP were associated with the prognosis of pediatric severe sepsis.

## Author contributions

**Data curation:** Juanzhen Li.

**Formal analysis:** Hong Ren, Jian Zhang.

**Investigation:** Juanzhen Li, Biru Li, Juan Qian, Hong Ren.

**Methodology:** Biru Li, Juan Qian, Hong Ren, Xiaowei Hu, Jian Zhang.

**Resources:** Ying Wang, Juan Qian, Jian Zhang.

**Supervision:** Ying Wang, Botao Ning.

**Writing – original draft:** Juanzhen Li.

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