Acta Biomed 2025; Vol. 96, N. 2: 16572 DOI: 10.23750/abm.v96i2.16572

Original article

Early predictors of 28-day mortality in children with septic shock: Results from a prospective cohort study

Phuong Minh Nguyen[1], Ly Cong Tran[1], Duy-Truong Khac Le[1], Viet Trieu Nguyen[2]

[1]Department of Pediatrics, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho City, Vietnam; [2]Department of Otolaryngology, Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho City, Vietnam

Abstract. *Background and aim:* Septic shock is a leading cause of mortality in children, particularly in Vietnam. Limited intensive care resources in low- and middle-income countries make it crucial to identify predictors of 28-day mortality to optimize patient outcomes. This study aimed to identify factors associated with 28-day mortality in pediatric patients with septic shock. *Methods:* A prospective cohort study was conducted on pediatric patients aged 2 months to 15 years who were diagnosed with septic shock in the Pediatric Intensive Care Unit of a tertiary pediatric hospital in southern Vietnam between July 2022 and June 2024. *Results:* Clinical and laboratory manifestations of septic shock at diagnosis varied widely among patients. The cumulative 28-day mortality rate was 64.1% (95% CI: 45.7–76.2%), with most fatal outcomes (53.8%; 95% CI: 35.6–66.8%) occurring within the first week. Although infants and male patients had the highest incidence rates of septic shock, these demographic factors were not significantly associated with mortality. Neurological, renal, and hematological dysfunctions, along with a lactate-to-albumin ratio (LAR) ≥ 1.84, were identified as independent predictors of 28-day mortality. A LAR ≥ 1.84 was associated with a 7.14-fold increase in mortality risk (95% CI: 2.56–24.9, $p < 0.001$). *Conclusions:* Pediatric septic shock is associated with a high 28-day mortality rate and diverse clinical presentations. Neurological, renal, and hematological dysfunctions, as well as a lactate-to-albumin ratio ≥ 1.84, were identified as independent prognostic factors for mortality, underscoring the need for focused management of these risk factors. (www.actabiomedica.it)

Key words: septic shock, mortality, prognostic factors, child, pediatric intensive care units, prospective studies, critical illness, risk assessment

Introduction

Pediatric septic shock persists as a substantial contributor to childhood mortality worldwide, with a disproportionate burden observed in low-middle-income countries (1,2). The mortality rate due to septic shock is approximately 35% in developing countries (1). Besides that, this figure is notably higher, reaching over 60% in Vietnam (3,4). Therefore, identifying factors that can predict mortality is essential. Numerous studies have attempted to determine mortality predictors in children (5,6). However, most of these studies have been conducted in developed countries, while such data remains limited in Vietnam, especially concerning factors associated with 28-day mortality prediction. Therefore, we conducted this study to identify factors associated with 28-day mortality prognosis in pediatric patients with septic shock. These findings will help bridge the existing gap in monitoring and treating septic shock in Vietnamese pediatric patients.

Materials and Methods

Study design and subjects

The prospective cohort study was conducted in the Pediatric Intensive Care Unit (PICU) of Can

Tho Children's Hospital between July 2022 and June 2024. Study participants were pediatric patients aged 2 months to 15 years with septic shock diagnosed according to the International Pediatric Sepsis Consensus Conference (IPSCC) 2005 criteria (7). Exclusion criteria were: (i) pediatric patients previously diagnosed with septic shock at other hospitals who were admitted in stable condition, (ii) mortality within the first 6 hours from diagnosis, (iii) withdrawal from the study by the patient's family during the follow-up period. The primary outcome measure was 28-day mortality. Survival was defined as hospital discharge with complete recovery or survival at 28 days post-diagnosis. Mortality was defined as in-hospital death or death within 24 hours post-discharge. Secondary outcomes included follow-up duration, defined as the time from shock onset until recording the primary outcome (maximum 28 days), and organ dysfunctions, which was determined according to the IPSCC 2005 criteria (7). The sample size for this cohort study was determined as previously described (8). Using non-probability convenience sampling method, we enrolled 41 patients who met the inclusion criteria without exclusion criteria.

Data collection

At the time of septic shock diagnosis, all patients underwent comprehensive clinical assessment. Clinical parameters documented included vital signs, peripheral perfusion status, and neurological, cardiovascular, and respiratory manifestations. Laboratory investigations were conducted within 6 hours of diagnosis, including complete blood count, coagulation profile, liver and renal function tests, serum lactate, serum albumin, arterial blood gas analysis, electrolyte panel, C-reactive protein (CRP), procalcitonin, and blood cultures. Patients were monitored until the primary outcome was reached, with a maximum follow-up period of 28 days. Data were managed using EpiData 3.1 software (EpiData Association, Odense, Denmark).

Statistical analysis

We presented quantitative variables as mean (standard deviation) for normally distributed data and median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies (percentages). Categorical data were analyzed using Fisher's exact test. For continuous variables, comparisons were made using Student's t-test for normally distributed data or Wilcoxon rank-sum test for non-normally distributed data. Based on previous studies and pathophysiological mechanisms, the following variables were selected for survival analysis: age, sex, mechanical ventilation requirement, organ dysfunction, and lactate/albumin ratio (LAR) ≥ 1.84 (3,5,8–10). These variables were first analyzed using univariate Cox regression with Firth's correction. Significant variables from the univariate analysis were then incorporated into multivariate Cox regression models with Firth's correction, adjusting for demographic factors (age and sex). All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Statistical analyses were performed using R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Cox regression with Firth's correction was performed using the coxphf package version 1.13.4.

Results

Clinical and laboratory characteristics of children with septic shock

During the study period, 41 cases met the inclusion criteria, with infants comprising the largest proportion (39%) and the ratio of males to females was 1.4 to 1. At diagnosis, patients presented with typical shock manifestations including cardiovascular dysfunction (weak pulse, tachycardia, unmeasurable blood pressure) and hypoperfusion signs (prolonged CRT and altered consciousness). Most patients (87.8%) required respiratory support, with a notably higher proportion in non-survivors (96.2% vs 73.3%, p=0.051), while their respiratory rate (median: 46 breaths/min) and SpO_2 (median: 89%) showed no significant differences between groups. Regarding infection indicators, the majority had fever (core temperature > 38.5°C), with gastrointestinal tract being the predominant source of infection (56.1%), followed by respiratory (19.5%), central nervous system (7.3%), and unknown sources (17.1%), showing no significant distribution

Table 1. Clinical characteristics of participants

		All patients	Survivor	Non-survivor	*p*-value
Age, n (%)	<1 year	16 (39.0)	6 (40.0)	10 (38.5)	0.999[a]
	1-5 years	11 (26.8)	4 (26.7)	7 (26.9)	
	>5 years	14 (34.2)	5 (33.3)	9 (34.6	
Male, n (%)		24 (58.5)	9 (60.0)	15 (57.7)	0.999[a]
Core temperature > 38.5°C		40 (97.6)	15 (100)	25 (96.2)	0.999[a]
Heart rate (bpm), median (IQR)		185 (160-200)	185 (170-200)	184 (160-200)	0.838[b]
Pulse characteristics, n (%)	Weak	28 (68)	12 (43)	16 (57)	0.305[a]
	Unpalpable	13 (32)	3 (23)	10 (77)	
Blood pressure, n (%)	Narrow	5 (12.2)	2 (13.3)	3 (11.5)	0.999[a]
	Hypotension	12 (29.3)	4 (26.7)	8 (30.8)	
	Unmeasurable	24 (58.5)	9 (60.0)	15 (57.7)	
Cold extremities, n (%)		37 (90.2)	11 (73.3)	26 (100.0)	0.013[a*]
CRT (s), median (IQR)		4 (4-5)	4 (3-4)	4 (4-5)	0.009[b*]
Glasgow coma score, median (IQR)		9 (8-11)	12(10-12)	8 (8-9)	<0.001[b*]
Positive pupillary light reflex, n (%)		34 (82.9)	13 (86.7)	21 (80.8)	0.999[a]
Respiratory rate (breaths/minute), median (IQR)		46 (32-52)	47 (33.5-52)	46 (32-51.5)	0.694[b]
SpO_2 (%), median (IQR)		89 (80-92)	89 (86.5-91.5)	85.5 (80-92)	0.559[b]
Requires ventilator, n (%)		36 (87.8)	11 (73.3)	25 (96.2)	0.051[a]
Underlying disease, n (%)		4 (9.8)	2 (13.3)	2 (7.7)	0.615[a]
Route of bacterial infection, n (%)	Gastrointestinal	23 (56.1)	8 (53.3)	15 (57.7)	0.914[a]
	Respiratory	8 (19.5)	4 (26.7)	4 (15.4)	
	Central nervous system	3 (7.3)	1 (6.7)	2 (7.7)	
	Unknown	7 (17.1)	2 (13.3)	5 (19.2)	

Note. [*]p-value < 0.05 was considered significant; [a]Fisher's exact test; [b]Wilcoxon signed-rank test; *Abbreviations:* n: number of cases; IQR: interquartile range; bpm: beat per minute, s: seconds.

difference between survivors and non-survivors (as detailed in Table 1).

Laboratory findings demonstrated no significant differences in complete blood count parameters between the mortality and survival groups. However, coagulation profiles revealed significant prolongation of aPTT, PT, TT, and decreased fibrinogen levels in the mortality group ($p < 0.05$). Liver enzymes were markedly elevated, with significantly higher AST and ALT levels observed in the mortality group. Arterial blood gas analysis demonstrated a significant difference in the alveolar-arterial oxygen gradient ($AaDO_2$) between the two groups ($p = 0.015$), with an overall median of 263.8 mmHg (IQR: 137.1-490.9). The mortality group exhibited a higher median $AaDO_2$ of 354.5 mmHg (IQR: 218.4-521.4), indicating severe gas exchange abnormalities. The proportion of patients with PaO_2/FiO_2 ratio ≤ 300 was 53.7%, with no statistically significant difference between groups ($p = 0.21$). Inflammatory markers analysis revealed an overall median CRP concentration of 9.2 mg/L (IQR: 6.5-19.9). The mortality group demonstrated higher median CRP levels (14.9 mg/L (IQR: 8.6-46)) compared to the survival group (7.9 mg/L (IQR: 5.7-10.2)), although this difference was not statistically significant ($p = 0.083$). Serum procalcitonin levels were elevated with an overall median of 37.2 ng/mL (IQR: 2.95-100). The mortality group

Table 2. Laboratory characteristics of participants.

	All patients	Survivor	Non-survivor	*p*-value
Hb (g/dL), mean ± SD	11.6 ± 2.02	11.3 ± 1.9	11.7 ± 2.1	0.530[c]
WBC (x 1000/mm^3), mean ± SD	14.4 ± 7.6	12.3 ± 7.7	15.6 ± 7.4	0.191[c]
Neu (%), mean ± SD	60.9 ± 18.9	60.3 (58.2-71.1)	58.8 (37.9-80.3)	0.441[b]
Lym (%), mean ± SD	28.9 ± 16.4	27.0 (19.95-32.8)	29.4 (13.8-44.5)	0.516[b]
Platelet (x1000/mm^3), median (IQR)	218 (77-310)	228 (208-331)	117 (36.3-298.8)	0.060[b]
PT (s), median (IQR)	16 (13.6-18.7)	14.2 (11.8-16.02)	16.2 (15.3-20.2)	0.024[b*]
aPTT (s), median (IQR)	39.9 (30.7-72.7)	31.95 (27.9-37.4)	45.3 (37.6-109.5)	0.002[b*]
TT (s), median (IQR)	27.5 (19.7-81.7)	17.3 (16.2-20.2)	27.5 (19.7-81.7)	0.003[b*]
INR, median (IQR)	1.4 (1.1-1.7)	1.3 (1.1-1.4)	1.5 (1.2-1.7)	0.102[b]
Fibrinogen (g/L), mean ± SD	1.9 ± 1.3	2.4 ± 1.1	1.6 ± 1.2	0.030[c*]
D-dimer (µg/mL), median (IQR)	1.9 (1.7-7.4)	1.8 (1.7-1.8)	2.4 (0.9-7.5)	0.889[b]
Ure (mmol/L), median (IQR)	8.4 (5.9-12.4	8.1 (4.8-12.8)	8.4 (6.2-12)	0.965[b]
Creatinine (µmol/L), median (IQR)	93.0 (57.4-104.0)	93 (56.8-100.8)	92.4 (66.2-06.6)	0.598[b*]
AST (IU/L), median (IQR)	147.8 (49.7-703.4)	53.4 (42.3-97.6)	341.6 (72.8-1167.4)	0.015[b*]
ALT (IU/L), median (IQR)	67.1 (26.1-354.1)	26.1 (21.3-45.1)	126.5 (44.8-494.7)	0.004[b*]
Bilirubin (mmol/L), median (IQR)	9.7 (6.4-13)	9.5 (6.2-10.5)	11.6 (6.8-13.1)	0.327[b]
Na^+(mmol/L), mean ± SD	137.5 ± 9.6	140.5 ± 8.1	135.8 ± 10.2	0.112[c]
K^+(mmol/L), median (IQR)	3.5 (3.3-4.2)	3.5 (3.2-3.9)	3.6 (3.3-4.7)	0.379[b]
Ca^{2+}(mmol/L), mean ± SD	1.08 ± 0.2	1.14 ± 0.2	1.05 ± 0.2	0.265[c]
$AaDO_2$ (mmHg), median (IQR)	263.8 (137.1-490.9)	163 (69.50-296.9)	354.5 (218.4-521.4)	0.015[b*]
$PaO_2/FiO_2 \leq 300$	22 (53.7%)	6 (40%)	16 (61.5%)	0.210[a]
CRP (mg/L), median (IQR)	9.2 (6.5-19.9)	14.9 (8.6-46)	7.9 (5.7-10.2)	0.083[b]
Procalcitonin(ng/mL), median (IQR)	37.2 (2.95-100)	5.5 (1.3-100)	56.2 (11.7-100)	0.257[b]
Blood culture, n (%)	7 (17.1)	4 (26.7)	3 (11.5)	0.390[a]
LAR ≥ 1.84, n (%)	25 (61%)	3 (20%)	22 (84.6%)	<0.001[a*]

Note. [*]p-value < 0.05 was considered significant; [a]Fisher's exact test; [b]Wilcoxon signed-rank test; [c]Student T-test; *Abbreviations:* n: number of cases; IQR: interquartile range; SD: standard deviation; bpm: beat per minute; LAR: lactate/albumin ratio; WBC: white blood cell; $AaDO_2$: alveolar-arterial oxygen gradient; CRP: C-reactive protein.

exhibited higher levels (56.2 ng/mL (IQR: 11.7-100)) compared to the survival group (5.5 ng/mL (IQR: 1.3-100)), but this difference did not reach statistical significance (p = 0.257). The blood culture positivity rate was low (17.1%). The LAR ≥ 1.84 was observed in 61% of cases, with significantly higher prevalence in the mortality group (p < 0.001), shown in Table 2.

Outcomes of children with septic shock

Kaplan-Meier analysis revealed a 28-day cumulative mortality rate of 64.1% (95% CI: 45.7-76.2%). The majority of fatal events reached 53.8% (95% CI: 35.6-66.8%) within the first 7 days, followed by a slight increase to 64.1% at day 14, which remained stable until day 28 (Figure 1).

The follow-up duration differed significantly between groups, with most deaths occurring in the first week (median: 1.4 days, IQR: 0.9-4.1), while survivors had a considerably longer follow-up period (median: 18.8 days, IQR: 14.3-24.7), as detailed in Figure 2.

All patients presented with cardiovascular dysfunction. Non-survivors demonstrated significantly higher frequencies of respiratory, neurologic,

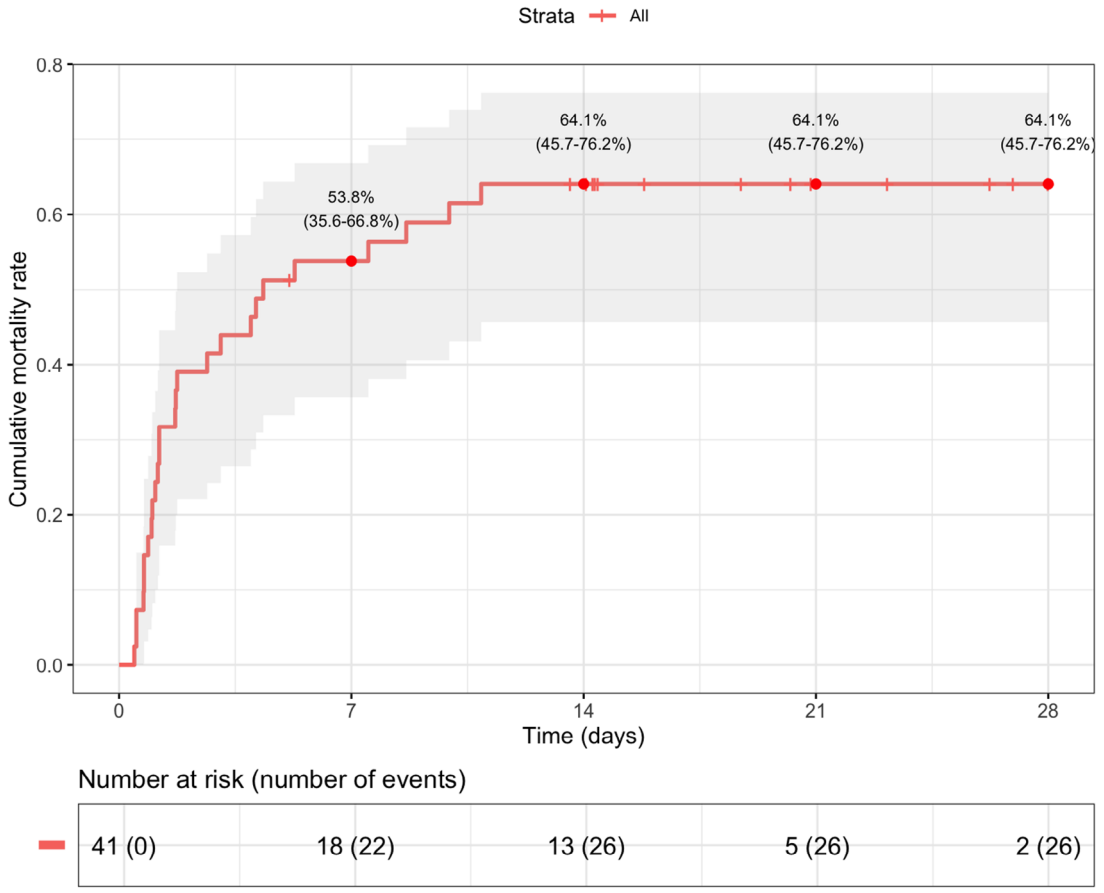

Figure 1. Cumulative mortality rate during 28 days.

hematologic, and renal dysfunction compared to survivors ($p < 0.05$). Hepatic dysfunction was common in both groups, but without statistical significance (Figure 3).

Risk factors associated with 28-day mortality in children with septic shock

In the univariate Cox regression analysis with Firth correction, neurologic (HR: 28.3, 95% CI: 3.94-3602.1), hematologic (HR: 2.49, 95% CI: 1.16-5.60), renal dysfunction (HR: 2.70, 95% CI: 1.24-5.87), and LAR ≥ 1.84 (HR: 5.46, 95% CI: 2.13-17.6) were identified as significant predictors of 28-day mortality, as shown in Table 3.

In the multivariate Cox regression analysis with Firth correction, after adjusting for age and sex, we found that neurological dysfunction, renal dysfunction, hematological dysfunction and LAR ≥ 1.84 were independent factors associated with 28-day mortality prediction, Figure 4.

Discussion

Clinical, laboratory characteristics and outcomes in children with septic shock

Our study found that males and children under 1 year of age were predominant. This finding aligns with previously published studies on septic shock, indicating these groups are most likely to develop septic shock (4,6,11). While the underlying mechanism remains unclear, numerous studies suggest it results

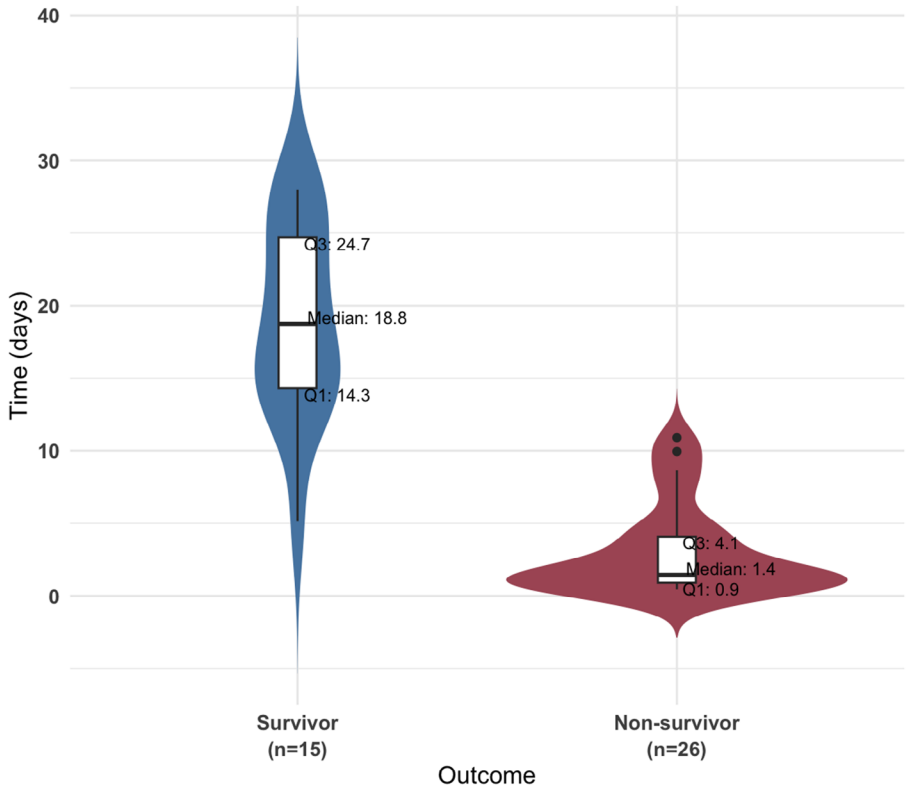

Figure 2. Time-to-event distribution by outcome.

from a combination of biological sex differences, including immune system function, sex hormones, inactivated X-chromosome gene expression, anatomical differences, and drug pharmacokinetics and pharmacodynamics (9). In addition, infant's immune systems are still developing and tend toward immune tolerance due to the continued influence of the intrauterine period. Furthermore, this age group has not yet been exposed to enough pathogens to develop protective antibodies, making infants more susceptible to infections and prone to more severe progression than other age groups. Moreover, the poor quality of immune responses from immune cells in infants is also an important factor contributing to increased disease incidence in this age group (12,13). In evaluating the clinical presentation of septic shock, we observed signs of cardiovascular function, organ hypoperfusion, respiratory and neurological symptoms, and signs associated with infection. At diagnosis, most patients presented with tachycardia, non-measurable blood pressure, cold extremities, and prolonged CRT reflecting cardiovascular dysfunction and tissue hypoperfusion in septic shock. These are common manifestations of shock. While the clinical presentation depends on the underlying cause, prolonged progression leads to organ dysfunction and death. In children with shock, the initial physiological response is sympathetic adrenergic system activation. This leads to common clinical manifestations such as tachycardia, possibly accompanied by tachypnea. Prolonged progression results in organ hypoperfusion and hypotension. This results in common clinical symptoms such as tachycardia, possibly accompanied by tachypnea, with prolonged progression leading to organ hypoperfusion and hypotension (14). Decreased blood pressure is a late sign of shock, indicating irreversible shock (14). This suggests that patients in our study presented with severe shock conditions, indirectly explaining why our mortality rate was higher compared to other studies. Additionally, studies have shown that prolonged CRT is associated

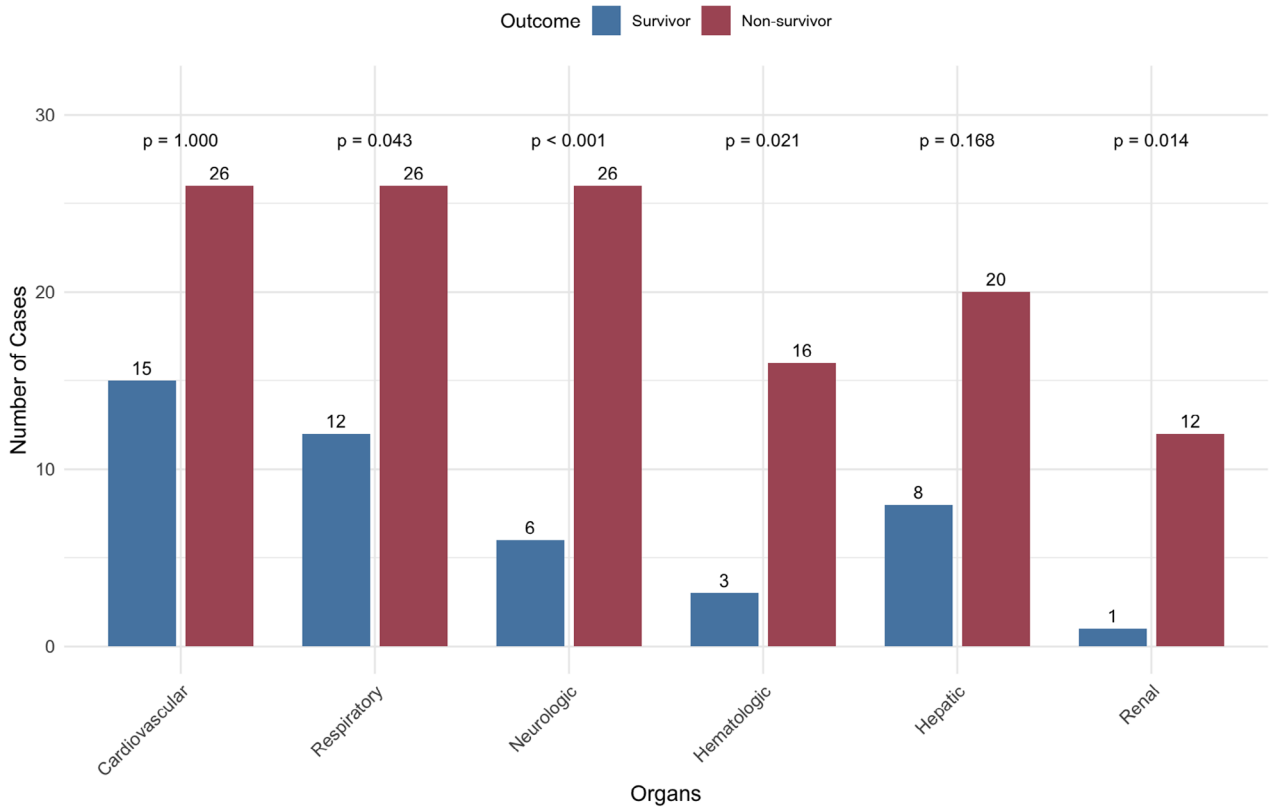

Figure 3. Organ dysfunction classified by outcome.

Note. Fisher's exact test was used, with p-value < 0.05 considered statistically significant.

Table 3. Univariate analysis of factors associated with 28-day mortality in children with septic shock.

Risk factors		**HR**	**95% CI**	***p*-value**
Age (infant)		0.75	0.33-1.62	0.471
Sex (male/female)		0.95	0.45-2.10	0.9
Requires ventilator (yes/no)		1.30	0.47-4.89	0.632
Organ dysfunction	Respiratory	6.18	0.86-783.98	0.078
	Neurologic	28.3	3.94-3602.1	<0.001*
	Hematologic	2.49	1.16-5.60	0.02*
	Hepatic	1.52	0.66-4.01	0.33
	Renal	2.70	1.24-5.87	0.014*
Lactate/albumin ≥ 1.84		5.46	2.13-17.60	<0.001*

Note. *p-value < 0.05 was considered significant

with increased glycocalyx degradation (a protective layer in capillaries). Glycocalyx deterioration leads to endothelial dysfunction and increased capillary permeability, exacerbating inflammatory responses and organ dysfunction in septic shock pathophysiology. Furthermore, prolonged CRT correlates with reduced small capillaries participating in tissue oxygen exchange, resulting in tissue hypoxia. Moreover, prolonged CRT

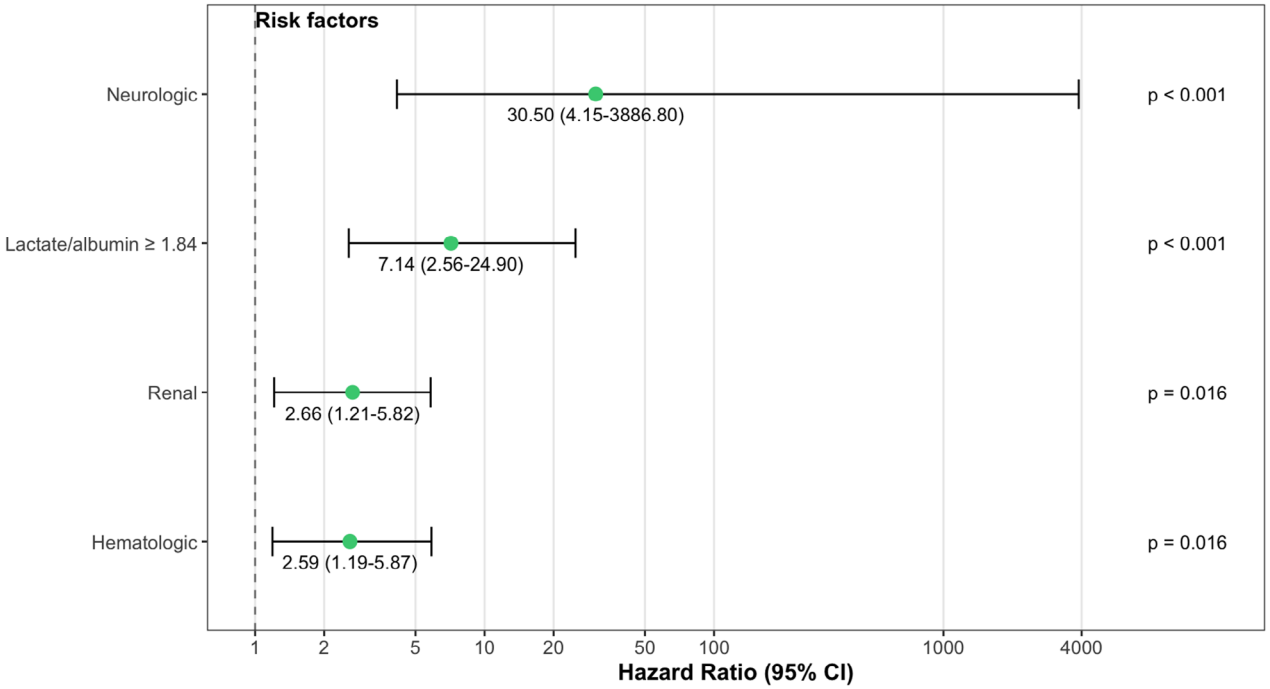

Figure 4. Forest plot of risk factors associated with 28-day mortality in children with septic shock in a multivariate analysis.

reflects hemodynamic heterogeneity between macro- and microcirculation. Therefore, CRT represents a valuable tool for assessing severity, monitoring treatment response, and predicting outcomes in pediatric patients (15,16). In terms of laboratory findings, we observed coagulation disorders in pediatric patients at the time of diagnosis, with non-survivors demonstrating prolonged PT, aPTT, TT, and lower fibrinogen levels compared to survivors ($p < 0.05$). In pediatric patients with sepsis, there exists a bidirectional interaction between inflammatory response and coagulation disorders, creating a pathological cycle. Initially, patients typically present with a prothrombotic state through activation of the extrinsic coagulation pathway, cytokine-mediated coagulation amplification (TNF-α, IL-6, etc.), suppression of anticoagulant pathways, and impairment of fibrinolysis. In the late stages of sepsis, with the development of disseminated intravascular coagulation (DIC), hypocoagulability occurs. These processes lead to severe consequences including microcirculatory dysfunction, endothelial damage, and multiple organ failure, resulting in increased mortality risk for pediatric patients (17). For biochemical tests, significant abnormalities were noted. For kidney function, we observed no significant differences in blood urea and creatinine values between the two outcome groups at the time of diagnosis. However, liver function abnormalities were demonstrated, with abnormally elevated AST and ALT levels, higher in the non-survivor group compared to the survivor group ($p < 0.05$). The clinical course in these patients led to liver dysfunction and death. The liver functions as a lymphoid organ in response to sepsis. Liver-mediated immune response has the effect of filtering bacteria and toxins, however, it also increases inflammatory response, suppresses the immune system, and causes organ damage (18,19). Considering inflammatory markers, we observed elevated levels of CRP and procalcitonin; however, there was no significant difference between the two outcome groups. Additionally, the positive blood culture rate was low (17.1%). These results differ from Nguyen-Huu et al.'s study, where CRP values were 110.1 (42.0-308.2) mg/L, though no difference was found between the two groups. Furthermore, the authors noted that the positive blood culture rate was higher in the mortality group compared to

the survival group, p < 0.05 (3). Meanwhile, Phung et al.'s study showed a positive blood culture rate of 38% in sepsis patients (4). Bansude A et al.'s study demonstrated that the positive culture rate (blood/urine) was only 16% in patients with septic shock (20). The differences in these results can be attributed to sample selection criteria, disease severity, prior antibiotic use, as well as the timing of laboratory tests. Regarding the LAR, previous studies have reported that LAR was higher in the mortality group compared to the survival group. Additionally, LAR with a cut-off point of 1.84 has excellent prognostic value for mortality (8). In fact, the data shows that LAR ≥ 1.84 accounts for a large proportion (61%), with the mortality group being significantly higher than the survival group (p < 0.001). In terms of outcomes, the 28-day cumulative mortality rate in our study was notably high at 64.1% (95% CI: 45.7-76.2), with a sharp increase in mortality observed during the first week of follow-up. This contrasts with global septic shock studies that report crude mortality rates averaging around 30% (6). However, studies conducted in Vietnam have demonstrated higher mortality rates, with reported rates reaching 69.2% (3). These outcome disparities can be explained by variations in disease patterns and differences in resuscitation capabilities across research centers.

Examining organ dysfunction, we observed that respiratory, neurological, hematological, and renal dysfunctions were significantly more prevalent in the mortality group compared to the survival group, with statistical significance (p < 0.05). Meanwhile, Nguyen et al.'s study reported that neurological and respiratory dysfunctions were significantly more common in the mortality group compared to the survival group (p < 0.05), with no significant differences between outcome groups for other organs (21). These differences in results stem from variations in sampling criteria, study populations, and the severity of illness in pediatric patients included in the studies.

Risk factors associated with 28-day mortality in children with septic shock

In our study, while males represented a higher proportion of septic shock cases, gender was not identified as a significant risk factor for 28-day mortality (HR: 0.75, 95% CI: 0.33-1.62, p = 0.471). The relationship between gender and sepsis mortality remains controversial in literature, with conflicting evidence across various studies. While some research suggests potential protective effects of estrogen, and others report varying mortality rates between genders, a recent meta-analysis in adult patients, comprising 13 studies (80,520 participants), found no significant gender-based differences in hospital or ICU mortality. Meanwhile, in children, Kondo et al.'s study showed lower mortality risks in females (HR: 0.74, 95% CI: 0.62-0.89, p = 0.001) (22). These inconsistent findings may be attributed to heterogeneous study designs, varying sepsis definitions, differences in baseline health status, comorbidities, disease severity, and sociocultural factors affecting treatment approaches between genders. Similarly, the study showed that infancy was not a factor associated with a 28-day mortality prognosis. This result is consistent with the study by Rusmawatiningtyas et al, where the authors also noted that age was not a factor associated with mortality (HR: 1.01, 95% CI: 0.99-1.03, p = 0.447) (5). In relation to the need for mechanical ventilation, we found no significant association with 28-day mortality in pediatric septic shock patients (HR: 1.30, 95% CI: 0.47-4.89, p = 0.632). Although ventilated patients showed a trend toward higher mortality risk with a 1.3-fold increase compared to non-ventilated patients, the wide confidence interval crossing unity (0.47-4.89) and non-significant p-value indicate that this association lacks statistical significance. Meanwhile, Rusmawatiningtyas et al.'s study demonstrated a significant association between mechanical ventilation support and mortality (HR: 2.7, 95% CI: 1.6-4.6, p < 0.001) (5). This discrepancy suggests that mechanical ventilation status alone may not be a reliable predictor of mortality in pediatric septic shock, and its prognostic value might vary across different clinical settings and patient populations. Our study focused on children who were already in shock at admission, therefore, most patients required mechanical ventilation support in the early phase, which may explain the lack of difference in outcomes between the two groups. As for organ dysfunction, our study shows notable findings. Although neurologic dysfunction demonstrated the strongest association with 28-day

mortality risk (HR: 30.50, 95% CI: 4.15-3886.80, p < 0.001), the wide confidence interval should be noted. LAR ≥ 1.84 showed a more precise estimate (HR: 7.14, 95% CI: 2.56-24.90, p = 0.001). Both renal dysfunction (HR: 2.66, 95% CI: 1.21-5.82, p = 0.016) and hematologic dysfunction (HR: 2.59, 95% CI: 1.19-5.87, p = 0.016) were also identified as significant predictors of 28-day mortality with narrower confidence intervals. Finally, our analysis identified LAR as an independent predictor of 28-day mortality. Multivariate analysis revealed that patients with LAR ≥ 1.84 demonstrated a significantly increased risk of mortality compared to those below this threshold (HR: 7.14, 95% CI: 2.56-24.9, p = 0.001). These findings are consistent with a systematic review by Choi et al., which reported that pediatric patients with septic shock having LAR ≥ 1.016 had a 7.636 times higher risk of mortality (23). A previous published study has demonstrated that LAR possesses robust discrimination and calibration properties for mortality prediction in pediatric septic shock (8). Therefore, our findings suggest that LAR represents a clinically applicable prognostic marker that can be effectively utilized at the time of initial diagnosis.

Strengths and limitations

Our study has several notable strengths and limitations. The prospective cohort design allows for direct assessment of causal relationships while minimizing recall information bias. Additionally, the evaluation of risk factors associated with 28-day mortality using Cox regression with Firth penalization is particularly suitable for studies with small sample sizes and rare events, yielding more precise hazard ratio estimates (24). However, the small sample size remains a major limitation, potentially reducing statistical power and resulting in wider confidence intervals. Furthermore, being a single-center study may limit the generalizability of our findings to diverse patient populations. Despite using appropriate statistical methods, unmeasured confounding factors cannot be excluded. Future multicenter studies with larger sample sizes are needed to validate our findings in pediatric septic shock mortality prediction.

Conclusion

Based on our analyses, the findings revealed a high mortality rate among pediatric patients with septic shock. At the time of diagnosis, pediatric patients with septic shock presented with varied clinical and paraclinical manifestations. Although septic shock predominantly affected infants and males, these demographic characteristics were not predictive of 28-day mortality. Meanwhile, neurological dysfunction, hematological dysfunction, renal dysfunction, and LAR ≥ 1.84 were independent prognostic factors for mortality in pediatric patients with septic shock.

Ethics Approval: The study was approved by the Ethics Committee in Biomedical Research at Can Tho University of Medicine and Pharmacy (IRB approval No. 22.158.HV/PCT-HĐĐĐ, dated July 29, 2022). All research procedures were conducted in strict compliance with ethical guidelines for scientific research, prioritizing children's benefit while ensuring no harm, maintaining patient confidentiality, ensuring objectivity and fairness in data collection, and avoiding interference with therapeutic interventions.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: PMN, DTKL, LCT (concept and design); PMN, DTKL, LCT, VTN (acquisition, analysis, and interpretation of data); PMN, DTKL, LCT (drafting of the manuscript); PMN, LCT, DTKL, VTN (critical review of the manuscript for important intellectual content). All authors approved the final version to be published and agreed to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration on the Use of AI: None.

Acknowledgments: We appreciate the continuous support from Can Tho University of Medicine and Pharmacy in this scientific endeavor and extend our thanks to the patients and their parents for participating in this study.

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Correspondence:
Received: 15 October 2024
Accepted: 20 November 2024
Duy-Truong Khac Le, MD, MSc
Department of Pediatrics, Faculty of Medicine,
Can Tho University of Medicine and Pharmacy
No.179 Nguyen Van Cu Street, 900000 Can Tho City,
Vietnam.
ORCID: 0009-0001-8908-0021
E-mail: duytruong.01126899@gmail.com