FACTORS SIGNIFICANTLY ASSOCIATED WITH DEATH AMONG PEDIATRIC SEPTIC SHOCK PATIENTS IN A RESOURCE-LIMITED SETTING

Nutnicha Preeprem and Suwannee Phumeetham

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract. Septic shock is a life-threatening condition. However, there is little data from developing countries regarding the epidemiology and factors associated with death in pediatric septic shock patients. In this study we aimed to determine the epidemiology and factors associated with death in pediatric septic shock patients at Siriraj Hospital, Bangkok, Thailand in order to help physicians identify patients at greater risk of dying so they can be monitored more closely. We retrospectively reviewed the charts of all patients aged 1 month to 18 years admitted to the pediatric intensive care unit at the study hospital during January 2013-December 2017. Factors recorded from the charts included demographic characteristics, the Pediatric Risk of Mortality (PRISM) III score, site of infection and therapeutic interventions. The data were examined and multivariable logistic regression analysis was used to determine the factors significantly associated with in-hospital mortality. A total of 94 subjects were included in the study; 48% male. The median (interquartile range (IQR)) age of study subjects was 7.5 (1.2-12.3) years, the in-hospital mortality rate was 33% and the median (IQR) PRISM III score was 11.5 (5.0-19.0). On multivariate analysis, the factors significantly associated with in-hospital mortality were age <1 year (adjusted odds ratio (aOR): 36.5; 95% confidence interval (CI): 3.03-441.03; p=0.005) and a PRISM III score ≥14 (aOR: 54.68; 95%CI: 5.70-524.78; p=0.001). In summary, the mortality rate from septic shock among our subjects was high. Age <1 year and PRISM score ≥14 were significantly associated with death. These patients should be monitored more closely. Further studies are needed to determine what modifications can reduce the risk of mortality in subjects with these factors.

Keywords: children, death, pediatric, risk factors, septic shock

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Correspondence: Suwannee Phumeetham, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi District, Bangkok 10700, Thailand
Tel: +66 (0) 2419 5673; Fax: +66 (0) 2419 5661
E-mail: suwannee.phu@mahidol.edu

INTRODUCTION

Septic shock is life threatening. The mortality rate among children with septic shock has been reported to range from 11% to 40% (Schlapbach *et al*, 2015; Weiss *et al*, 2015; Jaramillo-Bustamante *et al*, 2012) depending on the demographic characteristics of the study population and the types of healthcare resources available.

The best care practice for pediatric sepsis has been suggested by the Surviving Sepsis Campaign International Guidelines, which state that the essential factors for improving clinical outcomes are timely and appropriate fluid resuscitation, appropriate antibiotics, vasoactive-inotropic drugs and an appropriate intensive care setting (Weiss *et al*, 2020). Successful management of pediatric sepsis in a resource-limited setting is challenging.

Data regarding factors significantly associated with death in pediatric patients in the developing world are limited. Such data can guide efforts to improve patient care and allocate resources more effectively. The aim of this study was to determine the epidemiology and factors associated with death among pediatric patients with septic shock treated at Siriraj Hospital, Bangkok, Thailand in order to help physicians identify patients at higher risk of mortality and raise the level of concern in patient care.

MATERIALS AND METHODS

Study design and population

In this study we retrospectively reviewed the records of all children aged 1 month to 18 years admitted to the pediatric intensive care unit (PICU) at Siriraj Hospital, Bangkok, Thailand from 01 January 2013 to 31 December 2017 who were diagnosed with septic shock. Septic shock was defined using the criteria of the International Pediatric Sepsis Consensus Conference (Goldstein *et al*, 2005). Exclusion criteria for the study subjects were: being a transfer patient from another facility, being diagnosed with having dengue shock syndrome and dying within 4 hours of admission.

This study was approved by the Institutional Review Board of Siriraj Hospital, Bangkok, Thailand (approval number: Si 207/2018).

Data collection

Study subjects were divided into two groups (survivors and non-survivors) based on in-hospital mortality. The following data were obtained from each patient's chart: demographic characteristics, presence of comorbidities; severity of the illness assessed by the Pediatric Risk of Mortality III (PRISM III) score (Pollack *et al*, 1996), presence of organ dysfunction (Goldstein *et al*, 2005); level of pharmacologic cardiovascular support assessed by the vasoactive-inotropic score (VIS) (Gaies *et al*, 2010), site of infection, the etiological organism, the duration of stay in the PICU, the duration of hospitalization, whether endotracheal intubation and mechanical ventilation were used, use of renal replacement therapy, use of corticosteroids, use of extracorporeal membrane oxygenation (ECMO), use of a blood transfusion, time to initiation of sepsis resuscitation bundle care as determined by time to the administration of fluid bolus, antibiotics and vasoactive-inotropic drugs and treatment time being measured from the start of the first fluid bolus. The VIS was calculated as follows (Gaies *et al*, 2010): VIS = the dopamine dose (mcg/kg/min) + the dobutamine dose (mcg/kg/min) + 100 x the adrenaline dose (mcg/kg/min) + 100 x the noradrenaline dose (mcg/kg/min) + 10 x the milrinone dose (mcg/kg/min).

Statistical analysis

We tested the normality of distribution of continuous variables using the one-sample Kolmogorov-Smirnov test. We expressed baseline characteristics as medians with interquartile ranges (IQR) for continuous variables and as proportions for categorical variables. We compared the quantitative variables between the survivor and the non-survivor groups using the Mann-Whitney U test. We compared the frequencies of categorical variables using the Chi-square test or Fisher's exact test where appropriate. We considered a p-value <0.05 as statistically significant. We evaluated independent variables potentially associated with in-hospital mortality using univariate analysis with significance set at a p-value <0.2. Variables that were significant on univariate analysis were included in multivariable logistic regression analysis. We used the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM, Armonk, NY) to conduct all statistical analyses.

RESULTS

A total of 94 subjects were included in the study; 48% male. The median (IQR) age of study subjects was 7.5 (1.2-12.3) years. Thirty-three percent of subjects (n = 31) died. Non-survivors had a greater prevalence of hematologic and immunologic comorbid conditions (39% *vs* 16%; p = 0.010); had a higher PRISM III score (20.0 *vs* 8.0; p<0.001); had more VIS on the day of admission (50.0 *vs* 12.0; p<0.001); and exhibited more organ dysfunction particularly hematologic (68% *vs* 37%; p = 0.004), renal (48% *vs* 19%; p = 0.003) and hepatic function (36% *vs* 16%; p = 0.030) on the day of admission (Table 1).

Forty percent of subjects had a respiratory tract source of their sepsis and 26% had a gastrointestinal source. Pseudomonas species were the most common cause of sepsis in our subjects (16%) followed by Acinetobacter species (13%). Non-survivors had significantly more skin/bone/soft tissue infections (16% *vs* 0%; p = 0.030), positive fungal tests (16% *vs* 2%; p = 0.010) and positive blood cultures (48% *vs* 25%; p = 0.026) (Table 2).

Table 1

Characteristics of study subjects (N = 94)

Variables	Of total 94 subjects	In-hospital mortality		*p*-value
		Alive (*n* = 63)	Dead (*n* = 31)	
Age in years, median (IQR)	7.5 (1.2-12.3)	7.6 (1.4-12.2)	7.4 (0.7-12.2)	0.930
Subjects aged <1 year, *n* (%)	22 (23)	12 (19)	10 (32)	0.197
Males, *n* (%)	45 (48)	32 (51)	13 (42)	0.420
Subjects with comorbid conditions, *n* (%)				
Cardiovascular	13 (14)	9 (14)	4 (13)	1.000
Respiratory	19 (20)	15 (24)	4 (13)	0.220
Neurological or neuromuscular	25 (27)	19 (30)	6 (19)	0.270
Gastrointestinal	13 (14)	9 (14)	4 (13)	1.000
Renal	17 (18)	14 (22)	3 (10)	0.140
Hematologic or immunologic	22 (23)	10 (16)	12 (39)	0.010
Malignancy	30 (32)	21 (33)	9 (29)	0.670
Metabolic	19 (20)	13 (21)	6 (19)	0.880
Congenital or genetic abnormalities	22 (23)	17 (27)	5 (16)	0.240
Comorbid conditions, *n* (%)				
0	10 (11)	9 (14)	1 (3)	0.160
≥1	84 (89)	54 (86)	30 (97)	0.160
≥2	53 (56)	37 (59)	16 (52)	0.510

Table 1 (cont)

Variables	Of total 94 subjects	In-hospital mortality		*p*-value
		Alive (*n* = 63)	Dead (*n* = 31)	
PRISM III score, median (IQR)	11.5 (5.0-19.0)	8.0 (3.5-13.5)	20.0 (15.0-24.5)	<0.001
Subjects with a PRISM III score ≥14, *n* (%)	40 (43)	16 (25)	24 (77)	<0.001
Vasoactive-Inotropic Score on day of hospital admission, median (IQR)	18.0 (10-40)	12.0 (8.9-28.0)	50.0 (16.5-110.0)	<0.001
Organ systems with dysfunction				
Subjects with OD on day of admission, median (IQR)	3 (2-4)	3 (2-3)	4 (3-5)	<0.001
Subjects with 2 or more OD on day 1, *n* (%)	87 (93)	57 (91)	30 (97)	0.420
Subjects with OD by type on day of admission, *n* (%)				
Cardiovascular	94 (100)	63 (100)	31 (100)	
Respiratory	79 (84)	50 (79)	29 (94)	0.130
Neurologic	17 (18)	8 (13)	9 (29)	0.050
Hematologic	44 (47)	23 (37)	21 (68)	0.004
Renal	27 (29)	12 (19)	15 (48)	0.003
Hepatic	21 (22)	10 (16)	11 (36)	0.030

IQR: interquartile range; PRISM: Pediatric Risk of Mortality; OD: organ systems with dysfunction

Table 2

Site of infection and microbiological data (N = 94)

Variables	Of total 94 subjects	In-hospital mortality		*p*-value
		Alive (n = 63)	Dead (n = 31)	
Site of infection, n (%)				
CRBSI	5 (5)	1 (2)	4 (13)	0.039
Respiratory	41 (44)	24 (38)	17 (55)	0.124
Gastrointestinal	38 (40)	27 (43)	11 (36)	0.493
Central nervous system	3 (3)	1 (2)	2 (7)	0.252
Genitourinary	10 (11)	4 (6)	6 (19)	0.076
Skin/bone/soft tissue	5 (5)	0 (0)	5 (16)	0.003
Unknown	6 (6)	5 (8)	1 (3)	0.660
Organism identification, n (%)				
Positive hemoculture	31 (33)	16 (25)	15 (48)	0.026
More than 1 organism identified	21 (22)	12 (19)	9 (29)	0.275
Organism not identified	29 (31)	23 (37)	6 (19)	0.090

Table 2 (cont)

Variables	Of total 94 subjects	In-hospital mortality		*p*-value
		Alive (*n* = 63)	Dead (*n* = 31)	
Identified organism, *n* (%)				
Bacteria	55 (59)	34 (54)	21 (68)	0.200
Gram-negative bacilli	41 (44)	24 (38)	17 (55)	0.124
Pseudomonas species	15 (16)	12 (19)	3 (10)	0.370
Acinetobacter species	12 (13)	4 (6)	8 (26)	0.017
Escherichia coli	5 (5)	3 (5)	2 (7)	1.000
Klebsiella species	5 (5)	3 (5)	2 (7)	1.000
Stenotrophomonas maltophilia	4 (4)	2 (3)	2 (7)	0.596
Salmonella species	3 (3)	2 (3)	1 (3)	1.000
Enterobacter species	2 (2)	1 (2)	1 (3)	1.000
Aeromonas species	3 (3)	2 (3)	1 (3)	1.000
Shigella species	1 (1)	1 (2)	0 (0)	1.000
Vibrio species	1 (1)	1 (2)	0 (0)	1.000
Moraxella catarrhalis	1 (1)	1 (2)	0 (0)	1.000
Haemophilus influenzae	1 (1)	0 (0)	1 (3)	0.330

Table 2 (cont)

Variables	Of total 94 subjects	In-hospital mortality		p-value
		Alive (n = 63)	Dead (n = 31)	
Gram-positive cocci	16 (17)	10 (16)	6 (19)	0.673
Staphylococcus aureus (MSSA)	6 (6)	4 (6)	2 (6)	1.000
Coagulase-negative *Staphylococcus*	1 (1)	0 (0)	1 (3)	0.330
MRCNS	3 (3)	1 (2)	2 (7)	0.252
Group-A *Streptococcus*	1 (1)	1 (2)	0 (0)	1.000
Streptococcus hemolyticus	1 (1)	1 (2)	0 (0)	1.000
Streptococcus agalactiae	1 (1)	1 (2)	0 (0)	1.000
Streptococcus pneumoniae	1 (1)	1 (2)	0 (0)	1.000
Enterococcus species	2 (2)	0 (0)	2 (7)	0.106
Micrococcus species	1 (1)	1 (2)	0 (0)	1.000
Bacillus species	1 (1)	1 (2)	0 (0)	1.000
Mycoplasma pneumoniae, n (%)	1 (1)	1 (2)	0 (0)	1.000
Viruses, n (%)	14 (15)	10 (16)	4 (13)	1.000
Parainfluenza	5 (5)	2 (3)	3 (10)	0.327
Influenza	3 (3)	2 (3)	1 (3)	1.000
Respiratory syncytial virus	3 (3)	2 (3)	1 (3)	1.000
Adenovirus	1 (1)	1 (2)	0 (0)	1.000
Enterovirus	1 (1)	1 (2)	0 (0)	1.000
Rota virus	2 (2)	2 (3)	0 (0)	1.000

Table 2 (cont)

Variables	Of total 94 subjects	In-hospital mortality		p-value
		Alive (n = 63)	Dead (n = 31)	
Fungi, n (%)	6 (6)	1 (2)	5 (16)	0.010
Aspergillus species	3 (3)	1 (2)	2 (7)	0.252
Candida tropicalis	1 (1)	0 (0)	1 (3)	0.330
Trichosporon	1 (1)	0 (0)	1 (3)	0.330
Yeast	1 (1)	0 (0)	1 (3)	0.330

CRBSI: catheter-related bloodstream infection; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRCNS: methicillin-resistant coagulase negative staphylococci

Non-survivors had significantly less time to receive initial vasoactive-inotropic drugs (89.6 minutes *vs* 11.4 minutes; p = 0.020) and required significantly more invasive respiratory support (54.5% *vs* 45.5%; p<0.001), renal replacement therapy (29.0% *vs* 3.2%; p = 0.010) and blood transfusions (90.3% *vs* 60.3%; p = 0.003). The time to reach at least 40 ml/kg of fluid resuscitation and time to initial antibiotics was not significantly different between survivors and non-survivors (Table 3).

On multivariate logistic regression analysis, the factors significantly associated with in-hospital mortality were age <1 year (adjusted odds ratio (aOR): 36.54; 95% confidence interval (CI): 3.03-441.03; p = 0.005) and PRISM III score ≥14 (aOR: 54.68; 95%CI: 5.70-524.78; p = 0.001) (Table 4).

DISCUSSION

Timely initiation of the pediatric septic shock recommendations of the American College of Critical Care Medicine has been shown to improve outcomes, hospital and PICU length of stay and mortality (Larsen *et al*, 2011; Paul *et al*, 2012; Lane *et al*, 2016; Evans *et al*, 2018). These recommendations are considered best practice but their implementation remains difficult in many developing countries because of infrastructure limitations. In spite of efforts to implement these recommendations the mortality rate in our study was still high (33%). It is difficult to compare septic shock

Table 3

Resuscitation and treatment variables (N = 94)

Variables	Of total 94 subjects	In-hospital mortality		*p*-value
		Alive (*n* = 63)	Dead (*n* = 31)	
Time to fluid bolus in minutes[a], median (IQR)	60.5 (39.1-100)	55.0 (39.1-94.7)	100.1 (50.5-119.4)	0.120
Time to initial antibiotics in minutes, median (IQR)	89.6 (41.5-148.5)	89.6 (42.6-128.9)	87.4 (39.3-320.0)	0.460
Time to initial VI-drugs in minutes, median (IQR)	100.5 (67.7-171.5)	111.4 (80.8-190.1)	89.6 (19.7-123.4)	0.020
Required mechanical ventilation, *n* (%)	55 (59)	25 (46)	30 (55)	<0.001
Required renal replacement therapy, *n* (%)	11 (12)	2 (3)	9 (29)	0.001
Required corticosteroids, *n* (%)	47 (50)	29 (46)	18 (58)	0.270
Required blood transfusion, *n* (%)	66 (70)	38 (60)	28 (90)	0.003
Required ECMO, *n* (%)	2 (2)	0 (0.0)	2 (7)	0.110
Length of stay in the PICU in days, median (IQR)	3.72 (2.12-10.19)	3.93 (2.30-10.16)	3.45 (2.10-10.08)	0.840
Length of stay in the hospital in days, median (IQR)	19.94 (10.15-30.66)	19.69 (12.05-32.37)	20.90 (9.02-27.15)	0.470

ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; PICU: pediatric intensive care unit; VI-drug: vasoactive-inotropic drugs

[a]time to fluid bolus refers to the time to reach at least 40 ml/kg of fluid resuscitation

Table 4

Factors significantly associated with in-hospital mortality among study subjects using multivariable logistic regression analysis

Variable	aOR (95% CI)	*p*-value
Age <1 year	36.543 (3.028, 441.026)	0.005
PRISM III score ≥14	54.680 (5.698, 524.779)	0.001
Comorbid hemato/immune	3.513 (0.798, 15.462)	0.097
Time to initial antibiotics	1.002 (0.999, 1.006)	0.117

aOR: adjusted odds ratio; CI: confidence interval; hemato/immune: hematologic or immunologic conditions; PRISM: Pediatric Risk of Mortality

mortality rates due to differences in intensive care, populations and epidemiologic settings. The mortality rate in our study is comparable to a study from Colombia (34% in a multicenter setting; Jaramillo-Bustamante *et al*, 2012). Possible explanations include resource-limited healthcare services in developing countries and the etiologic diagnosis. Respiratory tract infections and Gram-negative bacilli causing sepsis were found more frequently in these populations. Some studies have reported lower mortality rates, such as a multicenter study from Australia and New Zealand (17%) (Schlapbach *et al*, 2015), a single-center study from the United States (23%) (Lautz *et al*, 2020), a multicenter study from Germany (25%) (Breuling *et al*, 2015), a single-center study from Korea (26%) (Kim *et al*, 2013). These studies with lower mortality rates could be attributed to their resource-rich setting, resulting in a better infrastructure, a lower patient-to-physician/nurse ratio, a greater knowledge level and better adherence to standard treatment guidelines. Tan *et al* (2019) reported a lower case-fatality rate in children with severe sepsis and septic shock in developed countries than in developing countries.

In our study, factors independently associated with in-hospital mortality included study subject age <1 year and a PRISM III score >14. Our findings are consistent with those of a previous study (Tan *et al*, 2019) that reported higher mortality in younger pediatric patients with septic shock. However, the association between young age and mortality was not supported by the previous large SPROUT study (Weiss *et al*, 2015). The reason for this discrepancy is unclear. The PRISM III score has been shown to be useful in identifying PICU patients a greater risk of dying (El-Nawawy, 2003;

Brady *et al*, 2006; Gonçalves *et al*, 2015; Kaur *et al*, 2020). It exhibited good discrimination ability using a cutoff point of ≥14 according to the analysis conducted by Zhang *et al* (Zhang et al, 2021) reported using a cutoff point with the PRISM III score of >14 was associated with a greater risk of mortality, similar to the results seen in our study.

Our study had some limitations. Because it was a retrospective review of the records of patients from a single center, it cannot be applied to other study populations and cannot be used to predict risk factors for death, which would require a prospective study. The small sample size and large confidence interval suggest the results are less reliable. The time to treatment measured from the time of recognition of septic shock until the time treatment was initiated, which can affect the clinical outcome, was not assessed in this study due to limited data. However, our results are useful and insight into this serious disease in a resource-limited setting.

In summary, the in-hospital mortality rate among our study subjects was high (33%). The factors significantly associated with in-hospital mortality rate were age <1 year and a PRISM III score ≥14. These findings highlight the importance of patient classification in order to guide appropriate monitoring, care and application of resources which could improve outcomes in a resource-limited setting.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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