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ORIGINAL ARTICLE

Prognostic roles of time to positivity of blood culture in children with *Streptococcus pneumoniae* bacteremia

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Abstract

We aimed to investigate the relationship between time to positivity (TTP) of blood cultures and clinical outcomes in children with *S. pneumoniae* bacteremia. Children with *S. pneumoniae* bacteremia hospitalized in Children's Hospital of Chongqing Medical University from May 2011 to December 2017 were enrolled retrospectively. Overall, 136 children with *S. pneumoniae* bacteremia were enrolled. The standard cutoff TTP was 12 h. We stated that in-hospital mortality is significantly higher in the early TTP (≤ 12 h) group than that in the late TTP (> 12 h) group (41.70% vs 8.00%, $P < 0.001$). Septic shock occurred in 58.30% of patients with early TTP and in 21.00% of patients with late TTP ($P < 0.001$). Independent risk factors of in-hospital mortality and septic shock in children with *S. pneumoniae* bacteremia included early TTP, need for invasive mechanical ventilation, and PRISM III score ≥ 10. Overall, TTP ≤ 12 h appeared to associate with the worse outcomes for children with *S. pneumoniae* bacteremia.

Keywords Time to positivity · Blood culture · *Streptococcus pneumoniae* · Bacteremia · Outcomes · Children

Introduction

Streptococcus pneumoniae (*S. pneumoniae*) can cause invasive diseases, such as sepsis, meningitis, and pneumonia [1]. Invasive pneumococcal disease is a major cause of morbidity and mortality in children. The WHO estimates that nearly 1 million children die of pneumococcal disease every year [2]. Early predictors of illness severity and poor prognosis are useful for the management of patients with *S. pneumoniae* bacteremia. They contribute to assessing the need for intensified therapy and monitoring, or for intensive care unit (ICU) admission. Some studies have developed prognostic scores to identify patients at high risk of death [3, 4]. However, these score calculation methods are complex. Therefore, early and easily attainable clinical predictors of pneumococcal bacteremia are desirable.

Previous studies demonstrated that the time to positivity (TTP) of blood culture may serve as an early predictor of clinical outcomes for *Staphylococcus aureus* [5], *Escherichia coli* [6], and *Klebsiella pneumoniae* bacteremia [7], which indicates that short TTP was associated with worse clinical outcomes. Three studies have stated the associations between TTP and the clinical outcomes of patients with *S. pneumoniae* bacteremia. Two studies in adults demonstrated that early TTP was associated with worse clinical outcomes [8, 9], while Neuman et al. [10] stated that no correlation was found between TTP and clinical or laboratory parameters in children with *S. pneumoniae* bacteremia. As the relationships between TTP and clinical outcomes of children with *S. pneumoniae* bacteremia remain controversial, few studies were performed in children with *S. pneumoniae* bacteremia. In this study, we aim to evaluate the relationship between TTP and clinical outcomes and assess the risk factors of in-hospital mortality and septic shock incidence in children with *S. pneumoniae* bacteremia.

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Materials and methods

Study designs and patients

This study was conducted in Children's Hospital of Chongqing Medical University, a 1500-bed tertiary teaching hospital in Chongqing, China, ranked in the top three of all the domestic children hospitals. Children with *S. pneumoniae* bacteremia hospitalized in Children's Hospital of Chongqing Medical University from May 2011 to December 2017 were enrolled retrospectively. The inclusion criteria were all of the following: (i) age < 18 years; (ii) inpatients; (iii) with systemic inflammation reaction syndrome status; and (iv) with ≥ 1 *S. pneumoniae* blood culture positive. The exclusive criteria included any of the following: (i) patients with incomplete clinical information; (ii) patients who missed their TTPs; and (iii) patients who were lost to follow-up.

Blood culture

Approximately 3 ml of blood was inoculated into BACTEC plus aerobic bottles, which were then transported to the laboratory and incubated in an automated continuous monitoring system immediately. The Becton-Dickinson diagnostic systems were used for blood culture; it monitors CO_2 production every 5 min by means of a fluorescent signal. Bottles with positive results were examined by Gram staining, and their contents were subcultured. Species identification and susceptibility tests were performed using Vitek identification and susceptibility cards (bioMe'rieux Vitek).

Definitions

S. pneumoniae bacteremia was defined as more than 1 positive *S. pneumoniae* blood culture with systemic inflammation reaction syndrome status. TTP of blood culture was defined as the time period between blood incubation and the positive signal. When multiple TTPs existed, the shortest one was enrolled as all individuals were included only once. The positive blood samples detected within 48 h after admission were defined as community-acquired infection. Immunosuppression was defined with cytotoxic chemotherapy or high-dose steroid therapy daily for ≥ 2 week and primary immunodeficiency disease. Pulmonary complications were confirmed by clinical and chest CT manifestations. *S. pneumoniae* meningitis was diagnosed by neurological manifestations, cerebrospinal fluid (CSF) abnormality, accompanied with growth of *S. pneumoniae* in CSF. *S. pneumoniae* osteomyelitis was diagnosed when positive culture of *S. pneumoniae* from pyogenic fluids combined with localized signs or symptoms and imaging changes. Sepsis shock was defined by criteria in the Guidelines for Management of Sepsis and Septic Shock: 2016 [11]. Severity of illness was measured by Pediatric Risk of Mortality (PRISM) score III [12]. The drugs sensitive to *S. pneumoniae* applied within 24 h after blood culture sample collection were defined as appropriate empirical antimicrobial therapy [6]. Penicillin-resistant *S. pneumoniae* (PRSP) was determined based on minimum inhibitory concentration (MIC) criteria in susceptibility test in vitro [13].

Data collection

The collected data included TTP of blood culture, demographic characteristics, underlying conditions, pulmonary and extrapulmonary complications, severity of illness assessed by PRISM score III [12], clinical outcome, the appropriateness of empirical antibiotics use, the delivery of antibiotic prior to blood culture, the time from specimen collection to receipt in the laboratory, and the infection with PRSP.

Clinical outcomes

The primary outcome was in-hospital mortality. The second outcome was incidence of septic shock.

Statistical analysis

Continuous variables with non-normal distribution were compared by Mann–Whitney *U* test and were presented as medians with inter-quartile ranges (IQRs). Categorical variables were analyzed using the X^2 test or the Fisher's exact test and expressed as numbers (*n*) and percentages (%). The possible application of TTP as a predictive marker was assessed by receiver-operating characteristic

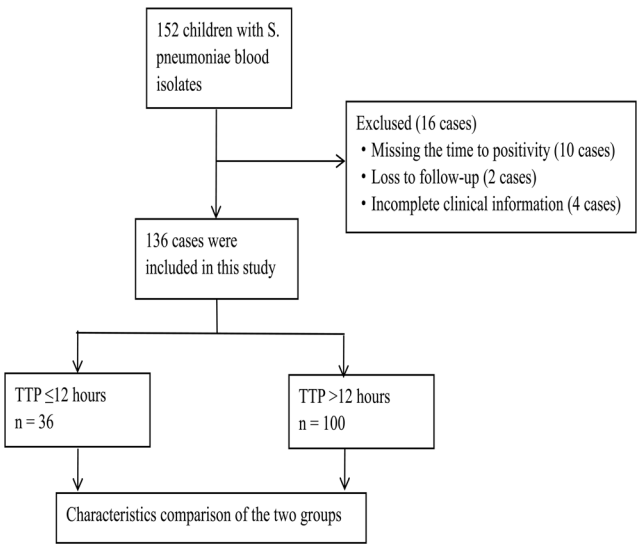

Fig. 1 Flow diagram of the population

Table 1 Demographical, clinical characteristics of 136 children with *S. pneumoniae* bacteremia

Characteristics	*n*/ median	%/IQR
Demographic characteristics		
Age (years)	1.88	0.85–4.48
Gender		
Male	79	58.10
Female	57	41.90
Weight (kilogram)	11.50	9.00–16.00
Length of hospital stay (days)	13.84	8.33–23.33
Underlying conditions		
Immunosuppression	22	16.20
Immunosuppressants use	20	14.70
Primary immunodeficiency disease	2	1.47
Hematologic malignancy	10	7.40
Congenital heart disease	5	3.70
Pulmonary complications		
Empyema	19	14.40
Atelectasis	11	8.10
Pneumothorax	6	4.40
Necrotizing pneumonia	5	3.70
Extrapulmonary complications		
Meningitis	44	32.40
Sepsis shock	42	30.91
Osteomyelitis	3	2.21
PRISM III score		
PRISM III score < 10	113	83.09
PRISM III score ≥ 10	23	16.91
Intensive care unit admission		
Yes	30	22.06
No	106	77.94
Invasive mechanical ventilation		
Yes	23	16.91
No	113	83.09
In-hospital mortality		
Yes	23	16.91
No	113	83.09
Community-acquired infections		
Yes	109	80.10
No	27	19.85
Antibiotic given prior to blood culture		
Yes	73	53.70
No	63	46.32
Appropriate empirical antimicrobial therapy		
Yes	92	67.60
No	44	32.35
TTP		
TTP ≤ 12 h	36	26.47
TTP > 12 h	100	73.53
Penicillin resistant *Streptococcus pneumoniae*		
Yes	25	18.38
No	111	81.62
The duration from specimen collection to receipt in the laboratory (minutes)	48.00	28.00–91.50

PRISM, Pediatric Risk of Mortality; TTP, time to positivity

(ROC) analysis. The area under the ROC curve (AUC) was computed to assess the predictive capability of TTP. $0.5 < AUC \leq 0.7$ indicated less predictive, $0.7 < AUC \leq 0.9$ implicated moderately predictive, and $0.9 < AUC < 1$ referred to highly predictive [14, 15]. The maximum Youden's index [16] was used as a criterion for selecting the optimum cutoff point for TTP. Univariate analysis was performed for associations between risk factors and in-hospital mortality, incidence of septic shock. The variables with P value < 0.10 in the univariate analysis were further included in the multivariate logistic regression models with forward LR selection. ORs and the 95% CIs were calculated. Hazard curves were generated by the Kaplan–Meier method, and differences in survival were compared using the log-rank test. P value < 0.05 (two-sided) was considered significant. Statistical analysis was conducted using SPSS software for Windows, v.22 (SPSS Inc., Chicago, IL, USA).

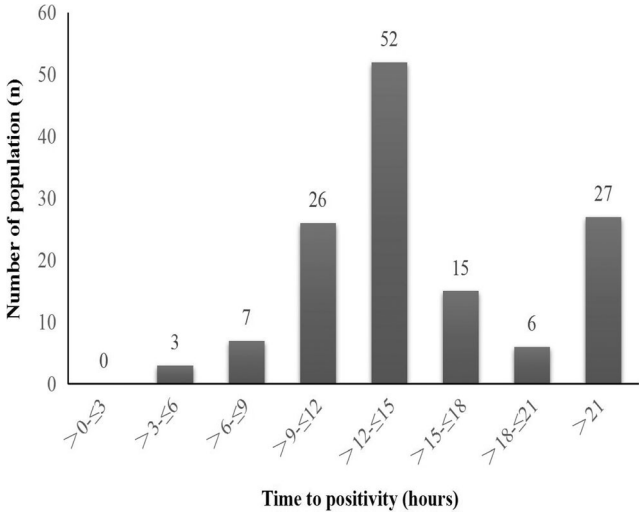

Fig. 2 Bar chart of TTP in children with *S. pneumoniae* bacteremia. Out of a total of 136 children with *S. pneumoniae* bacteremia, the number of children in each TTP period was plotted against the corresponding TTP, as shown

Results

Study population

During the study period, 152 inpatients with ≥ 1 *S. pneumoniae* blood culture positive and systemic inflammation reaction syndrome status were enrolled retrospectively. Sixteen of them were excluded, ten cases missed their TTPs, two cases were lost to follow-up, and four cases had incomplete clinical information. Therefore, 136 cases were finally included in this study (Fig. 1).

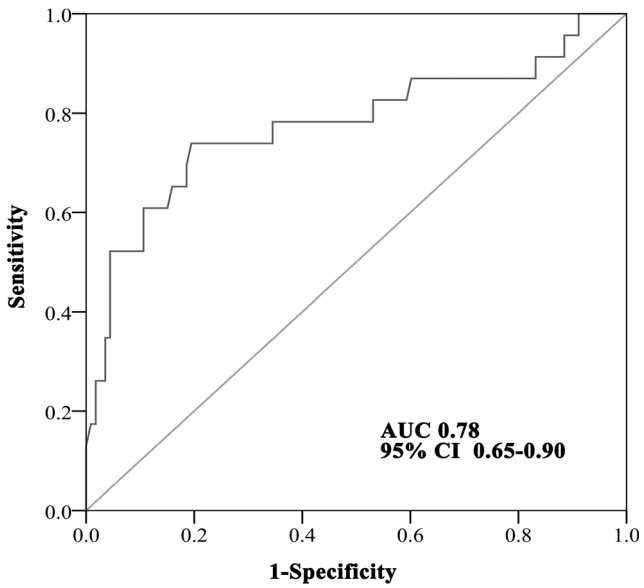

Fig. 3 ROC curves of TTP to predict in-hospital mortality

Clinical characteristics of *S. pneumoniae* bacteremia in children

The median (IQR) age of enrolled patients was 1.88 (0.85–4.48) years, the median (IQR) weight was 11.50 (9.00–16.00) kilogram, and 58.1% (79 /136) of them were male. The average duration of hospitalization was 13.84 (8.33–23.33) days. Twenty-two patients had immunosuppression, 20 due to immunosuppressants use (11 had cytotoxic chemotherapy, nine had high-dose steroid therapy daily for ≥ 2 week), and two with primary immunodeficiency disease. The most common pulmonary complications were empyema (14.40%) and atelectasis (8.10%). Meningitis is the most common extrapulmonary complications (32.40%), followed by sepsis shock (31.60%) and osteomyelitis (2.21%). 16.91% (23 /136) patients had PRISM III score ≥ 10. 22.06% (30/136) patients admitted to ICU, and 16.91% (23 /136) patients had invasive mechanical ventilation. The in-hospital mortality was 16.91% (23 /136). The detailed demographical and clinical characteristics of these patients were listed in Table 1.

TTP of *S. pneumoniae* bacteremia in children

The median TTP of 136 children with *S. pneumoniae* bacteremia was 13.75 h (IQR 8.33 to 23.33 h). The bar chart of TTP was shown in Fig. 2. Receiver operating characteristic (ROC) curvy of the TTP was plotted according to in-hospital mortality. TTP showed a significant AUC of 0.78 (95% CI, 0.65–0.90), indicating a moderate predictive capability when predicting in-hospital mortality (Fig. 3). Following Youden's index methodology, 12.25 h was found to be the optimal point for TTP. We thus selected 12 h as the standard cutoff, with 65.22% sensitivity and 81.42% specificity for predicting in-hospital mortality. Based on the standard cutoff, patients were divided into early detection group (TTP ≤ 12 h) and late detection group (TTP > 12 h). The Kaplan–Meier survival curve of patients with early or late TTP is shown in Fig. 4.

Comparison of clinical characteristics and outcomes between early and late detection groups

Clinical characteristics and outcomes of the two TTP groups were shown in Table 2. More patients in early TTP group had immunosuppression (30.60% vs. 11.00%, $P = 0.006$) and congenital heart disease (11.00% vs. 1.00%, $P = 0.025$) when compared with the late TTP group. Patients in early TTP group had significantly higher in-hospital mortality (41.70% vs. 8.00%, $P < 0.001$) and higher incidence of developing sepsis shock (58.30% vs. 21.00%, $P < 0.001$), a PRISM III score ≥ 10 (30.60% vs. 12.00%, $P = 0.011$) and meningitis

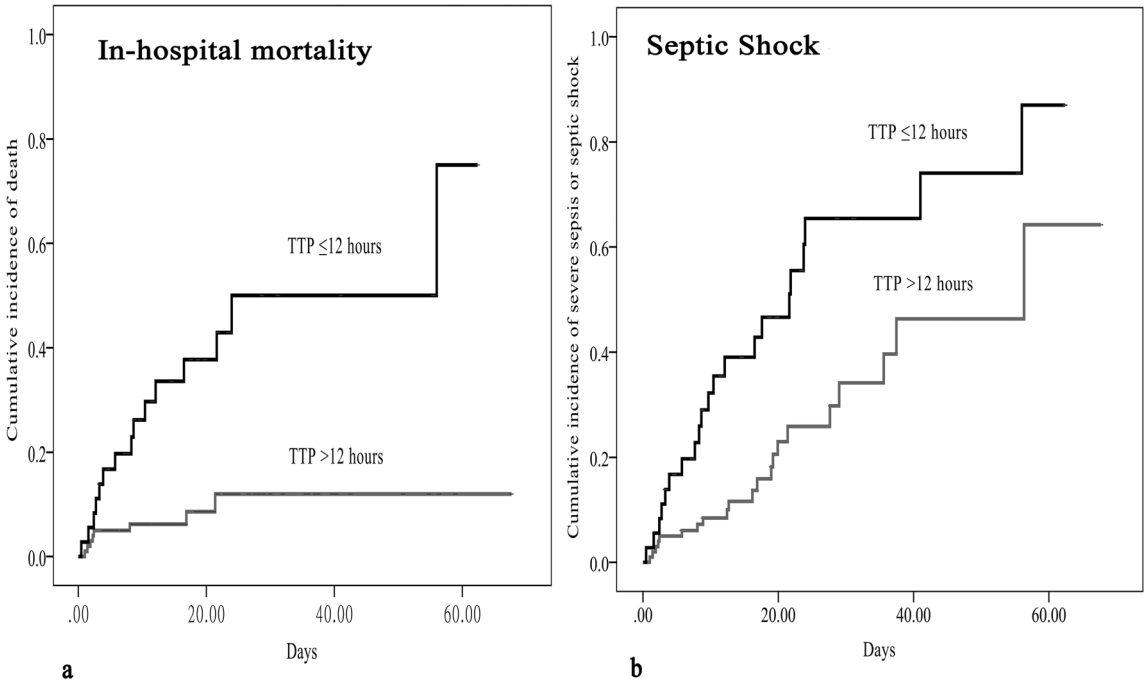

Fig. 4 The comparison of TTP according to in-hospital mortality (**a**) and the incidence of septic shock (**b**)

(50.00% vs. 26.00%, $P = 0.008$) than those in late TTP groups. No remarkable differences were detected between TTP and demographic characteristics, pulmonary complications, osteomyelitis, ICU admission, invasive mechanical ventilation, the delivery of antibiotic prior to blood culture, *S. pneumoniae* penicillin susceptibility, and the duration from specimen collection to receipt in the laboratory.

Comparison of clinical characteristics and outcomes between the survival and the non-survival groups

The clinical characteristics and outcomes of the survival and the non-survival groups are shown in Table 3. The median (IQR) TTP in the non-survival group was 9.70 (7.97–13.18) hours, which was much shorter than that in the survival group [14.15 (12.57–18.93)]. Non-survival groups had remarkably higher incidence of immunosuppression, sepsis shock, meningitis, a PRISM III score ≥ 10, ICU admission, and need for invasive mechanical ventilation when compared with the survival group ($P < 0.05$).

Risk factors of in-hospital mortality

Univariate logistic regression test demonstrated in-hospital mortality was correlated with need for invasive mechanical ventilation, early TTP, a PRISM III score ≥ 10, ICU admission, meningitis, and immunosuppression. Multivariate logistic regression test showed need for invasive mechanical ventilation (OR 20.52; 95% CI 3.50–120.47), early TTP (OR 18.91; 95% CI 3.36–106.59), and a PRISM III score ≥ 10 (OR 17.08; 95% CI 3.54–82.40) were independent risk factors of in-hospital mortality (Table 4).

Risk factors of septic shock

The univariate logistic regression test demonstrated that septic shock was correlated with need for invasive mechanical ventilation, early TTP, a PRISM III score ≥ 10, ICU admission, and meningitis. Multivariable logistic regression showed that need for invasive mechanical ventilation (OR 38.08; 95% CI 7.24–200.13), early TTP (OR 6.65; 95% CI 2.36–18.69), and a PRISM III score ≥ 10 (OR 4.31; 95% CI 1.04–17.79) were independent risk factors of septic shock (Table 5).

Discussion

The median TTP in our study was 13.75 h (IQR 8.33 to 23.33 h), which was similar to Peralta's results (median TTP: 14.1 h) [9], while longer than that reported in Cilloniz's and Neuman's studies (mean TTP: 10.5 h, 11.5 h, respectively) [8, 10] for *S. pneumoniae* bacteremia. The difference in TTP might be associated with age, the duration from specimen collection to laboratory receipt, the delivery of antibiotics prior to blood culture, and the volume of blood drawn.

Studies indicated earlier TTP was associated with higher bacterial load [17, 18], which was related to worse outcomes in patients with bacteremia [18, 19]. We demonstrated that

Table 2 Clinical characteristics and outcomes associated with time to positivity of blood cultures in 136 children with *S. pneumoniae* bacteremia

Characteristics	TTP ≤ 12 h (n = 36)	TTP > 12 h (n = 100)	P
Demographic characteristics			
Age, median (IQR)	2.71 (0.92–6.48)	1.71 (0.81–3.83)	0.146
Gender, male (n, %)	20 (55.60%)	59 (59.60%)	0.719
Weight, median (IQR)	12.00 (9.00–20.00)	11.25 (9.00–15.38)	0.270
Length of hospital stay, median (IQR)	11.90 (6.15–23.68)	13.92 (8.90–22.64)	0.468
Underlying conditions			
Immunosuppression (n, %)	11 (30.6%)	11 (11.00%)	0.006*
Congenital heart disease (n, %)	4 (11.1%)	1 (1.00%)	0.025*
Hematologic malignancy (n, %)	4 (11.1%)	6 (6.00%)	0.525
Pulmonary complications			
Empyema (n, %)	5 (13.90%)	14 (14.00%)	0.987
Atelectasis (n, %)	3 (8.30%)	8 (8.00%)	1.000
Pneumothorax (n, %)	1 (2.80%)	5 (5.00%)	0.933
Necrotizing pneumonia (n, %)	0 (0.00%)	5 (5.00%)	0.395
Extrapulmonary complications			
Sepsis shock (n, %)	21 (58.30%)	21 (21.00%)	0.000*
Meningitis (n, %)	18 (50.00%)	26 (26.00%)	0.008*
Osteomyelitis (n, %)	0 (0.00%)	3 (3.00%)	0.565
Pediatric Risk of Mortality III score ≥ 10	11 (30.60%)	12 (12.00%)	0.011*
Intensive care unit admission	10 (27.80%)	20 (20.00%)	0.335
Invasive mechanical ventilation	9 (25.0%)	14 (14.00%)	0.131
In-hospital mortality (n, %)	15 (41.70%)	8 (8.00%)	0.000*
Community-acquired infections (n, %)	30 (83.30%)	79 (79.00%)	0.576
Antibiotic given prior to blood culture (n, %)	19 (52.80%)	54 (54.00%)	0.900
PRSP (n, %)	5 (13.90%)	20 (20.00%)	0.417
The duration from specimen collection to receipt in the laboratory	42.00 (61.00)	52.00 (65.00)	0.921

TTP, time to positivity; PRSP, penicillin-resistant *S. pneumoniae*

*Indicates statistical significant results, $P < 0.05$

patients with TTP ≤ 12 h had nearly 19 and 7 folds higher risk of in-hospital mortality and sepsis shock than those with TTP > 12 h, respectively. TTP ≤ 12 h was an independent predictor of poor outcomes in children with *S. pneumoniae* bacteremia. Our results were similar with those in Cilloniz's and Peralta's studies [8, 9]. The associations between short TTP and worse clinical outcomes have been proved in patients with *S. aureus* [5], *E. coli* [6], and *K. pneumoniae* bacteremia [7], while Neuman et al. [10] demonstrated no correlations between TTP and clinical or laboratory parameters in *S. pneumoniae* bacteremia children. The possible explanations for different results may be as follows. Patients with immunodeficiency in Neuman's study [10] were excluded. Studies demonstrated that immune status affects TTP dramatically [7, 9]. Moreover, they only analyzed the association between TTP and fever height, WBC and neutrophil count, and source of infection. Some important clinical outcome parameters (such as in-hospital mortality, septic shock, PRISM score) have not been included in their study.

Severe condition is correlated with poor clinical outcomes. The PRISM III score is the most widely known and commonly used model to evaluate disease severity in pediatric patients [12]. High PRISM III scores indicated critically severe condition [19]. Some studies reported the median PRISM scores were significantly higher in the dead patients than those in the survived groups [20–22]. Farris et al. [23] showed that patients with PRISM scores more than 10 had increased risk of poor clinical outcome when compared to patients with PRISM scores fewer than 10. We found patients with a PRISM III score ≥ 10 had nearly 17 and 4 folds higher risk of in-hospital mortality and sepsis shock than those with a PRISM III score < 10, respectively. Our results were in accord with these previous studies. Need for invasive mechanical ventilation could also reflect severe condition. Sepsis may

Table 3 Clinical characteristics and outcomes comparison in survival and non-survival groups in 136 children with *S. pneumoniae* bacteremia

Characteristics	Non-survival ($n = 23$)	Survival ($n = 113$)	P
Demographic characteristics			
Age, median (IQR)	1.58 (0.84–3.67)	2.00 (0.85–4.59)	0.590
Gender, male (n, %)	12 (52.20%)	67 (59.30%)	0.528
Weight, median (IQR)	10.00 (8.00–15.00)	12.0 (9.00–16.00)	0.400
Underlying conditions			
Immunosuppression (n, %)	8 (34.80%)	14 (12.40%)	0.008*
Congenital heart disease (n, %)	2 (8.70%)	3 (2.70%)	0.199
Hematologic malignancy (n, %)	2 (8.70%)	8 (7.10%)	1.000
Pulmonary complications			
Atelectasis (n, %)	4 (17.40%)	7 (6.20%)	0.169
Empyema (n, %)	4 (17.40%)	15 (13.30%)	0.850
Pneumothorax (n, %)	1 (4.30%)	5 (4.40%)	1.000
Necrotizing pneumonia (n, %)	0 (0.00%)	5 (4.40%)	0.589
Extrapulmonary complications			
Sepsis shock	19 (82.60%)	19 (16.80%)	0.000*
Meningitis	14 (60.90%)	30 (26.50%)	0.001*
Osteomyelitis (n, %)	0 (0.00%)	3 (2.70%)	1.000
Pediatric Risk of Mortality III score ≥ 10	16 (69.60%)	7 (6.20%)	0.000*
Intensive care unit admission	15 (65.20%)	15 (13.30%)	0.000*
Invasive mechanical ventilation	15 (65.20%)	8 (34.80%)	0.000*
TTP, median (IQR)	9.70 (7.97–13.18)	14.15 (12.57–18.93)	0.000*
Community-acquired infections (n, %)	19 (82.60%)	90 (79.60%)	0.970
Antibiotic given prior to blood culture (n, %)	13 (56.5%)	60 (53.10%)	0.764
PRSP (n, %)	7 (30.40%)	18 (15.90%)	0.180

TTP, time to positivity; PRSP, penicillin-resistant *S. pneumoniae*

*Indicates statistical significant results, $P < 0.05$

cause pulmonary inflammation, fluid extravasation, and alveolar epithelial cell damage [24, 25]. Invasive mechanical ventilation is necessary in critical cases to maintain adequate gas exchange. Cillo'niz et al. [8] revealed that need for invasive mechanical ventilation was a risk factor for 30-day mortality. We found patients with invasive mechanical ventilation had approximately 20 and 38 folds higher risk of in-hospital mortality and sepsis shock than those without invasive mechanical ventilation, respectively. Therefore, PRISM III score ≥ 10 and need for invasive mechanical ventilation, reflecting severe condition, could serve as risk factors of adverse clinical outcomes in children with *S. pneumoniae* bacteremia.

We showed immunosuppression correlated with short TTP. Peralta et al. [9] found immunosuppression induced short TTP in adult patients with *S. pneumoniae* bacteremia. For *Pseudomonas aeruginosa* infection, patients with

Table 4 Logistic regression analysis of risk factors of in-hospital mortality among 136 children with *S. pneumoniae* bacteremia

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Need for invasive mechanical ventilation	24.61	8.03–75.38	0.000*	20.52	3.50–120.47	0.001*
Early TTP	8.21	3.08–21.89	0.000*	18.91	3.36–106.59	0.001*
PRISM III score ≥ 10	34.61	10.72–111.76	0.000*	17.08	3.54–82.40	0.000*
Intensive care unit admission	12.25	4.44–33.83	0.000*			
Meningitis	4.30	1.69–10.97	0.002*			
Immunosuppression	3.77	1.35–10.51	0.011*			

TTP, time to positivity; PRISM, Pediatric Risk of Mortality

*Indicates statistical significant results, $P < 0.05$

Table 5 Logistic regression analysis of risk factors of septic shock among 136 children with *S. pneumoniae* bacteremia

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Need for invasive mechanical ventilation	46	10.00–211.57	0.000*	38.08	7.24-200.13	0.000*
Early TTP	5.27	2.32–11.96	0.000*	6.65	2.36-18.69	0.000*
PRISM III score ≥ 10	13.35	4.50–39.65	0.000*	4.31	1.04-17.79	0.044*
Intensive care unit admission	15.05	5.64–40.12	0.000*			
Meningitis	3.6	1.67–7.78	0.001*			
Immunosuppression	1.7	0.66–4.36	0.270			

TTP, time to positivity; PRISM, Pediatric Risk of Mortality

*Indicates statistical significant results, $P < 0.05$

immunosuppressants also had earlier TTP [26]. Immune status and the immune response to bacteria infection play crucial roles in bacteria clearance [8]. The reduced bacteria clearance in immunosuppressive patients may lead to higher bacteria load and earlier TTP [17, 18].

There are some limitations in our study. Firstly, the retrospective study design may preclude us to include more meaningful variables. For example, neurological sequelae may be important clinical indicators to reflect the long-term prognosis of *S. pneumoniae* bacteremia. We could not collect these data due to retrospective study. Secondly the relatively small sample size of our study may lead to heterogeneity in results and may limit the ability to obtain solid conclusions. Third, this is a single-center study, which has different research facilities and population; it may influence the extrapolation of our data to other centers. Therefore, multi-center, prospective studies in the future, using a larger sample size, could strengthen the results of this study.

In conclusion, early TTP (TTP ≤ 12 h), along with need for invasive mechanical ventilation and a PRISM III score ≥ 10, could serve as independent risk factors of in-hospital mortality and septic shock for children with *S. pneumoniae* bacteremia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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