Mortality Prediction in Pediatric Patients with Sepsis of Abdominal Origin: A Retrospective Study

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Abstract

Aims: The aim of this study was to assess the prediction of mortality in pediatric patients with sepsis of abdominal origin. **Methods:** We performed a retrospective study of patients with sepsis of abdominal origin admitted to the pediatric intensive care unit (PICU) in Shanghai Children's Hospital between May 2014 and April 2018. **Results:** A total of 143 patients were enrolled in this study. The mortality rate in pediatric patients with sepsis of abdominal origin was 11% (17/143). PRISMIII score, the grade of acute gastrointestinal injury (AGI), hematologic malignancy, acute kidney injury, the initial number of organ dysfunction, alanine aminotransferase (ALT), and blood platelet (PLT) were potential risk factors for increased mortality. Multivariate logistic regression analysis indicated that higher Pediatric risk of mortality III (PRISM III) score and the grade of AGI were independent risk factors of mortality in patients with sepsis of abdominal origin. Furthermore, the area under receiver-operating characteristic (ROC) curve (AUC) for PRISM III score and the grade of AGI were 0.91 (95% confidence interval (CI) 0.86–0.96, $P < 0.001$) and 0.83 (95% CI 0.74–0.92, $P < 0.001$), in which the optimal cut-off value was 10.5 and 2.5, respectively. In addition, the Kaplan-Meier curve indicated that the 28-day survival rate was significantly lower in patients with higher PRISM III score (>10.5) and the grade of AGI (>2.5). **Conclusions:** Higher PRISM III score and the grade of AGI were associated with poor outcomes in pediatric patients with sepsis of abdominal origin.

Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a high mortality rate in pediatric[1, 2]. The abdomen is the common site of sepsis in 8.3%–19.6% of the patients in the pediatric intensive care unit (PICU)[3-6].

Abdominal infections, injuring the gut barrier which leads to systemic bacterial translocation, are more often associated with septic shock, acute kidney injury, and the development of the systemic inflammatory response syndrome and multiple organ dysfunction syndrome (MODS) with high mortality. The pathogenesis may be related to intestinal damage, gut barrier dysfunction, and intestinal proinflammatory response. Intestinal hypoperfusion and enteric microcirculatory disturbances lead to intestinal damage and gut barrier dysfunction. Gut microbes activate the defense of the intestinal immune system. An intestinal proinflammatory response aggravates intestinal damage, and Danger-Associated Molecular Patterns released in the mesenteric lymphatics enters to the systemic circulation, which promotes a systemic inflammatory response associated with MODS[7]. Early detection and evaluation of sepsis of abdominal origin are important for improving the clinical outcomes.

The objective of this study was to describe the characteristics and outcome of patients with sepsis of abdominal origin in PICU and the clinical and laboratory indicators associated with death. In addition, we tried to identify the most valuable prognostic indicator of patients with sepsis of abdominal origin.

Materials And Methods

Study Design

We performed a retrospective analysis of patients with sepsis admitted to the PICU in Shanghai Children's Hospital between May 2014 and April 2018. Sepsis was defined according to the criteria of the Surviving Sepsis Campaign International Guidelines in 2012[8]. All the patients enrolled in the study were confirmed to have the original infection of the abdomen. This study was approved by the Ethics Committee of Shanghai Children's Hospital (No. 2016R010-E02). Informed content was waived because of its retrospective design.

Patients

Patients aged 29 days to 18 years old who were diagnosed with sepsis of abdominal origin between May 2014 and April 2018 were screened for inclusion. Patients with PICU stay less than 48 hours were excluded.

Sepsis and organ dysfunction were diagnosed according to the criteria of Surviving Sepsis Campaign International Guidelines in 2012[8]. Patients were treated in accordance to current guidelines for treatment of sepsis. The patients with acute kidney injury, fluid overload or hemodynamic instability were treated with continuous renal replacement therapy (CRRT). If the patients presented respiratory failure, mechanical ventilation was used as an adjuvant treatment.

Data Collection and Definitions

All the data were retrieved from electronic medical records. Data included demographic data (such as, age, gender, weight, etc.), comorbid diseases, the length of PICU stay, the initial number of organ dysfunction, and [Pediatric Risk of Mortality score](#) (PRISM III)[9] within 24 hours following admission, the need for mechanical ventilation, CRRT, positive bacterial cultures, the grade of acute gastrointestinal injury (AGI)[10] and the outcome on discharge. Additional data about laboratory indexes included total bilirubin level (TBIL), creatinine (CREA), prothrombin time (PT), lactate (LAC), blood platelet (PLT), C-reactive protein (CRP) and procalcitonin (PCT), etc within 24 hours following admission.

Statistical Analyses

Data were analyzed using SPSS (v.22.0). Continuous variables were summarized as means $\pm$ standard derivations (SD) for normal distribution data and as median (Inter-Quartile Range) for abnormal distribution data. T-test was used to compare the continuous variables with normally distributed data; otherwise, the Mann–Whitney U test was used. The *chi*-square test was used to compare the categorical data. To identify factors associated with mortality, a multivariable logistic regression model was constructed using variables for which the *P*-value was ≤ 0.001 in univariable analysis. In order to appreciate the accuracy of independent risk factors as a prognostic marker, a receiver operating characteristic (ROC) curve was generated. A value of $P < 0.05$ was considered statistically significant.

Result

From May 2014 to April 2018, 1012 patients diagnosed with sepsis were admitted to the PICU in Shanghai Children's Hospital. Of these, 143 patients originated from abdominal infection who met the criteria were enrolled in this study, which included 85 male children and 58 female children with a median age 17 (6–72) months. A total of 126 patients survived, and 17 patients died. The mortality of sepsis of abdominal origin was 11% (17/143). The full data of patients' demographics and characteristics are detailed in **Table 1**.

Table 1. Demographic and clinical characteristics of patients enrolled in this study.

Characteristics	Survivor (n=126)	Non-survivor (n=17)	P
Age, month, median (IQR)	16(6-71)	31(12-86)	0.25
Male, n (%)	78(62)	7(41)	0.10
Weight, kg, median (IQR)	10.5(7.5-17.0)	13.0(6.5-17.0)	0.67
PRISM III, median (IQR)	5(3-10)	15(14-18)	<0.001*
The length of PICU stay, day, median (IQR)	7(4-10)	7(3-15)	0.75
Initial Number of Organ dysfunction, median (IQR)	2(0-3)	3(2-4)	0.001*
Cardiovascular, n (%)	60(48)	12(71)	0.08
Respiratory, n (%)	23(18)	6(35)	0.10
Renal, n (%)	14(11)	5(29)	0.04*
Neurologic, n (%)	7(6)	3(18)	0.07
Gastrointestinal, n (%)	55(44)	11(65)	0.10
Hepatic, n (%)	25(20)	6(35)	0.15
Hematologic, n (%)	51(41)	11(65)	0.06
Comorbidities			
Surgery, n (%)	26(21)	2(12)	0.39
Hematologic malignancy, n (%)	13(10)	7(41)	0.001*
Autoimmune disease, n (%)	9(7)	2(12)	0.50
Hereditary metabolic disease, n (%)	2(2)	1(6)	0.25
Adjuvant treatment			
CRRT, n (%)	29(23)	8(47)	0.03*
Mechanical ventilation, n (%)	34(27)	12(80)	<0.001*
Organ dysfunction indicator			
The grade of AGI, median (IQR)	2(1-2)	3(2-3)	<0.001*
TBIL, umol/L, median (IQR)	11.1(5.7-26.8)	9.1(5.0-47.1)	0.93
ALT, umol/L, median (IQR)	27(15-48)	66(24-231)	0.02*
ALB, g/L, mean±SD	35.5±6.7	35.8±6.6	0.88
BUN, mmol/L, median (IQR)	4.3(2.7-6.2)	4.3(3.7-9.5)	0.17
CREA, umol/L, median (IQR)	26(20-37)	31(20-46)	0.52
PT, s, median (IQR)	13.7(12.7-15.3)	15.0(12.6-15.8)	0.38

APTT, s, median (IQR)	39.6(33.0-47.4)	40.3(33.8-60.8)	0.36
FIB, g/L, median (IQR)	2.35(1.62-4.04)	2.14(1.17-2.45)	0.10
LAC, mmol/L, median (IQR)	1.7(1.2-3.1)	2.4(1.4-9.2)	0.07
PLT, 10 ⁹ /L, median (IQR)	270(122-409)	101(34-247)	0.02*
Glasgow coma scale score<8, n (%)	6(5)	4(24)	0.004*
Inflammatory mediators			
CRP, mg/L, mean±SD	77.0±58.3	92.6±74.6	0.32
PCT, ng/ml, median (IQR)	2.42(0.38-12.60)	8.28(0.77-30.00)	0.17
Major pathogen	n=56	n=6	
Gram-negative bacterium, n (%)	25(45)	5(83)	0.07
Escherichia coli	7	2	
Klebsiella pneumoniae	6	0	
Pseudomonas aeruginosa	5	2	
Others	7	1	
Gram-positive bacterium, n (%)	16(30)	1(17)	0.53
Staphylococcus aureus	6	0	
Enterococci	4	0	
Streptococcus pneumoniae	2	0	
Others	4	1	
Virus, n (%)	9(16)	0(0)	0.29
Rotavirus	4	0	
Norovirus	2	0	
EBV	3	0	
Fungus, n (%)	6(11)	0(0)	0.40
Candida albicans	6	0	

* p<0.05; AGI: acute gastrointestinal injury; TBIL: Total bilirubin; ALT: Alanine transaminase; ALB: Albumin; BUN: Urea nitrogen; CREA:

Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; Lac: Lactate; Plt: Platelet.

The characteristics of patients in the survivor group and the non-survivor group were similar in age, gender, weight, the length of PICU stay, the serum level of CRP and PCT, and major pathogen (all $P > 0.05$).

Microbiologic cultures were positive in 40% (57/143) of the patients with sepsis of abdominal origin, with a total of 62 microorganisms isolated. *Escherichia coli* was isolated most frequently among the Gram-negative isolates. *Staphylococcus aureus* was the most prevalent Gram-positive isolate.

Patients with hematologic malignancy, in this study, had higher PICU mortality ($P = 0.001$). Non-survivors had a higher PRISM III score ($P < 0.001$) and were more likely to have acute kidney injury on admission ($P = 0.04$). The rate of mechanical ventilation and CRRT was significantly higher in the non-survivor group compared with the survivor group (all $P < 0.05$).

The organ dysfunction indicators were compared between the survivors and non-survivors to evaluate the risk factor for the in-hospital mortality of patients with sepsis of abdominal origin. The grade of AGI, Glasgow coma scale score < 8 , the serum level of platelet, and alanine aminotransferase (ALT) were the risk factors for the PICU mortality (all $P < 0.05$).

Variables with a $P \leq 0.001$ were selected for a multivariate analysis using a stepwise logistic regression model. **Table 2** summarizes the results of the multivariate analysis. PRISM III score (RR 1.28, 95% CI: 1.11–1.48, P -value: 0.001) and the grade of AGI (RR 6.06, 95% CI: 1.65–22.25, P -value: 0.007) were the independent risk factors in the patients with sepsis of abdominal origin in PICU.

Table 2. Predictive capacity for PICU mortality of the selected variables in patients with sepsis of abdominal infection.

Variables	RR	95% CI	P
PRISM III	1.30	1.12-1.50	$<0.001^*$
Initial Number of Organ dysfunction	0.61	0.34-1.07	0.08
The grade of AGI	6.80	1.92-24.07	0.007*

* $p < 0.05$;

The ROC curves analysis was employed for the estimation of the predictive value of the PRISM III score, the initial number of organ dysfunction, and the grade of AGI (**Table 3** **Figure 1–3**). The results indicated that area under the curve (AUC) values of PRISM III score, initial number of organ dysfunction, and the grade of AGI were 0.91 (95% CI 0.86–0.96, $P < 0.001$), 0.74 (95% CI 0.63–0.85, $P = 0.001$), and 0.831 (95% CI 0.74–0.92, $P < 0.001$), respectively. The optimal cut-off level was determined as the value capable of maximizing the prognostic accuracy. The optimal cut-off of 10.5 for PRISM III score offered sensitivity of 94.1% and specificity of 66.2%. The optimal cut-off of 2.5 for the grade of AGI offered sensitivity of 70.6% and specificity of 81.0%.

Table 3. ROC analysis of PRISM III, the initial number of organ dysfunction, and the grade of AGI in the in-hospital mortality of patients with sepsis of abdominal origin.

Variables	AUC	95% CI	P	Cut-off	Sensitivity	Specificity
PRISM III	0.91	0.86-0.96	0.000*	10.5	94.1%	66.2%
Initial number of organ dysfunction	0.74	0.63-0.85	0.001*	1.5	88.2%	47.6%
The grade of AGI	0.83	0.74-0.92	0.000*	2.5	70.6%	81.0%

* $p < 0.05$;

We investigated the association between PRISM III score, the grade of AGI, and the 28-day survival rate in the patients with sepsis of abdominal origin in PICU by using the Kaplan-Meier method. The patients with a higher PRISM III score or the grade of AGI showed a shorter 28-day survival rate (**Figure 5**, $P < 0.001$ and **Figure 4**, $P < 0.05$). Therefore, elevated PRISM III score and a higher grade of AGI is associated with poor outcome of the patients with sepsis of abdominal origin.

Discussion

Abdominal is the common site of sepsis, and the mortality rate of patients with sepsis of abdominal origin is high. Therefore, it is urgently needed to identify predictors of mortality in patients with sepsis of abdominal origin. In the present study, we found that PRISM III score, the initial number of organ dysfunction, with hematologic malignancy, the grade of AGI, ALT, PLT, and GCS score < 8 were potential risk factors for the patients with sepsis of abdominal origin. Moreover, the higher PRISM III score and the grade of AGI were independent predictors for prognosis of pediatric patients with sepsis of abdominal origin. PRISM III score and the grade of AGI showed a good accuracy to predict the 28-day survival rate of pediatric patients with sepsis of abdominal origin.

In our study, the incidence of sepsis of abdominal origin in pediatric patients was 14% (143/1012), and the mortality rate was 11% (17/143). Similarly, in a study of 1051 pediatric patients from Colombian, the sepsis was of abdominal origin in 18.3% of the episodes, and the mortality rate was 18%[5]. In another study of the 7087 sepsis patients from 1265 ICUs in 75 countries, the abdominal contributed to 19.6% of sepsis with the ICU mortality of 29.4%[6].

Our study found that hematologic malignancy, acute kidney injury, the initial number of organ dysfunction, ALT, and PLT were the potential risk factors for increased mortality. Children with hematologic malignancy were at high risk of sepsis. Ruth et al.[11] reported that among patients with specific comorbidities, mortality was highest in patients with malignancies (22.4%), hematological or immunological disorders (20.3%). Higher intra-abdominal pressures may create a state of inadequate renal perfusion pressure, contributing to the development of acute kidney injury (AKI). Harris et al.[12] found that critically ill patients with AKI had higher mortality. Julie et al.[13] reported that sepsis of abdominal origin remained associated with both mild and severe AKI. The mortality in the present study also reflected the high rate of multiorgan dysfunction. Scott et al.[4] found that 67% of patients had MODS at sepsis recognition and relevant to the prognosis. Our study found that Gram-negative isolates were most frequently present in patients with sepsis of abdominal origin. Studies have found that endotoxin can cause mitochondrial dysfunction and ultrastructural damage of hepatocytes, resulting in a significant increase in ALT[14]. Thrombocytopenia is a well-known biomarker for disease severity in patients with sepsis and has been thought to result from platelet consumption and activation[15, 16].

The grade of AGI, suggesting poor gastrointestinal function and PRISM III score, might be considered an indicator of poor outcome. Our present study indicated that a higher grade of AGI (>2.5) and a higher PRISM III score (>10.5) were independently associated with an increased risk of PICU mortality. Consistently, Hu et al.[17] reported that the grade of AGI was positively correlated with the 28- and 60-day mortality ($P < 0.001$) and was independently associated with the 60-day mortality (HR 1.65, 95% CI 1.28–2.12; $P = 0.008$) among the 550 patients at 14 general intensive care units (ICUs). All these results suggested that the grade of AGI was useful for identifying the severity of gastrointestinal function and could be used as a predictor of sepsis of abdominal origin. In our study, ROC analysis indicated a strong predictive power for PRISM III (area under the curve = 0.91). Similarly, Bilan et al.[18] found that the PRISM III score had a strong predictive power (AUC = 0.898) and was well fit for the designed study (goodness-of-fit $P = 0.161$). In another study, PRISM III score (AUC=0.82, $P < 0.001$) and Lactate level (AUC = 0.79, $P < 0.001$) predicted mortality in 1109 critically ill children.

Our study has several limitations. First, This is a retrospective study with a limited number of patients from a single center. Second, long-term follow-up data was unavailable. If available, we would enable a more complete and robust analysis as to the risk of mortality in the future.

Conclusion

In summary, our study demonstrates that higher PRISM III score and the higher grade of AGI were independent risk factors of mortality in pediatric patients with sepsis of abdominal origin. PRISM III score and the grade of AGI may become an important clue for predicting prognosis in pediatric patients with sepsis of abdominal origin.

Abbreviations

PICU: pediatric intensive care unit

AGI: acute gastrointestinal injury

ALT: alanine aminotransferase

PLT: blood platelet

ROC: receiver-operating characteristic

AUC: the area under receiver-operating characteristic curve

PRISM III: Pediatric risk of mortality III

CI: confidence interval

MODS: multiple organ dysfunction syndrome

CRRT: continuous renal replacement therapy

CRP: C-reactive protein

PCT: procalcitonin

IQR: Inter-Quartile Range

TBIL: total bilirubin level

ALB: albumin

BUN: blood urea nitrogen

CREA: creatinine

PT: prothrombin time

APTT: activated partial thromboplastin time

FIB: fibrinogen

LAC: lactate

AKI: acute kidney injury

Declarations

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and its additional file).

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Contributors' Statement

YS and *JS* conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

TS, *YR*, and *GZ* collected data, carried out the initial analyses, and reviewed and revised the manuscript.

YZ and *YC* conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Children's Hospital (No. 2016R010-E02). Informed content was waived because of its retrospective design.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest relevant to this article to disclose.

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Figures

Figure 1

Receiver-operating characteristic curves for the prognosis of pediatric patients with sepsis of abdominal origin. The initial number of organ dysfunction is presented as a blue line and the reference value as a green line. Area Under the ROC Curve (AUC) is 0.74 (95% CI: 0.63–0.85, $P = 0.001$).

Figure 2

Receiver-operating characteristic curves for the prognosis of pediatric patients with sepsis of abdominal origin. PRISM III score is presented as a blue line and the reference value as a green line. Area Under the ROC Curve (AUC) is 0.91 (95% CI: 0.86–0.96, $P < 0.001$).

Figure 3

Receiver-operating characteristic curves for the prognosis of pediatric patients with sepsis of abdominal origin. The grade of AGI is presented as a blue line and the reference value as a green line. Area Under the ROC Curve (AUC) is 0.83 (95% CI: 0.74–0.92, $P < 0.001$).

Figure 4

The relationship between the grade of AGI and the 28-day survival rate of pediatric patients with sepsis of abdominal origin.

Figure 5

The relationship between PRISM III and the 28-day survival rate of pediatric patients with sepsis of abdominal origin.

Supplementary Files

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- [SepsisofabdomianloriginBMCPediatrics.xls](#)