Iran J Public Health, Vol. 45, No.7, Jul 2016, pp.875-884

Original Article

Development and Validation of a Disease Severity Scoring Model for Pediatric Sepsis

*Li HU [1], *Yimin ZHU [2], Mengshi CHEN [3], Xun LI [1], Xiulan LU [3], Ying LIANG [1], *Hongzhuan TAN [1]*

1. *School of Public Health, Central South University, Changsha, P. R. China*
2. *Institute of Emergency Medicine, People's Hospital of Hunan Province, Changsha, P. R. China*
3. *Pediatric Intensive Critical Unit, Children's Hospital of Hunan Province, Changsha, P. R. China*

***Corresponding Author:** Email: cszhuyimin@163.com

(Received 10 Sep 2015; accepted 24 Jan 2016)

Abstract

Background: Multiple severity scoring systems have been devised and evaluated in adult sepsis, but a simplified scoring model for pediatric sepsis has not yet been developed. This study aimed to develop and validate a new scoring model to stratify the severity of pediatric sepsis, thus assisting the treatment of sepsis in children.

Methods: Data from 634 consecutive patients who presented with sepsis at Children's hospital of Hunan province in China in 2011-2013 were analyzed, with 476 patients placed in training group and 158 patients in validation group. Stepwise discriminant analysis was used to develop the accurate discriminate model. A simplified scoring model was generated using weightings defined by the discriminate coefficients. The discriminant ability of the model was tested by receiver operating characteristic curves (ROC).

Results: The discriminant analysis showed that prothrombin time, D-dimer, total bilirubin, serum total protein, uric acid, PaO2/FiO2 ratio, myoglobin were associated with severity of sepsis. These seven variables were assigned with values of 4, 3, 3, 4, 3, 3, 3 respectively based on the standardized discriminant coefficients. Patients with higher scores had higher risk of severe sepsis. The areas under ROC (AROC) were 0.836 for accurate discriminate model, and 0.825 for simplified scoring model in validation group.

Conclusions: The proposed disease severity scoring model for pediatric sepsis showed adequate discriminatory capacity and sufficient accuracy, which has important clinical significance in evaluating the severity of pediatric sepsis and predicting its progress.

Keywords: Sepsis, Disease severity scoring model, Pediatrics, Discriminant analysis

Introduction

Sepsis is systemic inflammatory response syndrome (SIRS) resulting from a wide spectrum of infectious agents. This condition can further lead to severe sepsis and septic shock, and now it is the focus and challenge of critical care medicine (1,2). Recent data have shown that 18 million of new sepsis cases occur each year worldwide, with a high fatality rate of 30% (3, 4). The situation in children is even worse. Children especially infants are at high-risk of sepsis (5). They also have the highest fatality rate, especially those with severe sepsis (6, 7). Recent data suggests that sepsis and its induced septic shock and multiple organ dysfunctions (MODS) are among the leading causes of admission to intensive care units (ICUs) and it leads to an extremely high fatality rate in pediatric intensive care unit (PICU) (8,9).

The key to decrease the fatality rate of pediatric sepsis, especially severe sepsis, is early diagnosis, accurate assessment and timely treatment. However, the diagnosis of sepsis and evaluation of its severity only based on clinical signs and symptoms such as temperature, heart rate and respiratory rate is quite difficult, due to its untypical and diverse clinical signs as well as the complex and dynamic pathophysiologic process (10). Failure to recognize the severity of illness in the early course of disease may lead to inappropriate disposition or treatment. Therefore, it is of utmost importance to develop a clinical tool that is more accurate and objective than clinicians' experience to stratify severity of sepsis (11). In 2001, the North American and European sepsis definitions conference proposed the PIRO (predisposition, infection, response, organ dysfunction/failure) concept with the suggestion that sepsis could be stratified on the basis of easily measured biological indicators in a way similar to cancer, with the TNM (Tumor Node Metastasis) staging system (12).

In recent years, severity stratification scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHEII), Sequential Organ Failure Assessment (SOFA), Pediatric Risk of Mortality (PRISM) score have been applied to various septic populations (13,14). These scoring systems indeed played a part in assessing sepsis in children with relatively comprehensive parameters. However, they were computationally complex and devised either for adult patients or for general critical disease, and mainly focus on the prediction of survival or death (15,16), thus not suit for pediatric sepsis. Moreover, because of important differences between adults and children with respect to comorbidities, organ failure, and baseline mortality rate, efficacy from adults may not be generalized to children(5).

To our knowledge, scoring model established specifically for pediatric septic patients with high clinical application value has not yet been reported. The aim of this study was to develop a scoring model based on selected objective variables with high specificity and sensitivity, to aid severity assessment in children with sepsis.

Materials and methods

Study Population

Patients presenting with sepsis were retrospectively recruited from the PICU in Children's hospital of Hunan province between Mar 2011 and Mar 2013. This hospital is the only comprehensive children's hospital in this province, with 80 PICU beds and over 200 two-way referral hospitals. More than 80% of the serious children patients in Hunan province were admitted in this hospital. So, the patients in this hospital are highly representative of all serious children patients in Hunan province. Electronic management was implemented for all medical records in this hospital with complete and reliable information, which guaranteed the quality of data.

All selected patients met the pediatric-specific diagnostic criteria for sepsis established by the international pediatric sepsis consensus conference (17). In this study, mild sepsis refers to all sepsis except severe sepsis.

Patients who had been admitted for less than 24 h, and patients with important information such as age, gender and prognosis missing were excluded. To develop the scoring model, 75% of the patients were randomly assigned to the training group and the remaining 25% to the validation group, according to their admission number. We used the training group to establish the model, and the validation group to evaluate the model.

Data collection

The hospital electronic medical records for all patients were reviewed by specially trained doctors and eligible patients were selected according to the unified diagnostic criteria and exclusion criteria. Data were extracted anonymously using standardized data collection forms and database software.

The following information was collected: demographics, clinical and physiologic data, diagnosis data and prognosis data. In order to standardize data collection, clinical and physiologic data were taken as the worst value recorded during the first 24 h after admission. The independent variables considered for inclusion into the sepsis scoring model included demographic variables (age, gender) and vital signs (temperature, heart rate, systolic blood pressure etc.); infection related indicators (leukocyte platelet proealcitonin, C-reactive protein etc.); organ dysfunction related indicators (bilirubin, creatinine, total bilirubin, D-dimer, brain natriuretic peptide etc.). All variables were measured with international standard methods.

This study was approved by Xiangya Medical School Research Ethics Committee, Changsha, China. We didn't get written or verbal informed consent from participate or the next of kin, caretakers, or guardians on behalf of the minors/children since we have not access the patients. No any potential harm to the participants was apparent. To ensure anonymity, every participant was consecutively assigned an identification number, used for further analysis.

Statistical Analysis

Collection and analysis of data were performed with Epidata3.0 and SPSS 17.0. Regression estimation technique was used to impute the missing values (the proportion of data missing for individual variables was less than 5%). Results are presented as numbers with percentages in parentheses for categorical variables and mean (±SD) or median (quartiles) for continuous variables. Univariate analysis was used to select a subset of predictors associated with sepsis severity at P<0.1 level to be considered for inclusion in the multivariable scoring model. Statistical differences in quantitative data were determined using the Student's t-test. Variables with nonsymmetrical distributions were evaluated using the Mann-Whitney test. Pearson's chi-square test was used for qualitative data.

Continuous variables were categorized to binary or categorical indicators required for a clinically useful scoring system in sepsis. Multivariate analysis was performed by stepwise discriminant analysis to identify variables independently associated with the severity of sepsis (α=0.05, β=0.1). We established the accurate discriminate model based on the discriminant coefficients resulting from the stepwise discriminant analysis. The simplified scoring model was developed based on standardized canonical discriminant coefficients obtained from discriminant analysis, with the general rule of multiplying the coefficients by 10 and round off to the nearest integer.

To assess the accuracy of the models, we calculated the sensitivity (Sn) and specificity (Sp), and then constructed receiver operating characteristic (ROC) curves by plotting the Sn against (1-Sp) at different cutoff value. The discriminant performance of the scoring systems was assessed by the area under the ROC curve (AROC), with values close to 1.0 indicating high diagnostic accuracy. We determined the best cutoff value of the model according to the Youden index.

Results

Characteristics of Patients

During the 2-year study period, 687 patients admitted to PICU met the criteria of sepsis or severe sepsis, of whom 43 (6.3%) were excluded for less than 24 h of hospital stay. Another 10 (1.5%) children were excluded for incomplete information. 634 children were included in the final analysis, with a response rate of 92.3%.

Of the 634 patients, 231 (36.4%) had severe sepsis. 424 (66.9%) patients improved or recovered, 49 (7.7%) gave up treatment and were discharged, and 161(25.4%) patients died. The average age was 16.9 ± 24.4 months (range 1 month to 14 yr) and 65.3% were male. We randomly assigned all patients to the training group and validation group. The two groups had no statistical difference in gender, age, length of hospital stay, mechanical ventilation, blood culture; cause of sepsis and the proportion of patients with severe sepsis (Table 1). A total of 585 patients were included in the prognostic analysis due to 49 cases (7.7%) were abandoned or left hospital voluntarily with no available prognostic information. We compared the initial characteristic between the included 585 patients and the excluded 49 patients. Table 2 reveals that there were no statistic difference in sepsis severity and mean score between the two group (P>0.05), which indicated that our results resulted from the remained sample may be reliable.

Univariate analysis in the training group

Table 3 compares the characteristics and clinical variables of mild sepsis versus severe sepsis in the training group. Several clinical variables were strongly associated with severe sepsis in the univariate analysis, including D-dimer, heart rate, respiratory rate, platelets, potassium, capillary refill time, prothrombin time, PaO_2/FiO_2 ratio, base excess, blood lactate, total bilirubin, serum total protein, alanine aminotransferase, urea nitrogen, creatinine, uric acid, myoglobin, proealcitonin, brain natriuretic peptide, and troponin.

Discriminant analysis and discriminant model

The nineteen statistically significant factors identified by the univariate analysis were taken to Fisher stepwise discriminant analysis to construct a discriminant function (Table 4). As a result, seven variables were retained in the final discriminant model, including prothrombin time, D-dimer, PaO_2/FiO_2 ratio, total bilirubin, serum total protein, uric acid and myoglobin.

These results can be presented in the form of the following equation to establish the accurate discriminant model for severe sepsis:

Table 1: Clinical characteristics of patients in the training and validation groups*

Clinical parameter		Total (%)	Training group(N=476)	Validation group(N=158)	X²	*P* value
Gender	Male	414(65.3)	313(65.8)	101(63.9)	0.176	0.675
	Female	220(34.7)	163(34.2)	57(36.1)		
Age	1 month~	511(80.6)	380(79.8)	131(82.9)	0.846	0.655
	1 year~	90(14.2)	71(14.9)	19(12.0)		
	5-14 year	33(5.2)	25(5.3)	8(5.1)		
Length of PICU stay (days)	1-3	111(17.5)	76(16.0)	35(22.2)	3.156	0.206
	4-7	151(23.8)	116(24.4)	35(22.2)		
	>7	372(58.7)	284(59.6)	88(55.6)		
Mechanical ventilation	yes	295(46.5)	222(46.6)	73(46.2)	0.009	0.924
	no	339(53.5)	254(53.4)	85(53.8)		
Severe sepsis	yes	231(36.4)	172(36.1)	59(37.3)	0.075	0.785
	no	403(63.6)	304(63.9)	99(62.7)		

*Results are presented as numbers with percentages in parenthesis

Table 2: Characteristic of the included 585 patients and excluded 49 patients

Clinical parameter		Total (%)	Group A (N=585)	Group B (N=49)	X²/ t	*P* value
Severe sepsis	yes	403(63.6)	373(63.8)	30(61.2)	0.126	0.723
	no	231(36.4)	212(36.2)	19(38.8)		
Score group	0-7	198(31.2)	183(31.3)	15(30.6)	0.913	0.634
	8-15	239(37.7)	223(38.1)	16(32.7)		
	16-23	197(31.1)	179(30.6)	18(36.7)		
Mean score			11.52±6.13	12.00±6.18	-0.528	0.597

*Group A: 585 patients included in the prognostic analysis;
Group B: 49 patients excluded in the prognostic analysis due to lack of prognostic information

$Z=-7.312+0.702*X_{11}$ (total bilirubin) $+0.634*X_{15}$ (uric acid) $+0.680*X_6$ (D-dimer) $+0.934*X_{12}$ (serum total protein) $+0.795*X_5$ (prothrombin time) $+0.616*X_{16}$ (myoglobin) $+0.551*X_7$ (PaO_2/FiO_2 ratio).

The average discriminant function value for severe sepsis group was $Z_a=0.45$, and for mild sepsis group was $Z_b=0.92$, distinguishing value $Z_c=(Z_a+Z_b)/2=(0.45+0.92)/2=0.24$. Thus, $Z_i \geq 0.24$ was discriminated as severe sepsis, and $Zi < 0.24$ was discriminated as mild sepsis.

For convenience in clinical use, we generated a simplified score using weightings defined by the standardized discriminant coefficients of the model (multiplied by a constant and rounded to the nearest integer) (Table 5). The simple score ranges from 0 to 23 points.

Table 3: Univariate analysis of suspected factors of severe sepsis in training group (476 patients)

Variables	Mild sepsis (N=304)	Severe sepsis (N=172)	*P* value
Gender *			0.553
Male	203 (66.8)	110 (64.0)	
Female	101 (33.2)	62 (36.0)	
Age*			0.723
1 month~	241 (79.3)	139 (80.8)	
1 year~	48 (15.8)	23 (13.4)	
5 year~	15 (4.9)	10 (5.8)	
D - dimer*			0.000
positive	97 (31.9%)	109 (63.4%)	
negative	207 (68.1%)	63 (36.6%)	
Temperature (℃)†	38.5±1.0	38.4±1.3	0.668
HR (beats/min)†	153.7±24.4	161.2±31.8	0.008
Respiratory rate (breaths/min)†	44.2±12.3	47.8±13.8	0.004
Platelets (×10^9/l) †	347.4±184.2	270.7±180.8	0.000
Potassium (mmol/l)†	4.0±0.7	4.3±1.1	0.007
Systolic pressure (mmHg)	90(85-104)	89(82-105)	0.240
Capillary refill time(secs)	2 (1-5)	3 (2-10)	0.000
Leukocyte (×10^9/l)	12.9 (8.3-17.1)	12.8 (7.7-18.9)	0.686
PT(secs)	13.4 (12.4-14.3)	16.0 (13.7-20.4)	0.000
PaO_2/FiO_2 ratio	372 (250-444)	219 (332-400)	0.000
Base excess	-2.5 (-5.4-0.5)	-6.5 (-12.4~-1.0)	0.000
Blood lactate (mmol/l)	1.2 (0.9-1.9)	2.1(1.1-4.68)	0.000
PFG (mmol/l)	5.6 (4.6-6.7)	5.3 (4.1-7.0)	0.176
Sodium (mmol/l)	135 (133-138)	135 (131-138)	0.484
Total bilirubin (umol/l)	7.2 (5.1-11.5)	9.8 (6.5-18.3)	0.000
Serum total protein (g/l)	59.9 (54.9-65.3)	54.5 (46.9-60.0)	0.000
ALT (IU/L)	26.0 (17.2-41.7)	51.9 (28.0-137.3)	0.000
BUN (mmol/l)	3.6 (2.7-5.2)	6.5 (3.7-11.1)	0.000
Cr (umol/l)	27.4 (21.4-34.1)	40.5 (26.3-85.5)	0.000
Uric acid (umol/l)	194 (120-286)	304.5 (132-570)	0.000
Myoglobin (μg/l)	55.7 (22.0-107.3)	152.5 (49.4-774.4)	0.000
PCT (ng/ml)	0.70 (0.16-3.50)	6.17 (1.04-59.87)	0.000
BNP(pmol/l)	734 (281-2404)	7723 (1335-21379)	0.000
CRP(mg/l)	11.1 (2.3-38.1)	13.7 (2.31-51.5)	0.288
Troponin (ng/ml)	0.015 (0.004-0.075)	0.043 (0.004-0.28)	0.007

*Binary and categorical data are presented as *n* and percentages of totals, using the Pearson's chi-square test/† Normally distributed data are presented as mean (±SD), using Student's *t*-test/ Other nonsymmetrical distributed continuous data are presented as medians and 25th to 75th percentile ranges, using Mann-Whitney test/HR: Heart rate; ALT: alanine aminotransferase; PT: prothrombin time; PFG: fasting plasma glucose (FPG); BUN: Urea nitrogen; Cr: Creatinine; PCT: proealcitonin; BNP: Brain natriuretic peptide; CRP: C-reactive protein

Table 4: Evaluation of the categorical variable*

Variables		value
X_1	Heart rate	Normal =1, Abnormal =2
X_2	Respiratory rate	Normal =1, Abnormal =2
X_3	CRT(s)	≤2 =1, >3 =2
X_4	Platelet count (×10^9/L)	≤400 =1, >400 =2
X_5	PT(S)	≤14 =1, >14 =2
X_6	D-dimer	negative =1 positive =2
X_7	PaO_2/FiO_2 ratio	≥300 =1, <300 =2
X_8	Base excess	-3 ~ +3 =1, <-3 or >+3 =2
X_9	Lactate (mmol/L)	≤1.5 =1, >1.5 =2
X_{10}	Potassium (mmol/L)	3.5~5.5 =1, <3.5 or >5.5 =2
X_{11}	Total bilirubin (umol/l)	≤6 =1, >6 =2
X_{12}	Serum total protein (g/l)	≥35 =1, <35 =2
X_{13}	ALT(IU/L)	≤40 =1, >40 =2
X_{14}	Cr (umol/l)	20~120 =1, <20或>120 =2
X_{15}	Uric acid (umol/l)	90~350 =1, <90或>350 =2
X_{16}	Myoglobin (μg/L)	≤90 =1, >90 =2
X_{17}	PCT(ng/ml)	≤0.05 =1, >0.05 =2
X_{18}	BNP(pmol/L)	≤236 =1, >236 =2
X_{19}	Troponin (ng/ml)	≤0.15 =1, >0.15 =2
Y	Severe sepsis	Yes =1, No =2

*: All variables were defined by diagnostic criteria.

Table 5: Simplified scoring model developed based on the accurate discriminate model

Variables	Coefficient*	Score value†	
PT(S)	0.367	≤14 =0	>14 =4
D-dimer	0.318	negative =0	positive =3
PaO_2/FiO_2 ratio	0.270	≥300 =0	<300 =3
Total bilirubin (umol/l)	0.312	≤6 =0	>6 =3
Serum total protein(g/l)	0.450	≥35=0	<35 =4
Uric acid (umol/l)	0.295	90~350 =0	<90 or >350 =3
Myoglobin (µg/L)	0.287	≤90 =0	>90 =3

*Coefficient: standardized canonical discriminant coefficients
† The score is 0 if the variable is normal; for abnormal variables, the score equals to the coefficients multiplied by 10 and rounded to the nearest integer.

The performance of the discriminant model in discriminating mild sepsis and severe sepsis was estimated both in the training sample and validation sample using ROC curves. The AROCs (Fig.1A) of accurate discriminate model were 0.816 (95% CI 0.771 to 0.861) in the training group and 0.836 (95%CI 0.765 to 0.907) in the validation group. For simplified scoring model, the AROC remained relatively high with AROC 0.800 (95%CI: 0.753~0.846) in the training set and 0.825 (95%CI: 0.750~0.899) in the validation set (Fig.1B). Such large areas are generally acknowledged to be of excellent discrimination.

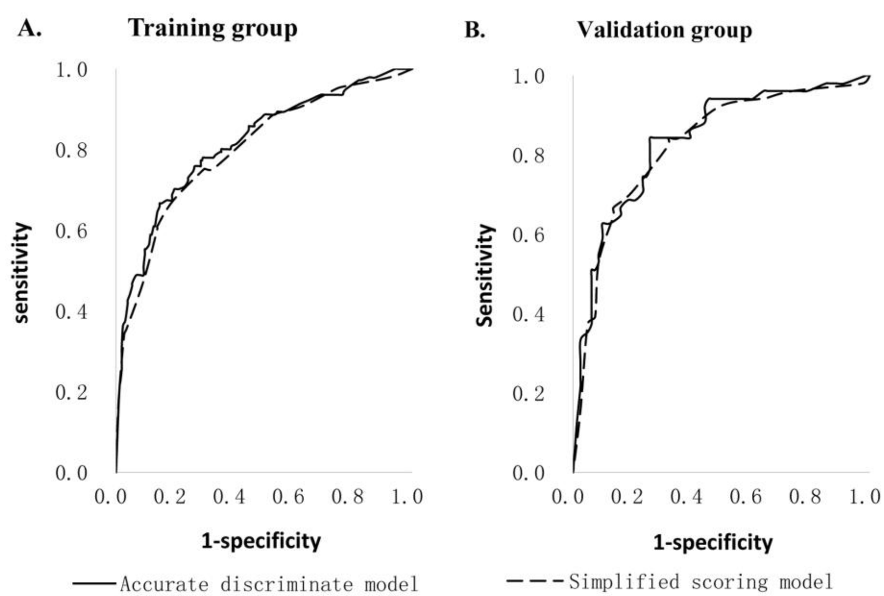

Fig.1 Receiver Operator Characteristic (ROC) curves for the accurate discriminate model and simplified scoring model in the training (A) and validation (B) groups.

Correlations of the score with sepsis severity and prognosis

We calculate the severity scores for each of the study subjects. These scores ranged from 0 to 23, with a mean (±SD) value of 11.6 (±6.2). Table 6 shows the prevalence of severe sepsis and fatality rate with each level of scores. As the score rises, the proportion of severe sepsis and the fatality rate increases significantly, and the percentage of improved or recovered decreases significantly (trend Chi-square tests P<0.05).

Table 6: Prevalence of severe sepsis and prognosis in total patients according to summed score *

Score Group	Total	Severe sepsis (%)	Death (%)	Improved or recovered (%)
0-7	198	24（12.1）	21（10.6）	162（81.8）
8-15	239	69（28.9）	48（20.1）	175（73.2）
16-23	197	138（70.1）	92（46.7）	87（20.5）
Trend test P		0.000	0.000	

*A total of 585 patients were included in the prognostic analysis due to 49 cases (7.7%) were abandoned or left hospital voluntarily with no available prognostic information.

Discussion

Sepsis is a severe condition triggered by systemic inflammation in response to infection (18), which remains one of the common critical illnesses encountered in the PICU. It is very complicated for clinicians to diagnose and assess pediatric sepsis due to its untypical symptoms, rapidly development and dynamic pathophysiological process (19,20). Thus, practical clinical scoring models with few indicators are urgently required in pediatric critical medical care to assess patients' condition (21). This study specially designed to stratify severity of sepsis for pediatric patients, using a score based on seven variables drawn from patient clinical findings and laboratory examinations.

Advances in statistical methods have supplied the tools necessary to model complex relationships among many variables relevant to outcomes. In this study we used discriminate analysis to develop our model. Other alternatives would have been the use of synthetic evaluation model, for example hierarchy method and Delphi method (22). However, those methods always select indicators subjectively or need other auxiliary methods to select indicators objectively. Besides, specialists were required to participate in and reach a high agreement coefficient to obtain reliable results. Therefore, the availability and comprehensiveness of discriminant analysis and the simplicity of presenting the results as simple scores have conducted us to this election. Discriminant analysis is a classification statistical method using the known categories of sample to establish the discriminant model. The unknown sample was then identified by the established model. The stepwise discriminant analysis is the ideal statistical method for our analysis by using fewer indicators to achieve stable discriminant effect (23). Receiver-operating curve (ROC) analysis has been used to determine the performance of a model in many studies (24). All of these ensure that our results are scientific and reliable.

In our study based on 634 patients, we selected 27 variables, which are readily available in most of the institutions and closely related with various systems of the body. Nineteen of them entered into discriminant analysis by univariate analysis, and 7 were retained in the final model. Most of the severity indicators found in our study are in concordance with previous study (25-27). Other indicators, such as C-reactive protein, tumor necrosis factor and procalcitonin, have been reported as potential biochemical markers of infection (28-30), however have not been shown to be associated with severity of pediatric sepsis in our study. One explanation may be that only children diagnosed with sepsis were included in this study, so the biochemical markers of infection cannot be used to distinguish the severity of infected children.

The present scoring models were derived from readily available clinical variables. These variables and their coefficients are different from the widely used but complicated scoring systems such as APACHEII, SOFA, and PRISM score (15,16). This difference may be related to our specific research objects, which fully shows the rationality and uniqueness of our model in assessing severity of sepsis in children.

Previous studies have attempted to derive clinical scores as a tool to identify seriously ill sepsis patients; however, most of them looked at factors which may be predictive of fatality (4,31). Shapiro et al. (32) firstly derived and validated the Mortality in Emergency Department Sepsis (MEDS) score to address the need for an early risk stratification tool for sepsis in adult patients. The score was based on nine variables drawn from patient profile, clinical findings, and initial laboratory examination. The performance of the MEDS score has been validated in various populations to predict the 28-d fatality rate, with AROC 0.76 to 0.82 (33,34). Then Corinne Alberti et al. developed a Risk of Infection to Severe Sepsis and Shock Score (RISSC) to estimate the risk of worsening sepsis in critically ill patients with infection (35). The score included 12 variables such as temperature, heart rate, platelets, which are subsequently simplified into four subclasses of risk. Unfortunately, scores in the above studies were devised based on adult groups whose average age were over 60 yr old, which were not suitable for assessment of disease severity in pediatric population. Yet there are some scoring systems for mortality prediction in pediatric sepsis have been developed in recent past. Okascharoen et al. (36) constructed and validated a prediction-scoring model for late-onset neonatal sepsis from clinical, laboratory, and management variables in a retrospective cohort. The validity of this score was good with AROCs from 0.80 to 0.85, but its practical application only suits for neonates. Wong et al. (37) derived a pediatric sepsis biomarker risk model using 12 gene probes associated with outcome in children with septic shock with an AROC 0.811. However, it only suits for sepsis shock children and has technical limitation for widely clinical application.

In the present study, we evaluated the accurate discriminate model with training sample and validation sample, which showed a good discriminatory performance in assessing the severity of sepsis (AROC 0.815 to 0.836). It was similar to the clinical value of prediction-scoring model for late-onset neonatal sepsis and pediatric sepsis biomarker risk model (36), better than the PRISM reported by De Araujo Costa et al (38) and APACHE score in assessing critical illness of children reported by Ana Lilia et al. (14).

Besides, our discriminant model only includes seven variables. It can be applied easily by clinicians with simple calculation procedures installed on their personal computers. For those inconvenient to use a computer, the accurate discriminate model is not convenient. In order to enhance availability, we provide a more convenient simplified scoring model with similar clinical discriminant effect (AUROC:0.800 ~ 0.825).The simplified scoring model was superior to the MEWS, SCS and REMS in predicting septic fatality reported by Ghanem-Zoub (39), and also better than the SOFA and CIS score reported by Shigeto Oda (13).

In addition, we provided the risk estimation of severe sepsis and fatality according to the summed score, which is not only of diagnosis value but also of clinical predictive value.

Although we used scientific statistical methods to develop and verify the model, some limitations should be noted. Firstly, the performance of the model can be optimized with more predictable factors included. In our analysis, not all variables that might be considered for inclusion into a severity score of sepsis were obtained. For example, we had no information on nervous system (Data regarding GSW were only available in 67 patients.), cytokines levels or patients' genetic predisposition in our population. However, examination of such indicators is costly and currently limited to few centers throughout the world. Different etiologies may confer different severity and prognoses but the underlying etiology is often unknown until relatively late in the course of hospitalization. Factors that account for the accuracy of the model also contribute to its complexity, and sophisticated parameters are not uniformly obtained in resource-limited settings. Accordingly, we intended to create a clinical tool based on commonly available clinical variables. All of these additional diagnostic tests merit further evaluation and incorporating such variables into a sepsis risk score might be feasible in a not-too-distant future. Secondly, our study was conducted at single center in Chinese population and may not be representative of all the PICUs worldwide. Thirdly, 49 patients exclusion from the prognostic analysis might have introduced a bias in this study. Therefore, more, larger and further prospective studies are necessarily needed.

Conclusion

An accurate discriminate model and simplified scoring model proposed in this study are new, applicable tools for severity assessment in pediatric sepsis patients. Using generally available indicators, clinicians can easily stratify the disease severity and predict the risk of severe sepsis in septic children, which are very important in guiding treatment and improving outcomes. We propose that this severity-scoring model should be further evaluated for severity stratification and mortality prediction in larger prospective study as well as in other ethnic groups.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication, and/ or falsification, double publication and/ or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

The authors thank the medical staff and all participants who made the effort to this study. This study was funded by the grants from the China Hunan Provincial Science & Technology Department (grant 2013SK3218). The authors declare that there is no conflict of interests.

References

1. Fry DE (2012). Sepsis, systemic inflammatory response, and multiple organ dysfunction: the mystery continues. *Am Surg,* 78(1): 1-8.
2. Booker E (2011). Sepsis, severe sepsis, and septic shock: current evidence for emergency department management. *Emerg Med Pract,* 13(5): 1-22, 22-23.
3. Jawad I, Luksic I, Rafnsson SB (2012). Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. *J Glob Health,* 2(1): 010404.
4. Wong HR, Weiss SL, Giuliano JJ, Wainwright MS, Cvijanovich NZ, Thomas NJ, et al. (2014). Testing the prognostic accuracy of the updated pediatric sepsis biomarker risk model. *PLoS One,* 9(1): e86242.
5. Wheeler DS, Jeffries HE, Zimmerman JJ, Wong HR, Carcillo JA (2011). Sepsis in the pediatric cardiac intensive care unit. *World J Pediatr Congenit Heart Surg,* 2(3): 393-399.
6. Wiens MO, Kumbakumba E, Kissoon N, Ansermino JM, Ndamira A, Larson CP (2012). Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. *Clin Epidemiol,* 4: 319-325.
7. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG et al. (2010). Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet,* 375(9730): 1969-1987.
8. Riley C, Wheeler DS (2012). Prevention of sepsis in children: a new paradigm for public policy. *Crit Care Res Pract,* 2012: 437139.
9. Edmond K, Zaidi A (2010). New approaches to preventing, diagnosing, and treating neonatal sepsis. *PLoS Med,* 7(3): e1000213.
10. Wong HR, Weiss SL, Giuliano JJ, Wainwright MS, Cvijanovich NZ, Thomas NJ, et al. (2014). The temporal version of the pediatric sepsis biomarker risk model. *PLoS One,* 9(3): e92121.
11. Vincent J, de Carvalho FB (2010). Severity of illness. *Semin Respir Crit Care Med,* 31(1): 31-38.
12. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI (2011). Proof of principle: the predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med,* 39(2): 322-327.
13. Oda S, Hirasawa H, Sugai T, et al (2006). Comparison of sepsis-related Organ Failure Assessment(SOFA) score and CIS(cellular injury score) for scoring of severity for patients with multiple organ dysfuction syndrome(MODS). *Intensive Care Med,* 26(12): 1786-1793.
14. De Leon AL, Romero-Gutierrez G, Valenzuela CA, Gonzalez-Bravo FE (2005). Simplified PRISM III score and outcome in the pediatric intensive care unit. *Pediatr Int,* 47(1): 80-83.
15. Le Gall J (2001). Modeling the severity of illness of ICU patients. *Eur J Intern Med,* 12(4): 321.
16. Moreno RP, Diogo AC, Afonso S (2009). Risk stratification in severe sepsis: organ failure scores or

PIRO? In *Management of sepsis: the PIRO Approach*. Eds, Jordi Rello, Emilio DiazandAlejandro Rodriguez. New York: Spinger,pp.1-9.
17. Goldstein B, Giroir B, Randolph A (2005). International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med,* 6(1): 2-8.
18. Levy MM, Fink MP, Marshall JC, et al (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med,* 31(4): 1250-1256.
19. Haeusler GM, Slavin MA (2012). Complications of sepsis: the role of risk prediction rules, biomarkers and host genetics. *Expert Rev Anti Infect Ther,* 10(7): 733-735.
20. Anderson IB, Sudhakar S, Keenan CR, Srinivasan M (2013). The elusive SIRS diagnosis. *J Gen Intern Med,* 28(3): 470-474.
21. Remington JS, Klein JO, Wilson CB, et al (2006). Infectious diseases of the fetus and newborn infant. *N Engl J Med,* 355: 531-532.
22. Tan H, Ping W, Yang T, Li S, Liu A, Zhou J, et al. (2007). The synthetic evaluation model for analysis of flooding hazards. *Eur J Public Health,* 17(2): 206-210.
23. Chen Z, Li Y, Tong Y, Gao Q, Mao X, Zhang W, et al. (2016). Stepwise discriminant function analysis for rapid identification of acute promyelocytic leukemia from acute myeloid leukemia with multiparameter flow cytometry. *Int J Hematol,* 103(3): 306-315.
24. Huang P, Tan H, Liu A, Feng S, Chen M (2010). Prediction of posttraumatic stress distorder among adults in flood district. *BMC Public Health,* 10(1): 207.
25. Pierrakos C, Vincent JL (2010). Sepsis biomarkers: a review. *Crit Care,* 14(1): R15.
26. Standage SW, Wong HR (2011). Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti Infect Ther,* 9(1): 71-79.
27. Meem M, Modak JK, Mortuza R, Morshed M, Islam MS, Saha SK (2011). Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a point-of-care diagnostics. *J Glob Health,* 1(2): 201-209.
28. Lee SH, Chan RC, Wu JY, Chen HW, Chang SS, Lee CC (2013). Diagnostic value of procalcitonin for bacterial infection in elderly patients - a systemic review and meta-analysis. *Int J Clin Pract,* 67(12): 1350-1357.
29. Tian Y, Tao T, Zhu J, Zou Y, Wang J, Li J, et al. (2013). Soluble tumor necrosis factor related apoptosis inducing ligand level as a predictor of severity of sepsis and the risk of mortality in septic patients. *PLoS One,* 8(12): e82204.
30. Yang SK, Xiao L, Zhang H, Xu XX, Song PA, Liu FY, et al. (2014). Significance of serum procalcitonin as biomarker for detection of bacterial peritonitis: a systematic review and meta-analysis. *BMC Infect Dis,* 14: 452.
31. Ratzinger F, Schuardt M, Eichbichler K, Tsirkinidou I, Bauer M, Haslacher H, et al. (2013). Utility of sepsis biomarkers and the infection probability score to discriminate sepsis and systemic inflammatory response syndrome in standard care patients. *PLoS One,* 8(12): e82946.
32. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW (2003). Mortality in Emergency Department Sepsis (MEDS) score: a prospectively derived and validated clinical prediction rule. *Crit Care Med,* 31(3): 670-675.
33. Carpenter CR, Keim SM, Upadhye S, Nguyen HB et al (2009). Risk stratification of the potentially septic patient in the emergency department: the Mortality in the Emergency Department Sepsis (MEDS) score. *J Emerg Med,* 37(3): 319-327.
34. Jones AE,Saak K,Kline JA (2008). Performance of the mortality in emergency department sepsis score for predicting hospital mortality among patients with severe sepsis and septic shock. *Am J Emerg Med,* 26(6): 689-692.
35. Alberti C, Brun-Buisson C, Chevret S, Antonelli M, Goodman SV, Martin C, et al. (2005). Systemic inflammatory response and progression to severe sepsis in critically ill infected patients. *Am J Respir Crit Care Med,* 171(5): 461-468.
36. Okascharoen C, Sirinavin S, Thakkinstian A, Kitayaporn D, Supapanachart S (2005). A bedside prediction-scoring model for late-onset neonatal sepsis. *J Perinatol,* 25(12): 778-783.
37. Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, et al. (2012). The pediatric sepsis biomarker risk model. *Crit Care,* 16(5): R174.
38. Costa GA, Delgado AF, Ferraro A, Okay TS (2010). Application of the pediatric risk of mortality (PRISM) score and determination of mortality risk factors in a tertiary pediatric intensive care unit. *Clinics (Sao Paulo),* 65(11): 1087-1092.
39. Ghanem-Zoubi NO, Vardi M, Laor A, Weber G, Bitterman H (2011). Assessment of disease-severity scoring systems for patients with sepsis in general internal medicine departments. *Crit Care,* 15(2): R95.