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ORIGINAL PAPER

PERFORMANCE OF SOFA SCORE IN PREDICTING THE RISK OF MORTALITY IN CHILDREN WITH SEPSIS

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Abstract

Introduction. Sepsis is a complex clinical condition and a leading cause of death in children. The Sequential Organ Failure Assessment (SOFA) score is a useful tool to assess the risk of death in patients with sepsis.
The objective of the study was to determine the usefulness of the SOFA score in predicting mortality in children with sepsis.
Materials and methods. A cross-sectional descriptive study was conducted on 90 children, aged 2 months to 15 years, diagnosed with sepsis at Can Tho Children's Hospital (Vietnam) between March 2018 and June 2020. The statistical analysis was carried out using the Chi-square test ($\chi 2$) and non-parametric tests. A p-value < 0.05 was considered statistically significant. The predictive ability of the SOFA score was evaluated using the area under the ROC curve (AUROC).
Results. Of the 90 children in the study, 35 (38.9%) died, and 55 (61.1%) survived. The mean SOFA score was 9.8±2.9 in the group of patients who died and 4.9±2.7 in the group of patients who survived (p = 0.001). Using an 8-point cutoff, the area under the curve (AUC) was 0.904 (p = 0.001, 95% CI:0.83-0.97). The SOFA score had a sensitivity of 88.6% and specificity of 87.3%, while the positive predictive value and

Résumé

La performance du score SOFA dans la prévision du risque de mortalité chez les enfants atteints de sepsis

Introduction. La septicémie est une maladie clinique complexe et l'une des principales causes de décès chez les enfants. Le score SOFA (Sequential Organ Failure Assessment) est un outil utile pour évaluer le risque de décès chez les patients atteints de septicémie.
L'objectif de l'étude était de déterminer l'utilité du score SOFA pour prédire la mortalité chez les enfants atteints de septicémie.
Matériels et méthodes. Une étude descriptive transversale a été réalisée sur 90 enfants, âgés de 2 mois à 15 ans, diagnostiqués avec une septicémie à l'Hôpital pour Enfants de Can Tho (Vietnam), entre mars 2018 et juin 2020. L'analyse statistique a été réalisée à l'aide du test du Chi Square ($\chi 2$) et tests non paramétriques. Une valeur de p < 0,05 était considérée comme statistiquement significative. La capacité prédictive du score SOFA a été évaluée à l'aide de l'aire sous la courbe ROC (AUROC).
Résultats. Sur les 90 enfants de l'étude, 35 (38,9%) sont décédés et 55 (61,1%) ont survécu. Le score SOFA moyen était de 9,8±2,9 dans le groupe des patients décédés et de 4,9±2,7 dans le groupe des patients

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negative predictive value were 81.6% and 92.3%, respectively.

Conclusions. The SOFA score has a high sensitivity and specificity in predicting mortality among sepsis patients when using an 8-point cutoff.

Keywords: sepsis, septic shock, SOFA score, children.

List of abbreviations

SOFA = Sequential Organ Failure Assessment
SIRS = systemic inflammatory response syndrome
CBC = complete blood count
CRP = C-reactive protein
SGPT = serum glutamic pyruvic transaminase
INR = international normalized ratio

survivants (p = 0,001). En utilisant un seuil de 8 points, l'aire sous la courbe (ASC) était de 0,904 (p = 0,001, 95%CI: 0,83-0,97). Le score SOFA avait une sensibilité de 88,6 % et une spécificité de 87,3 %, tandis que la valeur prédictive positive et la valeur prédictive négative étaient respectivement de 81,6% et 92,3%.

Conclusions. Le score SOFA a une sensibilité et une spécificité élevées pour prédire la mortalité chez les patients atteints de septicémie lors de l'utilisation d'un seuil de 8 points.

Mots-clés: septicémie, choc septique, score SOFA, enfants

Introduction

Sepsis is a severe clinical condition and the leading cause of death among children[1]. Globally, 1.2 million cases of childhood sepsis occur each year[2]. The mortality rate attributed to sepsis in children remains high across various countries in the world, including the US (14.4%)[3], Pakistan (24.0%)[4], China (34.6%)[5], and Thailand (49.7%)[6]. In addition, the diagnosis of sepsis is far more challenging as the significant physiologic reserve of children frequently masks the disease[7]. Therefore, early detection and active management are the key to improve the prognosis in children. There are many tools to assess the risk of death in patients with sepsis such as Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS), Acute Physiology, Age and Chronic Health Evaluation (APACHE II), The predisposition, infection (or insult), response and organ dysfunction (PIRO), Mortality Probability Models (MPM-0), etc. Among these, the SOFA score has been identified as an effective tool for predicting the risk of mortality in adult patients with sepsis[8] , and is widely used in current clinical practice[9].

Due to significant differences in the signs/symptoms and responses to treatment in sepsis between children and adults, there is a need for distinct diagnostic and treatment approaches.[10]. However, research on the application of SOFA in children is limited, with most studies focusing on the adult population.

The objective of our study was to evaluate the utility of SOFA score in predicting mortality in pediatric patients with sepsis.

Material and methods

We performed a cross-sectional descriptive study on 90 patients with sepsis, aged between 2 months to 15 years, who were admitted in the Intensive Care Unit of Can Tho Children's Hospital (Vietnam) from March 2018 to June 2020.

The inclusion criteria were based on the 2012 Surviving Sepsis Campaign diagnostic criteria for sepsis[7]. The patients meeting both criteria, those diagnosed with systemic inflammatory response syndrome (SIRS) and with clinical or subclinical evidence of infection, were included in the study. The patients with chronic organ failure prior to the diagnosis of sepsis, brain injury, prolonged corticosteroid use, coagulopathy, hematologic diseases causing leukocytosis or leukopenia such as acute leukemia or myelosuppression, were excluded from the study.

Sample size

The required sample size for the study was estimated to be 87 participants, based on the Cochran formula (equation (1)), with a $Z_{1-\alpha/2}$ value of 1.96, a confidence coefficient of 0.95, a d-value of 0.09, and a probability of type I error of 9%. The percentage of sepsis-related deaths (p) in children was set at 0.24, based on data from a previous study[4]. In this study, a total of 90 patients were included.

$$n = Z^2_{1-\alpha/2} \times \frac{p(1-p)}{d^2} \qquad (1)$$

Data collection

The participants data, including patient characteristics, clinical characteristics, laboratory parameters, SOFA score and treatment outcome, were collected.

The patients' characteristics included age (2-11 months, 12-59 months, >5 years old), sex (male, female), risk factors for death – including malnutrition or previous hospitalization (yes/no).

The clinical characteristics comprised the Glasgow score (≤10 points and >10 points), pulse

(normal, fast or low), blood pressure (normal, reduced), respiratory rate (normal, tachypnea), temperature (<36, 36-38.5, >38.5^{0}C), focal infection (respiratory, gastroenterology, skin, others) and sepsis stage (sepsis, severe sepsis and sepsis shock)[7].

The laboratory data consisted in complete blood count (CBC) (hemoglobin (≤10 g/dL, >10 g/dL), hematocrit (Hct) (≤30% and >30%), white blood cells (<4.000, 4.000-12.000, >12.000/mm^3), platelets (<150.000, 150.000-400.000, >400.000); C-reactive protein (CRP) (<10, 10-40 and >40 mg/L), procalcitonin (0.5, 0.5-2, >2 ng/mL), creatinine (normal, increased >1.5mg/dL in children <36 months, >2 mg/dL in children ≥36 months), serum glutamic pyruvic transaminase (SGPT), blood lactate (≤2.2, >2.2 mmol/L), international normalized ratio (INR) (<1.5 or ≥1.5), blood culture and Gram stain.

Statistical Analysis

Data was coded and analyzed using SPSS for Windows version 18 (IBM Corp., Chicago, Ill, USA). Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as mean and standard deviation if normally distributed or median (minimum and maximum) if not normally distributed. Data was analyzed using $\chi 2$ and non-parametric tests (Mann-Whitney U-test and Wilcoxon-test). All tests were 2 tailed and a p-value <0.05 was considered statistically significant. The area under the ROC curve (AUROC) was used to evaluate the predictive ability of the SOFA score. The optimal cutoff was taken when AUROC was >80%. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

The study was approved by the Scientific Council of Can Tho University of Medicine and Pharmacy (approval number 733/March 2018).

Results

A total of 90 patients were included in the study. The patients' characteristics are presented in Table 1.

Most patients with sepsis included in the study were under 5 years old (n=71; 78.9%). There were 33 patients with risk factors of sepsis, accounting for 36.7%. The patients <5 years old, as well as those with baseline sepsis risk factors, had a higher mortality rate, but this difference was not statistically significant (p > 0.05).

When analyzing clinical and paraclinical characteristics (Table 2), most patients did not exhibit signs of mental disturbance and had normal systolic blood pressure, while changes in temperature and respiratory rate were common. Statistical analysis revealed a significant difference in the risk of death between the groups of children with and without mental disorders (p = 0.001), with the risk of death being 18 times higher in those with mental disorders. Septic shock was identified in 70% of cases. The rate of recovery was the highest in the sepsis group, gradually decreasing in the severe sepsis and septic shock groups. This difference was also found to be statistically significant (p = 0.015). Laboratory data showed an increased white blood cell count in 50% of patients. Blood lactate was elevated in 51 patients (66.2%). Patients with INR >1.5 had a higher risk of death, statistically significant (p = 0.008). The risk of death increased with the rise in blood lactate or SGPT, but these results were not statistically significant (p=0.240). Blood cultures were positive in 17.8% patients (Table 3).

35 children (38.9%) died, of whom 6 patients died within 24 hours after treatment initiation. Septic shock was identified as the cause of death in 30 patients. During treatment, 72 children required at least one inotropic medication, of whom 13 patients (18.1%) needed the use of four inotropic drugs. The inotropic drugs used in the 72 children were

Table 1. Characteristics of the study group (n=90)

Patient characteristics		*n (%)*	*Dead (n=35)*	*Alive (n=55)*	*Odds Ratio, p-value*
Age at hospital admission	2-11 months	35 (38.9%)	16 (45.7%)	19 (54.3%)	0.540
	12-59 months	36 (40%)	13 (36.1%)	23 (63.9%)	
	5-15 years old	19 (21.1%)	6 (31.6%)	13 (68.4%)	
Sex	Male	52 (57.8%)	21 (40.4%)	31 (59.6%)	1.2, 0.700
	Female	38 (42.2%)	14 (36.8%)	24 (63.2%)	
Hospital presentation type	Self-presentation	85 (94.4%)	3 (60%)	2 (40%)	2.5, 0.370
	Hospital transfer	5 (5.6%)	32 (37.6%)	53 (62.4%)	
Risk factors for death	Yes	33 (36.7%)	17 (51.5%)	16 (48.5%)	2.3, 0.060
	No	57 (63.3%)	18 (31.6%)	39 (68.4%)	

Table 2. Associations between clinical, laboratory data and mortality in children with sepsis (n=90).

Clinical and paraclinical features			*n (%)*	*Mean ± SD/ Median (min-max)*	*Death (n=35)*	*Survival (n=55)*	*p-value*
concious level and vital signs	Glasgow	≤10 points	21 (23.3%)		18 (85.7%)	3 (14.3%)	0.001*
		>10 points	69 (76.7%)		17 (24.6%)	52 (75.4%)	
	Pulse (betas/ minute)	Normal	40 (44.4%)				
		Fast or slow	50 (55.6%)				
	Systolic blood pressure (mmHg)	Normal	68 (75.6%)				
		Hypotension	22 (24.4%)				
	Temperature (°C)	<36	1 (1.1%)				
		36-38.5	14 (15,6%)				
		>38.5	75 (83.3%)				
	Breathing rate (respirations/ minute)	Normal	4 (4.4%)				
		Tachypnea	86 (95.6%)				
Starting point of infection		Respiratory	47 (52.2%)		21 (44.7%)	26 (55.3%)	0.400*
		Digestive	29 (32.2%)		11 (37.9%)	18 (62.1%)	
		Skin	7 (7.8%)		1 (14.3%)	6 (85.7%)	
		Other	7 (7.8%)		2 (28.6%)	5 (71.4%)	
Sepsis stages		Sepsis	8 (8.9%)		0 (0%)	8 (100%)	0.015*
		Severe sepsis	19 (21.1%)		5 (26.3%)	14 (73.7%)	
		Septic shock	63 (70%)		30 (47.6%)	33 (52.4%)	
CBC	Hemoglobin (g/ dL)	≤10	45 (50%)	10.3 ± 2.1			
		>10	45 (50%)				
	Hematocrit (%)	≤30	28 (31.1%)	33.3 ± 6.4			
		>30	62 (68.9%)				
	White blood cells (/mm^3)	<4000	9 (10%)	13.408 ± 7.833			
		4000-12000	36 (40%)				
		>12000	45 (50%)				
	Platelets (/mm^3)	<150000	22 (24.4%)	269.500 ± 161.670			
		150000-400000	51 (56.7%)				
		>400000	17 (18.9%)				
Inflammatory and sepsis markers	CRP (mg/L) (n=54)	<10	25 (46.3%)	19.9 (0.2 – 290.4)	11 (44%)	14 (56%)	p=0.100*
		10-40	9 (16.7%)		6 (66.7%)	3 (33.3%)	
		>40	20 (37%)		5 (25%)	15 (75%)	
	Procalcitonin (ng/mL)	<0.5	16 (17.8%)	11.88 (0.02 – 742.08)	13 (81.3%)	13 (81.3%)	p=0.170*
		0.5-2	8 (8.9%)		4 (50%)	4 (50%)	
		>2	66 (73.3%)		28 (42.4%)	38 (57.6%)	
Other blood tests	Creatinine	Normal	86 (95.6%)	68.1 (35 – 285.7)			
		Increase	4 (4.4%)				
	SGPT (IU/L)	<100	63 (70%)	55.8 (4.6 – 2633)	13 (48.1%)	14 (51.9%)	OR=1.7 p=0.240
		≥100	27 (30%)		22 (34.9%)	41 (65.1%)	
	Lactate (mmol/L) (n=77)	≤2.2	26 (33.8%)	3.4 (0.9 – 19)	25 (49%)	26 (51%)	OR=1.8 p=0.230
		>2.2	51 (66.2%)		9 (34.6%)	17 (65.4%)	
	INR (n=60)	<1.5	36 (60%)	1.36 (0.84 – 8.18)	15 (62.5%)	9 (37.5%)	OR=4.3 p=0.008
		≥1.5	24 (40%)		10 (27.8%)	26 (72.2%)	
Blood culture		Positive	16 (17.8%)		5 (31.3%)	11 (68.8%)	OR=0.67 p=0.490
		Negative	74 (82.2%)		30 (40.5%)	44 (59.5%)	

* Fisher's exact test

Table 3. Bacteria identified in blood cultures (n=16)

Groups	Bacteria name	n (%)
Grams (+)	*Staphylococcus aureus*	2 (12.5%)
	Staphylococcus hominis	2 (12.5%)
	Staphylococcus epidermidis	3 (18.8%)
	Staphylococcus caprae	1 (6.3%)
Grams (-)	*Stenotrophomonas maltophilia*	1 (6.3%)
	Pseudomonas aeruginosa	1 (6.3%)
	Sphingobacterium thalpophilum	1 (6.3%)
	Sphingomonas paucimobilis	1 (6.3%)
	Chromobacterium violaceum	1 (6.3%)
	Achromobacter xylosoxidans	2 (12.5%)
	Delftia acidovorans	1 (6.3%)
	Total	16 (100%)

Table 4. SOFA score according to treatment results and sepsis stages

SOFA score		Mean ± SD	p
Treatment results	Survival group	4.9 ± 2.7	0.001
	Death group	9.8 ± 2.9	
Sepsis stages	Sepsis	0.9 ± 0.6	0.001
	Severe sepsis	4.7 ± 2.9	
	septic shock	8.2 ± 3.0	

adrenaline (90.3%), dopamine (76.2%), dobutamine (40.3%), and noradrenaline (34.7%).

SOFA score

The mean SOFA score was 6.8±3.7 points. The mortality group had a higher SOFA score compared to the recovered group (p = 0.001). The mean SOFA score increased with the severity of the clinical form, and this difference was also statistically significant, with p-value = 0.001 (Table 4).

Figure 1 shows the area under the curve of the SOFA scale as 0.904 (p = 0.001; 95%CI 0.83 – 0.97). To predict mortality, the optimal cutoff point of the SOFA was 8, with the sensitivity 88.6%, the specificity 87.3%, the positive predictive value 81.6% and the negative predictive value 92.3%.

Discussion

The respiratory tract was found to be the main starting point of infection (52.2%). These results were consistent with other studies in literature, that showed the respiratory infection in 37.2%[11], 47.9%[12], 94%[13] and 91.7%[14] patients with sepsis.

Among the patients from the study group, 63 patients (70%) progressed to septic shock. Other studies showed the progression to septic shock in 48%[15], 29.8%[16], 11%[13] of the patients. Sepsis shock was more common in developing than in developed countries. In developing countries, raising awareness about the

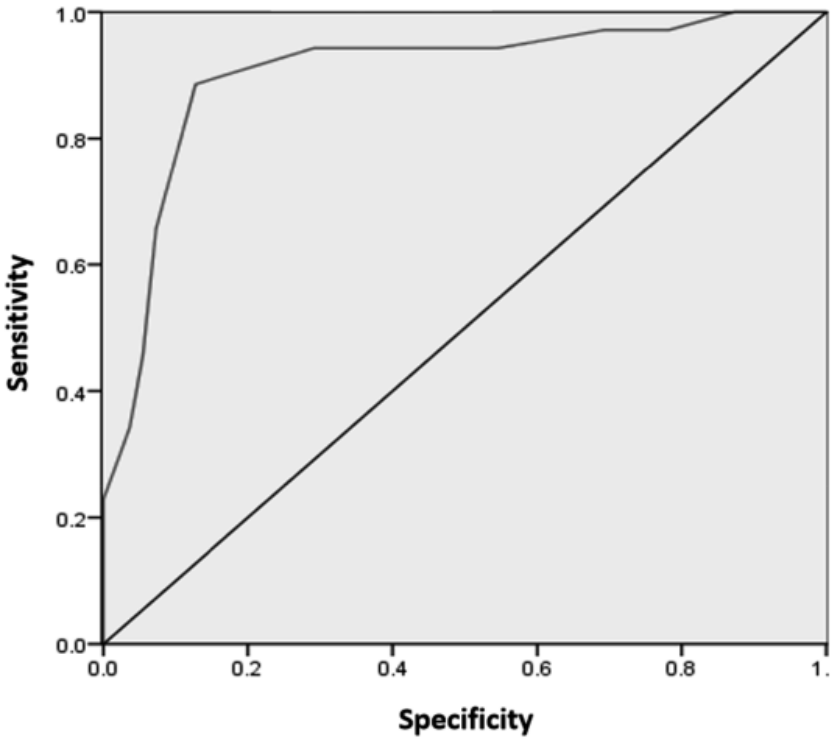

Figure 1. The area under ROC curve of SOFA.

prevalence of septic shock in children is necessary in order to create appropriate prevention and treatment strategies[17].

The increase in white blood cells, especially neutrophils, is an indicator of infection. However, as the severity of infection increases, the white blood cell count decreases. This is largely due to consumption in response to an infection, followed by bone marrow suppression. The increase in white blood cells (>12.000/mm^3) was recorded in 50% of patients, while low white blood cells (<4.000/mm^3) was recorded in 10% patients. Thrombocytopenia (< 150,000/mm^3) was reported in 24.4% of patients. To compensate for the platelets consumed in the early stages of infection, the bone marrow increases initially the platelets' production, but this capacity gradually diminishes, resulting in a decrease in peripheral platelet count[18].

CRP, as well as procalcitonin, were elevated in most patients in our study. Both these markers are used to assess and monitor sepsis, especially in infants. In addition, CRP is used to monitor the response to antibiotic treatment, while procalcitonin is useful for the early detection of an infection. Procalcitonin levels that remain elevated over an extended period of time are an indicator of a poor prognosis[19].

The mortality rate in children with severe sepsis and septic shock was higher than in those with sepsis alone.

Positive blood cultures were recorded in 17.8% of patients, like other studies which showed relatively low rates of positive blood cultures, ie. 34%[20] and 12.5%[13]. Though blood culture is considered the gold standard in the diagnosis of sepsis, its sensitivity is not high[21]. Various factors influence blood culture reports, ie the timing of blood collection, specimen preservation, specimen contamination as well as antibiotic use. In addition, blood culture reports are available only after few days, while in sepsis an urgent treatment is required. *Staphylococcus epidermidis* accounted for the highest proportion (18.8%) of bacteria detected in cultures. A study conducted in Switzerland recorded *Escherichia coli* as the most common pathogen, accounting for 20% of the total 1181 cultures[22].

The mortality rate of children with sepsis was 38.9% in our study. The mortality rate varied in different studies, some showing a higher mortality rate of 52%[23], 59.08%[12], while others showing a lower mortality rate of 29.1%[24], 9%[25], and 27%[26]. The high mortality rate in our study could be explained by the high rate of patients with septic shock. At the time of admission, 41.1% of patients had risk factors for mortality.

Compared to children with a Glasgow score of more than 10, those with a score of less than 10 had a 18 times higher mortality risk. The presence of unconsciousness in children with septic shock at presentation suggests a severe infection[27].

The mean value of the SOFA score was 6.8±3.7 points. Monteiro et al. in Brazil and Jones et al. in the US recorded similar mean SOFA scores of 6.54±2.71 and 7.1±3.6, respectively[23,28]. The SOFA score in the mortality group was significantly higher than in the survival group, as observed in other reports[12,29,30]. The mean SOFA score was found to gradually increase with progression of sepsis.

In our study, the cutoff value of the SOFA score to predict mortality was 8 points (AUROC: 0.904, p= 0.001, 95%CI 0.83-0.97). Acharya et al. found that when the SOFA score was over 11 points, the predicted mortality was 90%[31]. When the mean SOFA score in Intensive Care Unit patients was over 7 points, the predicted mortality was 73.9%[31]. Thus, the SOFA score is useful in predicting death, with a cutoff value of 8 points, and an elevated SOFA score aids in predicting mortality in sepsis patients.

This study has some *limitations*. This is a cross sectional study, so the sample does not appropriately represent the entire population. The sample size of the study was small, and the timeline of the study was limited. Prospective studies with larger sample sizes and longer follow-up period are required for a more objective assessment. However, the application of SOFA score in predicting mortality has only been studied in adults, the studies in children being limited.

Conclusions

The pediatric patients with sepsis admitted in the Intensive Care Units should have the Glasgow score monitored throughout the hospitalization. SOFA score plays an important role in predicting mortality in children with sepsis.

Author Contributions:

Q.N.B., T.H.H., D.L.T., T.D.N., P.T.T., and V.D.T. conceived the original draft preparation. Q.N.B., T.H.H., L.M..D., D.L.T. and P.T.T. were responsible for conception and design of the review. Q.N.B., T.H.H., and D.L.T. were responsible for the data acquisition. Q.N.B., L.M.D., T.D.N., D.L.T., P.T.T., and V.D.T. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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Data availability

The data that support the findings of this study are available from the corresponding author D.L.T. (i.e., upon reasonable request).

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