ORIGINAL ARTICLE

Threshold of Inotropic Score and Vasoactive–Inotropic Score for Predicting Mortality in Pediatric Septic Shock

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Abstract

Objective To determine the threshold of the inotropic score (IS) and vasoactive–inotropic score (VIS) for predicting mortality in pediatric septic shock.

Method This retrospective cohort study included children aged 1 mo to 13 y with septic shock, requiring vasoactive medication. The area under curve receiver operating characteristic (AUROC) was calculated using mean IS and mean VIS to predict PICU mortality, and Youden index cut points were generated. Sensitivity, specificity, and binary regression analysis were performed.

Results A total of 176 patients were enrolled (survivor, $n = 72$, 41% and nonsurvivor, $n = 104$, 59%). For predicting the PICU mortality, AUROC (95% CI) of IS was 0.80 (0.74–0.86) [sensitivity of 88.5 (80.7–94) and specificity of 58.3 (46.1–69.8)] and AUROC of VIS was 0.88 (0.82–0.92) [sensitivity of 83.7 (75.1–90.2) and specificity of 80.6 (69.5–89)]. The respective cutoff scores of IS and VIS were 28 and 42.5. On regression analysis (adjusted odds ratio, 95% CI), illness severity (PRISM-III) (1.12, 1.05–1.12), worst lactate value (1.31, 1.08–1.58), IS (> 28) (3.98, 1.24–12.80), and VIS (> 42.5) (4.66, 1.57–13.87) independently predicted the PICU mortality ($r^2 = 0.625$).

Conclusion Threshold of inotropic score (> 28) and vasoactive–inotropic score (> 42.5) were independently associated with PICU mortality. In addition to IS and VIS, severity and worst lactate value independently predicted septic shock mortality in PICU.

Keywords Children · Pediatric intensive care · Blood transfusion · Mortality · Morbidity · Septic shock · Vasoactive–inotropic score · Predictors

Introduction

Despite the improvement in sepsis care, the sepsis-related mortality rate was as high as 58%, especially in the under-five age group in low-middle income countries (LIMC) [1, 2]. Fluid resuscitation is a fundamental intervention in pediatric septic shock management. The FEAST trial from LMIC demonstrated an increased 48 h mortality rate in children who received fluid boluses [3]. Recently, sepsis-induced myocardial dysfunction is widely recognized in pediatric septic shock [4]. The degree of myocardial dysfunction and the amount of vasoactive (inotropic) therapy needed to achieve and maintain organ perfusion can predict clinical outcomes [4, 5]. Frequent screening of myocardial dysfunction by echocardiography may not be possible in a resource-limited setting. A bedside vasoactive/inotropic score that accurately quantifies the medication support points towards the degree of myocardial dysfunction [6]. Inotropic score (IS) was initially developed and used in pediatric postoperative cardiac patients [5]. IS was modified by adding commonly used other inotropic and vasoactive agents called vasoactive–inotropic score (VIS), giving equal weightage to each medication according to the potency [7]. The highest VIS score in the immediate postoperative period predicted a poor outcome [8]. Initially used in postoperative cardiac patients, VIS has been extrapolated to critically ill

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noncardiac patients. Few studies have validated the use of VIS in general pediatric intensive care unit (PICU) and pediatric septic shock [9–11]. Limited studies explored the VIS cutoff (> 20) and mortality in pediatric septic shock, especially from LMIC [12]. The present study aimed to define the IS and VIS cutoff to predict pediatric septic shock mortality in PICU.

Material and Methods

This retrospective cohort study was undertaken in the PICU of a tertiary care teaching hospital from July 2017 to June 2018. The institutional ethics committee approved the study with a waiver of written consent. Case records of children aged 1 mo to 13 y with septic shock and requiring vasoactive therapy were enrolled. Children who received vasoactive agent therapy for > 6 h before admission and those with ≥ 2 organ dysfunction at admission were excluded. Septic shock was managed as per unit protocol, which was adopted from the surviving sepsis campaign (SSC) and American college of critical care medicine (ACCM) guidelines [13, 14]. Sepsis and septic shock were defined using the international consensus conference on pediatric sepsis criteria [15]. The authors' unit is equipped with multimodal hemodynamic monitoring, including echocardiography (echo), and has the facility for kidney replacement therapy (KRT). There is no standby extracorporeal membrane oxygenation (ECMO) in their unit. Epinephrine and norepinephrine were started in cold and warm shock, respectively. Further need for fluid boluses, vasoactive agents, and blood products was decided according to the type of septic shock, hemodynamic status, and fluid balance by the treating team. Data regarding demographics (age, gender, diagnosis, pediatric risk of mortality-PRISM III score) and clinical variables including duration of vasoactive therapy, the worst lactate value, need for blood transfusion, steroid, the central line used, and side effects of vasoactive therapy, ventilation and PICU outcome (survived/nonsurvived) were collected. IS and VIS were calculated using following formula, [IS = Dobutamine dose (μg/kg/min) + Dopamine dose (μg/kg/min) + 100 × Epinephrine dose (μg/kg/min)] and [VIS = IS + 10 × Milrinone dose (μg/kg/min) + 10,000 × Vasopressin dose (units/kg/min) + 100 × Norepinephrine dose (μg/kg/min)] respectively [5, 7]. The IS and VIS were calculated every 2 h or more frequently as indicated by dose change or addition of drugs from the documents. The mean IS, and VIS values were calculated for analysis purposes.

The distribution of data was assessed using the Kolmogorov–Smirnov z test. The data were compared between survivors and nonsurvivors. Continuous data were compared using Student t-test if normally distributed or Mann–Whitney U test if non-normally distributed. Qualitative data were compared using the Chi-square test (or Fisher exact test if cell frequencies were < 5). Receiver operating characteristic (ROC) curves and area under the curve (AUC) with 95% confidence interval were developed using mean IS and mean VIS value to predict the PICU mortality, and Youden index cut values were generated. Sensitivity and specificity (with a 95% confidence interval) were calculated for the cutoff point of IS and VIS. Univariable followed by multivariable binary regression (Enter: Method) analysis using a Youden index cut points of IS and VIS determined from ROC were performed for PICU mortality, adjusting for age, gender, and illness severity (PRISM-III score). The final model fit was assessed using the Hosmer and Lemeshow test. The odds ratio with a 95% confidence interval was calculated. All tests were two-sided, and $p < 0.05$ was considered statistically significant. IBM SPSS version 20.0 and MedCalc 19.6 versions were used for data analysis.

Results

A total of 176 patients were enrolled (survivor $n = 72$, 41% and nonsurvivor $n = 104$, 59%) after the screening of 236 patients with septic shock (excluded: received > 6 h of vasoactive therapy, $n = 33$, ≥ 2 organ dysfunction, $n = 27$). Demographic and clinical variables of enrolled patients were given in Table 1. All patients in the nonsurvivor group and 54 patients in the survivor group received mechanical ventilation. In the survivor group, 18 patients received non-invasive ventilation. ROC curve analysis to predict PICU mortality using mean IS had an area under the curve (AUROC) of 0.80 (95%CI, 0.74–0.86; $p = < 0.001$) [Youden index $J = 0.4818$; sensitivity of 88.5 (95% CI, 80.7–94) and specificity of 58.3 (95% CI, 46.1–69.8)] (Fig. 1a). ROC curve analysis to predict PICU mortality using mean VIS had an AUROC of 0.88 (95%CI, 0.82 – 0.92; $p = < 0.001$) [Youden index $J = 0.6421$; sensitivity of 83.7 (95% CI, 75.1–90.2) and specificity of 80.6 (95% CI, 69.5–89) (Fig. 1b). The respective cutoff scores of IS and VIS were 28 and 42.5. On binary regression analysis, illness severity, worst lactate value, IS (> 28), and VIS (> 42.5) independently predicted the PICU mortality (Table 2). One patient had ventricular arrhythmia, and another patient had peripheral ischemic changes during the vasoactive agent administration.

Discussion

In this study, IS > 28 and VIS > 42.5 had good sensitivity and specificity for predicting mortality in pediatric septic shock with the area under the curve of 0.80 and 0.88, respectively. In addition to IS and VIS, illness severity and worst lactate value independently predicted mortality.

Table 1 Demographic and clinical variables of enrolled patients

Variables	Survivor ($n=72$)	Nonsurvivor ($n=104$)	p value
#Age, mo	11 (5–36)	12 (4–36)	0.88[a]
Male:Female, n (%)	39 (54.2):33(45.8)	59 (56.7):45 (43.3)	0.74[b]
Age < 5 y, n (%)	60 (83.3)	87 (83.6)	0.96[b]
#Pediatric risk of mortality-III score	14 (10–18)	22 (18–28)	<0.001[a]
Co-morbidity, n (%)	20 (27.8)	35 (33.7)	0.41[b]
##Lactate, mmol/L	3.2 (1.9)	6.1 (3.6)	<0.001[c]
Focus/Diagnosis, n (%)			0.13[b]
Lung	37 (51.4)	40 (38.5)	
Gastrointestinal	9 (12.5)	9 (8.6)	
Central nervous system	6 (8.3)	5 (4.8)	
Renal	5 (7)	9 (8.6)	
Postoperative	3 (4.2)	3 (2.9)	
Hematological	2 (2.8)	11 (10.6)	
Cardiovascular	-	4 (3.8)	
Others	10 (13.8)	23 (22.1)	
Central line, n (%)			<0.001[b]
Internal jugular vein	34 (47.2)	80 (77)	
Femoral vein	19 (26.4)	21 (20.2)	
Internal jugular & femoral vein*	18 (25)	2 (1.9)	
Peripherally inserted central line	1 (1.4)	1 (0.9)	
##Fluid bolus, mL/kg	44.3 (13)	49 (15.4)	0.040[c]
Blood transfusion, n (%)	41 (57)	75 (72.1)	0.037[b]
Steroid, n (%)	22 (30.6)	70 (67.3)	<0.001[b]
Kidney replacement therapy, n (%)	12 (16.7)	23 (22.1)	0.37[b]
##Inotrope score	23.2 (14.6)	42.2 (15.4)	<0.001[c]
##Vasoactive inotrope score	31.4 (24)	75.2 (29.6)	<0.001[c]
#Duration of vasoactive–inotropic score, h	25 (12–69)	34 (18–70)	0.24[a]
#Pediatric intensive care unit stay, d	10 (5–18)	3 (1–10)	<0.001[a]
#Mechanical ventilation, day	7 (5–12)	2 (1–7)	<0.001[a]

All data were presented number with percentage except #median (IQR) or ##mean (SD)

*Patients underwent both central venous line at some point of time during PICU stay

[a]Mann–Whitney U test

[b]Chi-square test

[c]Student t-test

There are limited studies that reported VIS and mortality in pediatric sepsis and septic shock [12, 16]. Haque et al. [12], in a retrospective study involving 71 pediatric septic shock children, reported 100% mortality in those who had VIS > 20 during the first 48 h. Similar to the present study, this study was from an LMIC, and the baseline mortality was high (42%). Nevertheless, in the present study, patients were sicker, and the authors took the mean IS and VIS values during the entire infusion duration rather than restricting them to the first 48 h.

Similarly, McIntosh et al. [16] found a strong correlation between VIS at 48 h and PICU length of stay ($r=0.53$) and ventilator days ($r=0.52$). In contrast to the present study, the VIS at 48 h was not significantly associated with mortality and other composite outcomes. The study setting was different, as it was from a high-income country with a low (5.8%) baseline mortality rate and access to ECMO service,

so probably the analysis was underpowered to detect a significant difference.

In the present study, both IS and VIS predicted mortality independent of the validated PRISM-III score. The commonly used PRISM-III and PIM-2 scores were developed in diverse PICU patients and included the most abnormal parameters in the first 24 h of admission [17, 18]. These predictive scores also lack specificity to any organ dysfunction. The progression of cardiovascular dysfunction beyond 24 h might be revealed by continuous monitoring of IS and VIS, which is not fully addressed by the PRISM-III and PIM-2 score. Similarly, McIntosh et al. [16] showed the association of VIS at 48 h and short-term outcomes independent of PIM-3 score in pediatric sepsis.

The timing of IS and VIS calculation is an ongoing debate. In the postoperative cardiac setting, studies took the first 24 to 48 h as a reasonable period, and persisting
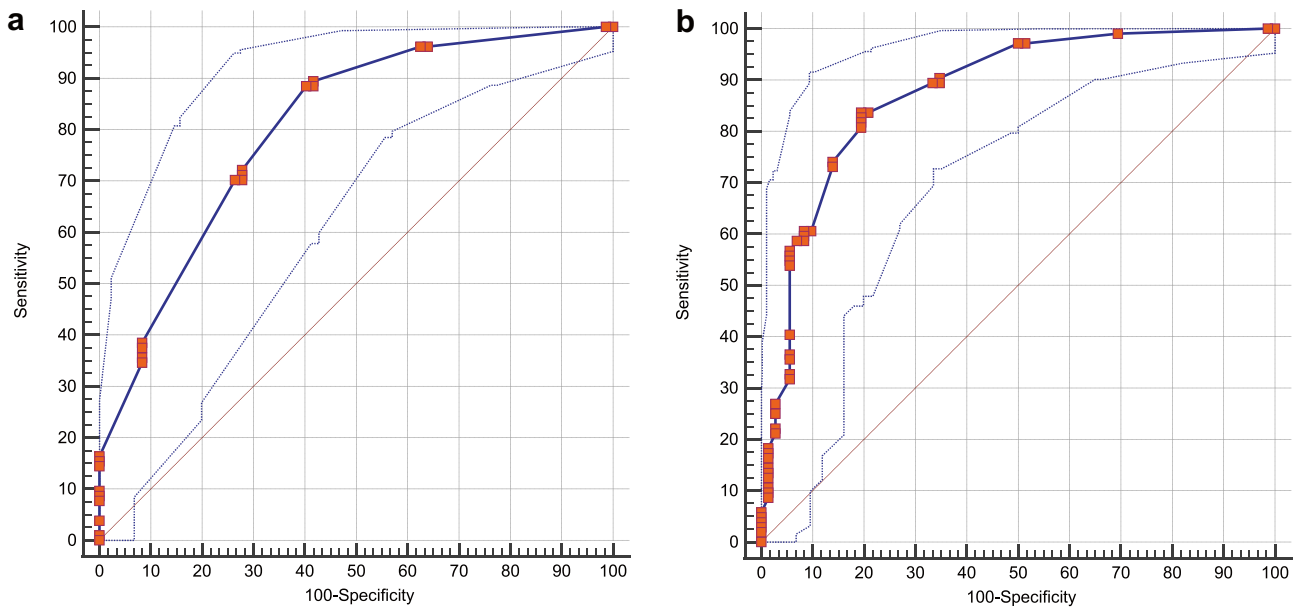
Fig. 1 **a** The area under receiver operating characteristic curve for inotropic score (IS) using cutpoint of 28 was 0.80, and **b** for vasoactive–inotropic score (VIS) using cutpoint of 42.5 was 0.88

cardiovascular dysfunction beyond this period indicates poor outcomes [7, 19]. Few studies used VIS at 48 h to avoid the effect of aggressive resuscitation and rapid escalation of vasoactive in the initial hours for predicting the outcomes in pediatric sepsis [16]. The initial VIS during the early hours of resuscitation may be falsely high. The clinical experience also supports this concept that de-escalation of vasoactive therapy is often possible at the end of 48 h if early resuscitation is initiated.

Musick et al. [9], in a retrospective study involving 2752 PICU patients, derived ROC curves at various time points (maximum score in 24 h, 48 h, any period, VIS at 24 h, VIS at 48 h) for predicting the mortality. AUC was almost similar

for the maximum score during the initial course and VIS at 48 h (0.788 and 0.736). However, the study population included heterogeneous PICU patients, and VIS was calculated after documented dose change of vasoactive medications. In the present study, the authors calculated IS and VIS during the entire duration of vasoactive infusion and took the mean value as a surrogate score of overall cardiovascular support during the entire PICU stay. The AUC for predicting the mortality by IS and VIS score in the present study are 0.80 and 0.88, respectively, which are higher than the other studies.

On multivariable analysis, only severity (PRISM-III score), lactate, IS > 28, VIS > 42.5 were independently predicted the

Table 2 Multivariable binary regression analysis for predictors of mortality in children with septic shock

Variables	Unadjusted odds ratio	95% confidence interval	p value	Adjusted odds ratio	95% confidence interval	p value
Age	1.00	0.99–1.01	0.92	1.00	0.99–1.01	0.66
PRISM-III	1.15	1.09–1.21	< 0.001	1.12	1.05–1.12	0.001
Lactate	1.58	1.32–1.88	< 0.001	1.31	1.08–1.58	0.005
Blood transfusion	1.96	1.04–3.68	0.037	1.09	0.39–3.01	0.87
Steroid received	4.68	2.45–8.94	< 0.001	1.81	0.67–4.89	0.25
Fluid bolus received	1.02	1.00–1.05	0.042	1.00	0.97–1.04	0.95
Inotropic score > 28	11.37	5.30–24.41	< 0.001	3.98	1.24–12.80	0.021
Vasoactive–inotropic score > 42.5	21.20	9.70–46.32	< 0.001	4.66	1.57–13.87	0.006

Variables entered in model are age (continuous variable), *PRISM-III* (continuous variable), lactate (continuous variable), blood transfusion (Yes/No), steroid received (Yes/No), fluid bolus received (continuous variable), inotropic score (cutoff point 28), and Vasoactive–inotropic score (cut-off point 42.5). Hosmer and Lemeshow goodness of fit model $p = 0.319$. Overall percentage of model is 84% with r^2 value of 0.625

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mortality. The mean fluid bolus received was 44.3 vs. 49 (mL/kg) among survivors and nonsurvivors, respectively, which is lower than the recommendation by ACCM guidelines [14]. Although the amount of fluid bolus received was significantly higher among the nonsurvivors, it did not independently predict the mortality after adjusting the confounders.

The present study's unique aspect is that the study population had high sepsis-related baseline mortality, similar to the other LMIC, and enrolled a reasonable sample size. The authors calculated IS and VIS during the entire duration of vasoactive infusion rather than restricting it to a particular time. The mean IS and VIS provides the overall picture of cardiovascular support during the PICU stay. The present study population was restricted to sepsis rather than the general PICU population, where many well-validated prognostic scores are available [17, 18]. There are a few limitations. First, it is a single-center, retrospective study. Fluid bolus and vasoactive medication usage may vary according to institutional and personal preferences. So the results may not be generalizable to other populations. Second, the calculation of IS and VIS includes commonly used inotropes and vasoactive medications. Nevertheless, other agents like levosimendan, phenylephrine were not taken into account in the calculation. However, these agents are not widely used in septic shock. Third, the authors did not compare the performance of these scores between patients with or without myocardial dysfunction. Fourth, long-term functional outcomes are not studied. The prospective, multicentric studies focusing on the discrete patient subgroups (myocardial dysfunction in sepsis), correlation with ECHO, and long-term follow-up are needed in the future to address these limitations.

Conclusion

The study concludes that the threshold of IS (> 28) and VIS (> 42.5) independently predicted the mortality in pediatric septic shock. Besides IS and VIS, PRISM-III and the worst lactate value also independently predicted pediatric septic shock mortality in PICU.

Declarations

Ethics Committee Approval Obtained (Approval No. JIP/IEC/2017/0464).

Conflict of Interest None.

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