Validation of the pediatric refractory septic shock definition: Posthoc analysis of a controlled trial

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Abstract

Background

The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) developed and validated a definition of pediatric refractory septic shock (RSS), based on two septic shock scores (SSS). Both bSSS and cSSS were found to be strongly associated with mortality. We aimed at assessing the accuracy of the RSS definition on a prospective cohort from India.

Methods

Post-hoc analysis of a cohort issued from a double-blind randomized trial that compared first-line vasoactive drugs in children with septic shock. Sequential bSSS and cSSS from 60 children (single center study, 53% mortality) were analyzed. The prognostic value of the ESPNIC RSS definition was tested for 28-day all-cause mortality.

Results

In this septic shock cohort, RSS was diagnosed in 35 patients (58.3%) during the first 24 hours. Death occurred in 30 RSS patients (85.7% mortality) and in 2 non-RSS patients (8% mortality), OR=60.9 [95% CI: 10.5-676.2], $p<0.001$ with a median delay from sepsis onset of 3 days [1.0-6.7]. Among patients diagnosed with RSS, the mortality was not significantly different according to vasopressors randomization. Diagnosis of RSS with bSSS and cSSS had a high discrimination for death with an area under the receiver operating curve of 0.916 [95% CI: 0.843-0.990] and 0.925 [95% CI: 0.845-1.000], respectively. During the first day of septic shock, the best interval for prognostication was after the 12th hour following septic shock as compared to 0-6 hours or 6-12 hours (AUC 0.973 [95% CI: 0.925-1.000] versus 0.876 [95% CI: 0.780-0.972] and 0.955 [95% CI: 0.899-1.000] respectively), $p=0.011$.

Conclusions

The ESPNIC SSS accurately identifies children in refractory septic shock with a best interval between 12 and 24 hour of septic shock. Both bSSS and cSSS had high discrimination for 28-day mortality.

Background

Septic shock, defined as fluid refractory sepsis with organ dysfunction is encompassing various clinical and pathophysiological entities. The Surviving Sepsis Campaign (1) and the American College of Critical Care Medicine guidelines for Hemodynamic Support in Neonates and Children (2) issued guidelines for patient with sepsis including the subset of patients who are unresponsive to vasopressors and labelled as having refractory septic shock (RSS). RSS is described as a circulatory failure due to septic cardiomyopathy (3, 4) with or without vasoplegia (5). Survival observed following short-term circulatory support with newer vasoactive agents or extra-corporeal life support (ECLS) (6) is an indicator that RSS is potentially reversible. To maximize the impact of these rescue therapies, a robust tool for early detection

of RSS was required. The European Society of Pediatric and Neonatal Intensive Care (ESPNIC) defined RSS as the association of high blood lactate with high vasopressor doses and/or myocardial dysfunction (7). This definition based on two septic shock scores showed excellent discriminative power and suggest that both RSS scores are powerful and potentially useful tool to categorize severity at the bedside and compare patients in future interventional randomized multicenter studies on septic shock in children. Nevertheless, this RSS definition was established on retrospective data. A prospective validation is mandatory as part of the validation of theses scores (8). Furthermore, it may not have been representative of the regional diversity of critically ill children etiology and management. In order to overcome these limitations, we evaluated the validity of the ESPNIC RSS definition and SSS scores in a post-hoc analysis of a double blind randomized trial (9) aimed at comparing first-line vasoactive drugs in children with septic shock in India.

Material And Methods

Patients

All patients (n = 60) included in the double-blind randomized trial at the Advanced Paediatrics Center, Post Graduate Institute of Medical Education and Research, Chandigarh, India, were included in the post-hoc analysis. The study protocol has been previously described (9). In summary, this was a monocentric randomized controlled trial on septic shock children comparing dopamine to epinephrine as first-line vasoactive agents. Patients aged between 3 months and 12 years were enrolled if they had fluid refractory septic shock and admitted in pediatric intensive care unit between July 2013 and December 2014. The study was registered (CTRI/2014/02/004393) and a local IRB approved the use of the database for this study and waived the need for informed consent.

Data

Patients baseline characteristics including gender, age, PRISM III and PELOD scores, blood lactate, central venous oxygen saturation (ScvO₂), vasoactive-inotropic score (VIS) as well as the occurrence of severe Acute Respiratory Distress Syndrome (ARDS) defined according to Berlin definition (10) and use of renal replacement therapy were analyzed. There was no missing data, as analyzed items were part of the main outcome measurements from the original study (8). Both bedside septic shock score (bSSS) and computed septic shock score (cSSS) were calculated every 6 hours for the first 24 hours. The bSSS is a 0 to 5 points score with 1 point for a lactate value above 8 mmol/L or increased > 1 mmol/L after 6 hour of management, 1 point for a VIS > 200 and 3 points for the presence of a severe cardiomyopathy defined by a cardiac index < 2.2L/min.m² or a left ventricle ejection fraction < 25%. The cSSS is calculated with: $cSSS = 1.1^{\text{blood lactate value}} + 1.001^{\text{VIS}} + 18$ (in the presence of a severe cardiomyopathy). The impact of the interventional group (dopamine or epinephrine) was considered in the analysis. Primary outcome was 28 days all-cause mortality.

Statistical analysis

Continuous variables were tested for normality with Kolmogorov–Smirnov test and compared with Student's t test or Mann–Whitney test, as appropriate. Non-continuous variables were tested with Chi-squared test or Fisher's exact test, as appropriate. Data were described as frequencies and percentages, means and standard deviations or median and interquartile range, as appropriate. Multivariable Cox's regression with backward-stepwise method was performed having as outcome 28 days all-cause mortality. Covariates inserted in the models were PRISM III and computed SSS. We measured the discrimination of each score using the area under the receiver operating characteristic curve (AUROC). The best thresholds for these scores were obtained with the calculation of sensitivity, specificity, positive and negative predictive values and the Youden's index ($Y = \text{sensitivity} + \text{specificity} - 1$). The DeLong test was used to compare the AUC of both scores. Survival of RSS patients according to both scores have been evaluated by Kaplan–Meier curves and these latter have been tested using Logrank test. A p value of less than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 19.0.0 (SPSS, Chicago, IL) software.

Results

Of the 210 patients diagnosed with sepsis and screened, 61 children were eligible for enrollment. One parent refused consent, 29 children were randomized to epinephrine group and 31 to dopamine group. All the enrolled subjects completed the study and were followed up to 28 days. Patients in the epinephrine group achieved earlier resolution of fluid-refractory hypotensive shock in children as compared to dopamine. The baseline characteristics are presented in Table 1. A RSS was diagnosed in 35 patients (58.3%) with a bSSS ≥ 2 or a cSSS ≥ 3.5 and mortality in the RSS patients ($n = 30/35$, 85.7% mortality) was higher than in non-RSS patients ($n = 2/25$, 8% mortality), $OR = 60.9$ [95% CI: 10.5-676.2], $p < 0.001$. The survival curves of the patients diagnosed with RSS are presented in Fig. 1A and 1B. There was no significant difference in discrimination of mortality between bSSS and cSSS with respectively an AUROC of 0.916 [95% CI: 0.843–0.990] and 0.925 [95% CI: 0.845-1.000] (Fig. 2). The best binary performance for bSSS was ≥ 2 for bSSS (Youden's index = 0.76) and > 20.5 for cSSS (Youden's index = 0.78). A bSSS ≥ 2 was associated with an in-hospital mortality of 50% [positive LR: 5.25, 95% CI = 2.4–11.7], a sensitivity of 93.7% and a specificity of 82.1%. A cSSS > 20.5 was associated with an in-hospital mortality of 43.3% [positive LR: 22.7, 95% CI: 3.3–157], a sensitivity of 81.2% and a specificity of 96.4%. The measure of bSSS between the 12th and 24th hour following septic shock diagnosis was the most discriminative for in-hospital mortality with an AUROC of 0.973 [95% CI: 0.924-1.000], compared to 0 to 6th hours 0.876 [95% CI: 0.780–0.972], $p = 0.011$ (Fig. 3).

Table 1
Baseline characteristics

	Population
Age	5.5 (1.0-8.3)
Sex (M:F)	1:1
PRISM III	20 (13.5–28.7)
PELOD (max)	32 (12–42)
Nosocomial infection	4 (6.6%)
Use of mechanical ventilation	47 (78.3%)
Severe ARDS	17 (28.3%)
Use of RRT	28 (46.7%)
Cardiac arrest	4 (6.7%)
Maximal Blood lactates (mmol/L)	4.3 (2.6, 6.8)
Lactate increase	34 (56.7%)
ScvO ₂ < 70%	52 (86.7%)
Myocardial dysfunction in cardiac ultrasound	35 (58.3%)
PICU mortality	32 (53.3%)
Number of days in PICU	5 (2.7-7.0)
Delay from septic shock onset to death	3 (1.0-6.7)
Bedside septic shock score (bSSS)	4.0 (0–4.0)
Computed septic shock score (cSSS)	20.4 (2.3–21.5)
bSSS ≥ 2	35 (58.3%)
cSSS ≥ 3.5	35 (58.3%)
Values are expressed as means (standard deviations) or median (interquartile range), as appropriate or number (percent)	

We did not find any effect of the group of interventions on the computed score (epinephrine group cSSS = 3.22 [95% IC: 2.32–21.53] and dopamine group cSSS = 20.68 [95% CI: 2.41–21.47], $p = 0.242$) or the bedside score (epinephrine group bSSS = 1 [95% CI: 0–4] and dopamine group bSSS = 4 [95% CI: 0–4], $p = 0.287$). Among patients diagnosed with RSS (bSSS > 2 or cSSS > 3.5), the mortality was not significantly different according to randomization to epinephrine (N = 13/14 death, 92.9% mortality) or dopamine (n = 17/21, 81% mortality), RR = 1.15 [95% CI: 0.89–1.48], $p = 0.627$. We compared the

association of the SSS and PRISM III to mortality using a backward logistic regression and found an independent association with PRISM III ($\exp(B) = 1.77$, 95% CI: [1.11–2.81], $p = 0.015$) and cSSS ($\exp(B) = 1.495$, 95% CI: [1.07–2.08], $p = 0.018$). The bSSS was not tested as it was not developed as a linear score, but a quick tool to assess patients at the bedside.

Discussion

This study showed that the bedside and computed septic shock scores discriminated the most severe cases in a prospective cohort from India and confirmed the accuracy of these scores, particularly after the first 12 hours of management. Patients diagnosed in RSS had a very high mortality. While the presence of a severe myocardial dysfunction is not mandatory for the diagnosis of RSS, it was present in all patients in this study. This point reinforces the importance of septic cardiomyopathy in the pathophysiology of RSS. El Nawawy et al. demonstrated in a small monocentric cohort the added value of myocardial and vascular evaluation with echocardiography (11) and confirmed the high incidence of myocardial dysfunction in pediatric septic shock (12). The vasoactive-inotropic score (VIS), used in the SSS, is validated in pediatric sepsis as a marker of severity. Interestingly, MacIntosh et al. found a similar pattern of evolution of the VIS with a best correlation with morbidity after the 12th hour of care (13). Meanwhile, the addition of blood lactate and myocardial dysfunction in the SSS may explain the excellent discrimination power as early as the diagnosis. Blood lactate with a cut-off value of 4 mmol/L was associated with mortality in a large cohort of pediatric sepsis patients (14). Despite having a higher lactate cut-off value of 8 mmol/L, the bSSS does not seem to have lower sensitivity than the cSSS. In this study, both bSSS and cSSS identified the same number of RSS patients with similar outcome. The high lactate cut-off value in the bSSS effectively selects patients at the highest risk of mortality and with catecholamine-refractory shock.

Our previous study's main limitation was the uncertainty about the simultaneity of the measure of lactate, VIS and/or the presence of cardiomyopathy. The present study focused on the first 24 h of management, all the measures were associated with discrimination for mortality. Nevertheless, the scores were best predictive of mortality after the first 12th hour of management. This may be explained by the need for the vasopressors to be progressively increased until the VIS cut-off is reached, or the patient deteriorates with the occurrence of septic cardiomyopathy. Timing is essential in RSS diagnosis. An early diagnosis of RSS in the first 24 hours associated with a 60% (7) to 85% (present study) estimated mortality should be a strong indicator of need for adjunct therapies.

A recent study found that RSS is the first cause of mortality in pediatric septic shock patients (15). This fact emphasizes the need for a definition of RSS, thus, its validation in this study. Despite being a less frequent cause of death, multiple organ dysfunction syndrome (MODS) can be diagnosed or assessed with several scores such as PELOD 2 and PIM 2. While PIM 2 may only be measured at admission (16), PELOD 2 can be measured sequentially. The assessment of a patient from sepsis diagnosis and throughout evolution is primordial in the dynamics of septic shock (17). The sepsis definition for adult has changed and now encompasses lactate level and need for vasopressor or inotrope in a sepsis patient

(18). Similarly, the pediatric sepsis definition is deemed to change. Recent concept for a new definition focus essentially on organ dysfunction considered as a unified concept rather than independent organ failure (19). Despite the focus of this RSS definition on hemodynamics and circulatory failure, the performances are excellent with high prediction of mortality. Neither PELOD 2 nor pediatric adjusted SOFA were available in this study to evaluate their utility in actual questions for prognosis of septic shock. Meanwhile a MODS score, the PRISM III, was independently associated with mortality, hence supporting the fact that children die from RSS and/or MODS (15).

The first limitation of this study is that it was a post hoc analysis on a single center randomized trial. The use of inotrope or vasopressor in the original study was protocolized, which may have affected the increase in the inotropes or vasopressors, hence the VIS and the predictive performances of the SSS in the first hour of management. Nevertheless, the randomization drug was not associated with increase mortality in the multivariable analysis. Secondly, all patients diagnosed with RSS had a severe cardiomyopathy diagnosed with cardiac ultrasound which is a sufficient criterion for the diagnosis of RSS. Indeed, cardiac ultrasound is questionable due to the subjectivity of the exam and the risk of error for the diagnosis of cardiac failure due to the presence of hypovolemia. Yet, this risk for over-diagnosis of RSS appears unlikely when considering the good performance of the scores and the high mortality in the RSS group. Thirdly, most scores used or currently discussed in the question of sepsis and septic shock diagnosis were unavailable in our cohort, hence we could not compare their performance with the SSS.

This study's strengths are the homogeneous and well characterized cohort of patients with septic shock with timely measured SSS. It is to our knowledge the first prospective study to evaluate the prognosis performances of these scores in pediatric septic shock patients. This study provides clear evidence that RSS is a specific entity responsible for most death in pediatric septic shock. The use of septic shock scores (bedside and computed SSS) had excellent performance for the diagnosis of RSS particularly after the 12th hour of management.

Conclusion

This post-hoc prospective single centre study validates both septic shock scores used to diagnose refractory septic shock, showing excellent discriminatory power for mortality. Future studies should explore the application of this definition in a multicentric prospective cohort of patients in high-resources units and investigate the benefits obtained from adjunct therapies dedicated to the patients with the highest risk of death.

Abbreviations

ESPNIC, European Society of Pediatric and Neonatal Intensive Care; RSS, Refractory Septic Shock; b-/c-SSS, bedside/computed Septic Shock Score; ECLS, Extracorporeal Life Support; PRISM, Pediatric Risk of Mortality; MODS, Multiple-Organ Dysfunction Syndrome; PELOD, Pediatric Logistic Organ Dysfunction; PIM, Pediatric Index of Mortality; VIS, Vaso-Inotropic Score; LR, Likelihood ratio; CI, Confidence Interval.

Declarations

Ethics approval and consent to participate

The study was registered (CTRI/2014/02/004393) and local IRB approved the use of the database for this study and waived the need for informed consent.

Consent for publication

All authors agreed for publication of this study.

Availability of data and materials

All materials are available upon request to Pr.Sunit Singhi at sunitcsinghi@gmail.com

Competing interest

Pr. Tissieres reports research grants from Merieux Foundation and Chiesi Inc, outside the submitted work, and consulting fee for Baxter, Bristol Myers Squibb, bioMerieux, Faron, Chiesi. All other authors declare that they have no conflict of interest.

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Author Contributions:

Study conception and design: LM, PT, KR, SS.

Acquisition, analysis, or interpretation of data: LM, PT, KR

Statistical analysis: KR, LM.

Drafting and revision of the work: All authors

Final approval of the submitted publication: All authors

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Figures

Figure 1

A. Survival curve of refractory septic shock patients diagnosed with a bedside septic shock score ≥ 2 . B. Survival curve of refractory septic shock patients diagnosed with a computed septic shock score ≥ 3.5

Figure 1

A. Survival curve of refractory septic shock patients diagnosed with a bedside septic shock score ≥ 2 . B. Survival curve of refractory septic shock patients diagnosed with a computed septic shock score ≥ 3.5

Figure 2

Receiver operating curve (ROC) and Area under the ROC for bedside Septic Shock Score (bSSS) calculated in the first 24 hours of admission for septic shock.

Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
cSSS	.925	.845	1.000
bSSS	.916	.843	.990

Figure 2

Receiver operating curve (ROC) and Area under the ROC for bedside Septic Shock Score (bSSS) calculated in the first 24 hours of admission for septic shock.

Diagonal segments are produced by ties.

bSSS score intervals	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
bSSS 0 to 6 hours	.876	.780	.972
bSSS 6 to 12 hours	.955	.899	1.000
bSSS 12 to 18 hours	.973	.924	1.000
bSSS 18 to 24 hours	.973	.925	1.000

Figure 3

Receiver operating curve (ROC) and Area under the ROC for bedside Septic Shock Score (bSSS) calculated in the first 24 hours following admission for septic shock.

Diagonal segments are produced by ties.

bSSS score intervals	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
bSSS 0 to 6 hours	.876	.780	.972
bSSS 6 to 12 hours	.955	.899	1.000
bSSS 12 to 18 hours	.973	.924	1.000
bSSS 18 to 24 hours	.973	.925	1.000

Figure 3

Receiver operating curve (ROC) and Area under the ROC for bedside Septic Shock Score (bSSS) calculated in the first 24 hours following admission for septic shock.