Comparative assessment of the prognostic ability of paediatric Sequential Organ Failure Assessment (pSOFA), paediatric logistic organ dysfunction 2 (PELOD 2) and Vasoactive-Inotropic Score (VIS) in children with septic shock: a retrospective observational study

Сравнительная оценка прогностической способности шкал органной дисфункции paediatric Sequential Organ Failure Assessment (pSOFA), paediatric logistic organ dysfunction 2 (PELOD 2) и оценочной системы Vasoactive-Inotropic Score (VIS) у детей с септическим шоком: ретроспективное наблюдательное исследование

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Abstract

INTRODUCTION: Septic shock is the most severe stage of sepsis in children accompanied by a highest mortality. **OBJECTIVE:** The aim of the work is to compare an informative significance of pSOFA, PELOD 2 scales and VIS as predictors of mortality in children with septic shock. **MATERIALS AND METHODS:** The design of the study is retrospective, observational, single-center trial. The study was performed in the Children's Regional Clinical Hospital of Krasnodar. The inclusion criteria were children with septic shock from 9 months to 17 years old. The endpoint of trial was 28-day mortality. Demographic and clinical characteristic were presented with median and average values, also interquartile intervals were counted. Mann-Whitney U-test was used for comparison data received. The discriminatory power, sensitivity and specificity were defined with receiver operating characteristic (ROC) analysis and determination of area under ROC curve (AUC). **RESULTS:** No one of this trial's score provides a prediction of children's survival with sepsis and shock

Реферат

АКТУАЛЬНОСТЬ: Септический шок у детей — это наиболее тяжелая стадия сепсиса, сопровождающаяся максимальной летальностью. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Выполнить сравнительную оценку информационной значимости шкал pSOFA, PELOD 2 и VIS в качестве предикторов прогноза летальности при септическом шоке у детей. **МАТЕРИАЛЫ И МЕТОДЫ:** Дизайн исследования — ретроспективное, обсервационное, одноцентровое. Исследование было осуществлено на базе Детской краевой клинической больницы г. Краснодара. Критерии включения — дети в возрасте от 9 мес. до 17 лет, у которых был диагностирован септический шок. Конечная точка исследования — 28-дневная летальность. Демографические и клинические данные представлены в виде медианных значений с межквартильными интервалами средних и стандартных отклонений. Непрерывные переменные сравнивали с использованием U-теста Манна—Уитни. Дискриминационную способность шкал определяли пу-

during first 24 hour PICU stay. PELOD 2 and pSOFA scores allow to estimate a prediction from day 3 from PICU stay. Furthermore PELOD 2 score shows a higher informative significance. The VIS has an ability to predict survival on day 5 from admission. **CONCLUSIONS:** Only the PELOD 2 score has a good discriminatory power regarding the prognosis of survival in children with septic shock after 48 hours of intensive care. The VIS scale allow to assess a severity of cardiovascular dysfunction in children with refractory septic shock with threshold critical value more than 21 points.

тем вычисления площади под ROC-кривой. **РЕЗУЛЬТА-ТЫ:** В первые 24 ч госпитализации прогноз выживаемости у детей с сепсисом и шоком не способна обеспечить ни одна из анализируемых нами оценочных систем. По завершении 2 сут интенсивной терапии прогноз позволяют осуществить шкалы PELOD 2 и pSOFA, причем лучшей информационной значимостью обладает система PELOD 2. Шкала VIS способна прогнозировать выживаемость лишь к 5-м сут лечения детей с септическим шоком. **ВЫВОДЫ:** Только шкала PELOD 2 имеет хорошую дискриминационную способность относительно прогноза выживаемости у детей с септическим шоком по истечении 48 ч интенсивной терапии. Шкала VIS может быть использована для оценки тяжести сердечно-сосудистой дисфункции у детей с рефрактерным септическим шоком, ее пороговое критическое значение > 21 балла.

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Introduction

Sepsis is a one of the main cause of pediatric morbidity and mortality over the world. There are annual over 80,000 admissions to pediatric hospitals in USA caused by sepsis with mortality rate around 5,000 children a year. A 25–40 % of children with sepsis have been suffering long-term complications [1–4]. Children with sepsis have a highest risk of mortality which is associated with septic shock. An occurrence of septic shock might leads to mortality during first 24–72 hour in pediatric intensive care unit (PICU) [5–7]. The recent multicenter trial showed that 35 % of surviving children with sepsis had a health's problem and a deterioration of life's quality compared to original level in 12 month from admission [8].

Septic shock is a most severe stage of sepsis which defined as presence of cardiovascular disturbances despite an initial fluid load. The diagnostic criteria of septic shock are an insufficient tissue perfusion and an arterial hypotension despite a rescue of fluid load with applying of inotropes and vasopressors for maintenance of arterial pressure. The evidence of poor tissue perfusion should be an oliguria, increased blood's lactate level, a capillary refill time prolongation and a metabolic acidosis [3]. Overall a septic shock has been identified in pediatric practice as a sepsis with cardiovascular dysfunction [3, 4, 8]. It would be perfect if the septic shock will be recognized before arterial hypotension occurrence and based on clinical features which includes hyper- or hypothermia, disturbances of mental status, failed tissue perfusion ("hot" or "cold" shock) [9]. The infusion of vasoactive drugs is one of the basic direction of cardiovascular dysfunction's intensive care associated with sepsis and septic shock resistance to fluid load [9, 14]. A refractory septic shock increases the children's mortality rate in several times [1, 3]. Currently the following scales are recommended for evaluation of sepsis severity in children: pSOFA (pediatric sequential organ failure assessment), PELOD 2 (pediatric logistic organ dysfunction). These scores include the variables of inotrope and vasopressor support with specific scoring sequence (dopamine/dobutamine followed by epinephrine/norepinephrine). It differs from real practice when norepinephrine is the vasoactive remedy of first line therapy [10]. The vasoactive — inotropic score (VIS) presents as quantitative index of vasoactive support in children with cardiovascular dysfunction associated with sepsis [11]. However the VIS application is very limited in pediatric practice [12, 13]. There are a few pilot trials concerning to informative significance of this score in children with sepsis. Furthermore these trials have ambiguous estimations about VIS score [14–17]. This fact leads us to necessity of further trials which would be focused on comparative analysis of VIS and other tools of sepsis severity evaluation. In this light it seems very important so previously recognition of compensated septic shock would be prevent its transformation to refractory mode and decrease a mortality rate.

Objectives

To compare prognostic abilities of pSOFA, PELOD 2 scores and VIS as a predictors of mortality children with septic shock.

Materials and methods

We performed retrospective observational single-center analysis using data from Children's Regional Clinical Hospital (Krasnodar, Russia). The inclusion criteria were children with septic shock from 9 months to 17 years old. The septic shock was basically identified according to the Project of Russian Clinical Recommendation "Diagnostics and treatment of sepsis in children" [19]. The exclusion criteria were inborn errors of metabolism, less than 24-hour staying in PICU, renal failure with request of renal replacement therapy during first 6 hour after admission. All children had got a central venous catheter for fluid load, inotropes and monitoring. A cardiovascular support was performed according to the Clinical recommendations [19]. A restoration of tissue perfusion was determined by following target endpoints: 1) good mental status; 2) arterial pressure (systolic pressure no less than fifth percentile for age); 3) adequate skin perfusion (capillary refill time less than 2 seconds); 4) urine output more than 1 ml/kg per hour. The endpoint of trial was 28-day mortality. A total 55 children had inclusion criteria, an average age 5.3 year. There were 28 (51 %) females, median age 5.9 years (interquartile interval (IQR) 6.5) and 27 (49 %) males, median age 4.7 years (interquartile interval (IQR) 8.0). Nine children had underlying diseases: six patients with spastic tetraparesis, one child with thrombophilia and congenital heart disease, one child with inheritable immunodeficiency, one patient with hermaphroditism. Twelve children deceased (mortality rate 21.8 %). Among deceased children 5 following had an underlying disease: four children had a spastic tetraparesis and one child had a thrombophilia and congenital heart disease. The most frequent cause of sepsis was a pneumonia (33 children, 60 %). Also children were included in trial with other causes of sepsis: ten children with peritonitis (18.2 %), five children with infection of soft tissues and phlegmona (9.1 %), three children with infection of ear, nose and trachea (ENT) such as otitis and pansinuitis (5.5 %), two children with sepsis in result of multiple trauma (3.6 %), one child had an haematogenous osteomyelitis and one child had an urogenital infection. Among deceased children seven patients had a pneumonia, two children had a peritonitis, two children had an infection of soft tissues and one of them had died with sepsis in result of multiple trauma. All children underwent an assessment with use pSOFA, PELOD 2 scores and VIS at the day of admission in PICU and the day 3, day 5–7 and day 10–14. Also all children underwent serial sampling of red blood, leukocytosis and formula, acid-base status of arterial and central venous samples, electrolytes, lactate, coagulolation sample, procalcitonin, C-reactive protein, biochemistry samples, urine samples, bacteriological profile. An X-ray examination and computer tomography (if indications presented) were performed. A respiratory mechanics were evaluated with peak pressure, mean airway pressure, positive end-respiratory pressure, lung compliance and airways resistance, capnometry and capnography. We used the PV-Tool for assessment of respiratory mechanics in cases of acute respiratory distress syndrome (Galileo Gold & G5, Hamilton Medical®). Hemodynamic variables were measured for all patients either with ultrasound using (HD 11 XE, Philips®) or invasive technology of pulse index counter cardiac output (PICCO

Table 1. Comparison of score's informative significance in children with septic shock on different terms of PICU stay

Score	Survivors M/m (IQR), n = 43	Non-survivors M/m (IQR), n = 12	p	AUC ROC
pSOFA (Day 1)	6/6.2 (4), 43	8/7.8 (4.5), 12	0.242	0.607
PELOD 2 (Day 1)	4/4.3 (3), 43	5.5/6.6 (3.5), 12	0.082	0.667
VIS (Day 1)	5/7.6 (8), 43	5/8.1 (12.5), 12	0.582	0.563
pSOFA (Day 3)	7/6.3 (5), 43	9/8.5 (4), 11	0.036	0.708
PELOD 2 (Day 3)	4/3.8 (3), 43	7/7.1 (6), 11	0.0035	0.789
VIS (Day 3)	7.5/10.7 (20), 43	10/11.8 (10), 11	0.528	0.569
pSOFA (Day 5–7)	5/5.1 (6), 39	12/11.1 (2), 10	0.00014	0.894
PELOD 2 (Day 5–7)	3/3.1 (3), 39	11/10.4 (6), 10	0.00001	0.926
VIS (Day 5–7)	5/5.6 (10), 39	20/21.5 (17.5), 10	0.00058	0.856
pSOFA (Day 10–14)	3/3.3 (4), 26	13/14.2 (9), 6	0.0003	0.984
PELOD 2 (Day 10–14)	1/1.8 (3), 26	16/15.3 (10), 6	0.00018	1.0
VIS (Day 10–14)	0/2.5 (5), 26	27.5/26.25 (5), 6	0.00016	1.0

plus, Pulsion®) and both of them. Demographic and clinical characteristic were presented with median and average values, also interquartile intervals were counted. Mann-Whitney U-test was used for comparison data received. The statistical significance was confirmed if p was less than 0.05. The discriminatory power, sensitivity and specificity were defined with receiver operating characteristic (ROC) analysis and determination of area under ROC curve (AUC).

Results

All children admitted to PICU later than 24 hour from start of disease. A 8 (14.5 %) children were delivered on 2 day, 21 (38.2 %) children — from 49 till 96 hours and 26 (47.3 %) — later than 4 days. Probably it caused by a 50 of 55 (90.9 %) patients were transferred from other hospitals. We analyzed score's values to compare this data between survivors and non-survivors (Table 1). Children were evaluated with these scores on day 1 (day of admission), day 3, day 5–7 and day 10–14 staying in PICU.

It shows that PELOD2 values of children with sepsis and cardiovascular dysfunction were inside of range of uncertainty at the day of admission according to Mann-Whitney U-test ($p > 0.05$), also the data of pSOFA score and VIS did not show a statistical significant difference between survivors and non-survivors group. Furthermore our assumption regarding to pSOFA and PELOD 2 values on day 1 had being confirmed with ROC analysis and determination an AUC. We had got the statistical significant difference of pSOFA and PELOD 2 values on day 3 between comparable children's groups of survivors and non-survivors. VIS values did not show statistical significant difference on day 3 again. Also it was confirmed with ROC analysis (Figure 1). Data of all scores demonstrated statistical difference between groups only on day 5–7 and day 10–14 of children's staying in PICU. Moreover we found the accomplished informative significance for all scores. Thus we can conclude that no one score has reliable information regarding to risk level of mortality of children with septic shock on day of admission in PICU. We can quite accurately estimate and predict patient's mortality with PELOD 2 and pSOFA score assessment after 48 hour of staying in PICU. From day 5 all scores have a high predictive significance. Furthermore probably VIS value > 21 demonstrates a high risk of mortality of children with septic shock. We estimated the area under ROC curve for pSOFA, PELOD 2 and VIS values on day 3 of staying in PICU for more accurate determination of informative significance. The comparison of scale's discriminatory power is presented on Figure 1.

The Figure 1 shows that PELOD 2 score demonstrated more significant discriminatory power concerning prognosis to survive than pSOFA score on day 3 of PICU stay. VIS did not have a predictive significance at the same term. Also we determined a threshold of VIS score value associated with increasing of mortality at the time of occurrence a predictive significance (≥ 5 day from admission to PICU). We found twenty-one children had a VIS value more than 5 points. Among them twelve children had survived and nine had deceased. We performed the comparison of mortality rate according to VIS values in different interquartile range (IQR). The Figure 2 presents results.

The diagram shows a huge increasing of mortality range (more than twice) in 4th IQR. The values of VIS divided in following order: 1st IQR — 5–10 points, 2nd IQR —

> 10 points, 3rdIQR — > 15 points, 4th IQR — ≥ 21 points. Thus it is possible to assume that VIS value ≥ 21 predicts a mortality of children with sepsis on day 5–7 of PICU stay.
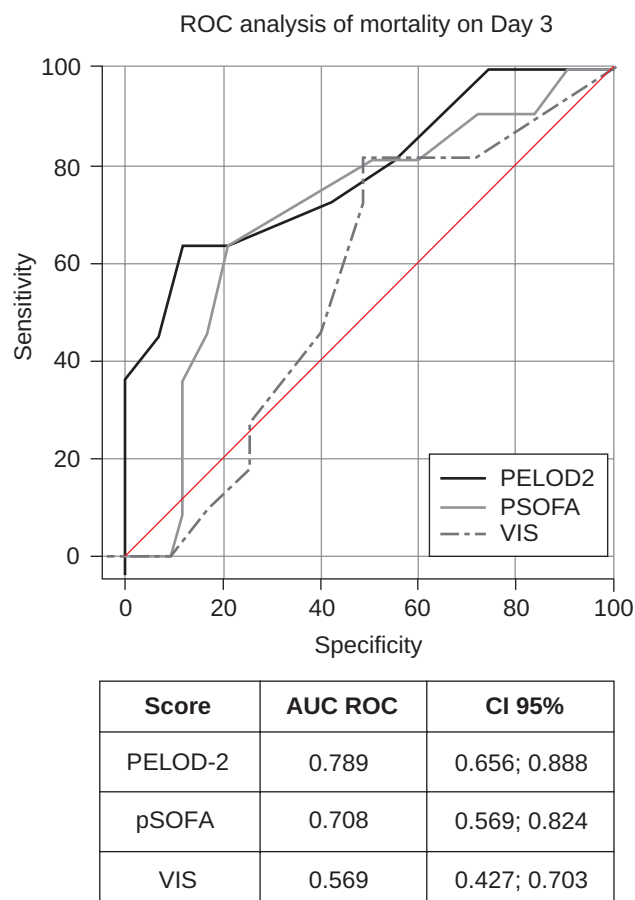
ROC analysis of mortality on Day 3

Score	AUC ROC	CI 95%
PELOD-2	0.789	0.656; 0.888
pSOFA	0.708	0.569; 0.824
VIS	0.569	0.427; 0.703

Fig. 1. Determination of area under ROC curve of studied scores in children with septic shock on 3 day of ICU admission

Discussion

This trial presents the retrospective analysis concerning a correlation between VIS value and outcomes of septic shock in children. Main results of this study are comparative assessments of PELOD 2, pSOFA scores and VIS abilities as predictors of septic shock outcomes. As known, an association sepsis with cardiovascular dysfunction impedes a prediction of outcome using current tools of status assessment. Vasoactive-inotropic score (VIS) is a quantitative index of vasoactive support required for patients. We tried to determine had VIS values correlated with deterioration of sepsis outcomes in pediatric patients during first 48–76 hour vasoactive drugs therapy. We found in this trial that no scales could be predictable in early stages (first 24 hour PICU stay) of surviving in children with sepsis and cardiovascular dysfunction. PELOD 2 and pSOFA scores allowed to realize it after 2 days of PICU stay. Furthermore PELOD 2 score showed a higher informative significance. Our data demonstrate that VIS had an ability to predict surviving of children with sepsis and cardiovascular dysfunction only to 5 day PICU stay. Indeed VIS has validity in case of refractory septic shock. Previously the large randomized trial of L. Morin et al. had already noted it [20]. Although a few trials had found that first 48 hour VIS value correlated with length of stay in hospital, length of mechanical ventilation and mortality of children with sepsis [16, 17]. Probably VIS mostly reflects a severity of cardiovascular failure in children with sepsis, while pSOFA and PELOD 2 scores contain an integral assessment of multiorgan dysfunction. For example recent trial of K. Pshenisnov et al. reported that a prediction of sepsis outcomes caused no by only systemic hypoperfusion but depended on level of hypoxia and metabolic disturbances [21].

Our trial results showed VIS value ≥ 21 points could be used as a predictor of hospital mortality of children with septic shock. Such identification would help to modify an intensive care tactics based on risk of mortality stratification.
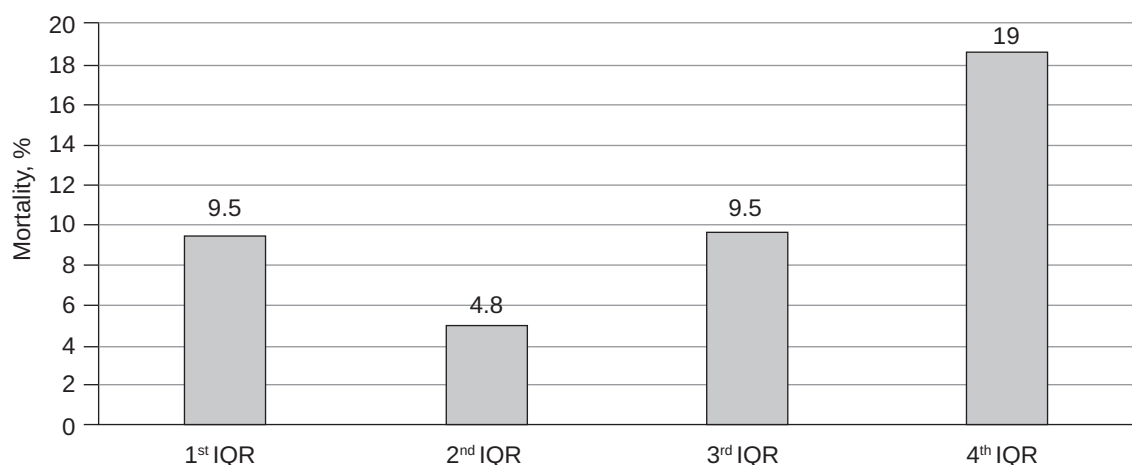

Fig. 2. Interquartile range mortality of children with septic shock associated with VIS value

The similar position (VIS value > 20 points as a threshold) was recently reported by P. Shah et al. [22]. Although some authors consider higher VIS value associated with mortality among children with shock [16, 17].

Our trial has a few limitations. It was completed as a retrospective trial. We enrolled very heterogeneous population of children with sepsis and shock. Not all the children had an isolated septic shock. It could have influenced on requirement and duration of vasoactive support. Furthermore another direction of intensive care (such as mechanical ventilation and extracorporeal haemocorrection) could also have influence on cardiovascular dysfunction leading to modification of titration/using vasoactive drugs. This assumption causes a necessity to continue of investigation and further analysis with involving greater quantity of patients.

Conclusion

1. VIS, pSOFA and PELOD 2 scores are not capable to predict an outcome of septic shock evidently on day of admission in PICU.

2. PELOD 2 sore have a high discriminatory power regard to surviving prediction of children with septic shock after 48 hour of PICU stay. All scores show a very high informative significance on day 5 of PICU stay.

3. VIS could be used for assessment of cardiovascular dysfunction severity in children with refractory shock only.

4. VIS ≥ 21 is a threshold value probability of high mortality.

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