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Predictor Prognosis of Pediatric Septic Shock: Literature review

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ABSTRACT

Introduction: The unpredictability of body response to organ dysfunction needs an effective tool to predict the prognosis of shock septic. Early recognition and treatment of septic shock improved prognosis and reduced mortality, especially in pediatrics. This review aimed to identify the predictor of mortality in pediatric septic shock.

Methods: We performed a literature review of the predictor of mortality in pediatric septic shock conducted between 2015 and 2020 in ProQuest, Google Scholar, PubMed, and Science Direct. We used keywords (predictor or predictive) and (septic shock or septic), and (prognostic or prognosis) and (pediatric or children). The study selection was using the Preferred Reporting Items for Systematic Review and Meta-Analysis PRISMA framework.

Results: 944 articles identified in ProQuest, 720 articles in Science Direct, 339 articles in Google Scholar, and 67 in Pubmed. Equally, the total articles were 2,070 articles, and there were 414 duplicates. After review of the complete texts was performed for 35 potential studies. In the full-text review, we excluded review articles (n = 3), different populations (n=8), and of poor quality (n = 20). Eventually, four papers were reviewed in this study. We found PELOD, PELOD-2, PIM, PIM 2, PIM 3, PMODS, PRISM, PRISM-III, PRISM-IV, and pSOFA as a predictor of sepsis in pediatrics.

Conclusion: In conclusion, pSOFA is a more accurate screening result for estimating the risk of death by being 10 times more sensitive and specific. However, adding biomarkers to pSOFA will improve the accuracy of the predictor prognosis of pediatric sepsis.

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1. INTRODUCTION

At the 2016 international meeting, the *Society of Critical Care Medicine* (SCCM) and the European Society of Intensive Care Medicine (ESICM) proposed a new definition of sepsis, with the term Sepsis-3 (Seymour *et al.,* 2016; Singer *et al.,* 2016). In the latest definition of sepsis, it is explained that sepsis is a life-threatening organ dysfunction caused by dysregulation of the body's response to infection. Sepsis is one of the most common causes of death in pediatric intensive care units (PICU), and its incidence has more than doubled over a decade (Kumar *et al.,* 2011). Understanding the pathophysiology of sepsis has changed dramatically in recent decades with the development of new diagnostic predictions and strategies to treat this complex disease, but sepsis remains one of the leading causes of death in childhood (Dellinger *et al.,* 2013; Levy *et al.,* 2018).

Hospital mortality due to sepsis in children is 25% in both developed and developing countries. about

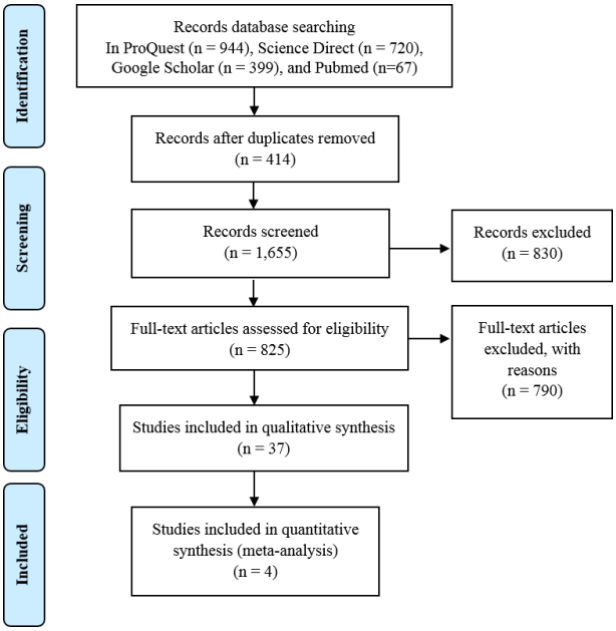
67% of patients develop multiorgan dysfunction when sepsis is recognized, with 30% progressing to progressive multiorgan dysfunction. Unfortunately, 17% had a moderate disability due to sepsis survivors (Weiss *et al.,* 2015). Severe sepsis and septic shock are one of the main causes of morbidity and mortality (60%) of children admitted to the pediatric intensive care unit (IDAI, 2016). Sepsis is caused by death worldwide in the pediatric population that estimated 7.5 million deaths each year (Hartman *et al.,* 2013; Mangia *et al.,* 2009; Weiss *et al.,* 2015).

The validity of sepsis criteria is still debated in the literature, it was caused by a lack of information on the validity and predictive accuracy of sepsis criteria for predicting mortality in critically children condition (Sun *et al.,* 2022). Generally, the sepsis predictor was SOFA score (Seymour *et al.,* 2016). However, SOFA score was not adapted for children (Nieves Ortega *et al.,* 2019). The ideal prognostic tools should be accurate, simple, easy to use, minimally invasive and inexpensive (Mohamed El-Mashad *et al.,* 2020).

There are many types of prognostic tools for the prediction of pediatric sepsis, there were PELOD, PELOD-2, PIM, PIM 2, PIM 3, PMODS, PRISM, PRISM-III, PRISM-IV, and pSOFA. However, there is no perfectly ideal score for predicting childhood mortality, and researchers are making great efforts to improve the accuracy of prognostic pediatric sepsis predictors. A comprehensive study of the prediction of pediatric sepsis that might play a significant role in determining the severity of pediatric sepsis levels is necessary. We performed a literature review to determine predictors of mortality of pediatric sepsis and to plan the most efficient interventions for children at high risk of death, thereby maximizing recovery**.**

2. METHOD

This article uses a *literature review* that includes original research discussing tools to predict the prognosis of pediatric sepsis patients. We searched



Picture 1. PRISMA Flowchart

the relevant studies from major scientific websites and databases to collect the data of interest. The literature review was recommended by *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA).

The literature search was conducted in ProQuest, Google Scholar, PubMed, and Science Direct from 2015 to 2020. It was searched and collected as of October 15-17, 2020. Keywords were linked using "OR", and "AND" to combine the words and "NOT" to exclude the specific criteria by utilizing the Boolean function. We used the keywords adapted from medical subject headings: (predictor or predictive) and (septic shock or septic) and (prognostic or prognosis) and (pediatric or children) not adult. Studies were included in this review following inclusion criteria were a predictor of pediatric septic patients. Published quantitative primary studies, evaluation research, as well as descriptive accounts without an explicit research design, were included.

3. RESULT

The search results were 944 articles identified in ProQuest, 720 articles in Science Direct, 339 articles in Google Scholar, and 67 articles in Pubmed. Equally, the total 2,070 articles and 414 duplicate articles

were removed using Mendeley application, of which 1,656 studies were excluded after title and abstract review. Thereafter, an additional full-text review was performed for 37 prospective studies. In the full-text review, we excluded studies because they were review articles (n = 3), different populations (n = 10), and poor quality (n = 20). Finally, 4 articles were included in our meta-analysis. The selection process of articles applied in our study is summarized in *Figure 1.* Reference lists of studies identified by the search were examined as well. Titles and abstracts were screened to identify relevant references for full text review. Articles were identified for full text review if the title or abstract included a predictor sepsis in pediatrics. The result of the review was presented in Appendix 1 and Table 1 show the AUROC score of the Pediatric Sepsis Predictive Score.

4. DISCUSSION

This review aimed to evaluate the predictive validity of the predictor mortality in children with sepsis. Generally, the sepsis predictor was SOFA score (Seymour *et al.,* 2016). However, the SOFA score is not adapted for children (Nieves Ortega *et al.,* 2019). The first scoring systems were developed for adults and is less suitable for use by children. Today's scores, which particularly relevant for children, for example, the *Pediatric Risk of Mortality* (PRISM) score, from which its further developments, namely the PRISM III and PRISM IV scores, the *Pediatric Index of Mortality* (PIM) score, were developed, the PIM2 and PIM3 scores and the *PELOD* (Pediatric Logistic Organ Dysfunction) score followed by the PELOD 2 score, and *Pediatric specific Sequential Organ Failure Assessment* (pSOFA) (Lalitha *et al.,* 2020b; Mehta *et al.,* n.d.; Niederwanger *et al.,* 2020; Qi *et al.,* n.d.; Schlapbach *et al.,* 2018; Slater & Pearson, 2015; Song *et al.,* 2020; Wulandari *et al.,* 2019).

In the Niederwanger *et al.* (2020) study, it was found that overall PIM have higher rate of accurate prognosis. The AUC of PIM, PIM 2, and PIM 3 analysis score were not very specific except for PRISM. PRISM showed the weakest predictor of death of all tested scores and was significantly weaker than PRISM III, PIM, PIM 2 and PELOD 2. In addition, the predictive ability of the scores PRISM IV and PELOD is as also poor, although with a slightly higher AUC. The most recent PRISM IV and PIM 3 scores did not show improvement in predicting mortality (Niederwanger *et al.,* 2020).

Of the many tools for assessing sepsis severity, PIM 2 was assessed within 1 hour of admission, did not require extensive laboratory testing and is

Table 1. The AUROC Score of Predictor Tools

Type of Pediatric Septic Scores	**AUROC score**
PELOD (Niederwanger *et al.,* 2020; Wulandari *et al.,* 2019)	(0.93, 0.66)
PELOD-2 (Mianling *et al.,* 2019; Niederwanger *et al.,* 2020; Wulandari *et al.,* 2019)	(0.94, 0.75, 0.91)
PIM (Niederwanger *et al.,* 2020)	0.76
PIM-2 (Niederwanger *et al.,* 2020; Teshager *et al.,* 2020)	0.78
PIM-3 (Niederwanger *et al.,* 2020)	0.76
PMODS (Mianling *et al.,* 2019)	0.76
PRISM (Niederwanger *et al.,* 2020)	0.63
PRISM-III (Niederwanger *et al.,* 2020)	0.75
PRISM-IV (Niederwanger *et al.,* 2020)	0.70
pSOFA (Mianling *et al.,* 2019; Wulandari *et al.,* 2019)	(0.94, 0.93)

Notes. AUROC Score ranges in value from 0 to 1. A model whose predictions are 100% wrong has an AUC of 0.0; one whose predictions are 100% correct has an AUC of 1.0.

unaffected by subsequent intervention since it is scored within 1 hour of admission resulting in early identification of the severity of illness and stratification of children for necessary intervention, thereby helping in counseling caregivers of sick children (Martha *et al.,* 2005; Qureshi *et al.,* 2007). A modified PIM 2 Score was no arterial blood gas analysis in PICU during the study period. The revised PIM 2 score unit increase doubled the risk of death. It showed that the score was sensitive to moral perception. This rating system had been validated and applied in many intensive care units worldwide (Teshager *et al.,* 2020).

A study comparing PELOD-2 score of ≥ 11 and score ≥ 8 based on the consensus guidelines on the Indonesian Pediatric Association for the diagnosis and management of sepsis in children (Hadinegoro *et al.,* 2016). Found that PELOD-2 score ≥ 8 lower prognostic value compared to other mortality predictors. Although it was not the best predictor of mortality, PELOD-2 score ≥ 8 was better than severe sepsis criteria based on diagnostic parameters. Both PELOD-2 scores of ≥ 11 and pSOFA scores had advantages in several diagnostic parameters (Teshager *et al.,* 2020). Another study showed that PELOD-2 scores had a lower risk of mortality and were not statistically significant (P=0.336 and P=0.072, respectively; P> 0.05). Therefore, pSOFA was accurate and more sensitive than PELOD-2 (Mianling *et al.,* 2019).

pSOFA had advantages in sensitivity, *negative predictive value* (NPV), negative Likelihood Rasio compare to the other tools. pSOFA was better than other assessment methods, if the aim is to get a more accurate screening result for estimating the risk of death, because pSOFA had the highest odds ratio (OR) value 10.11 (95%CI 1.054 to 97,.002; P<0.05) (Mianling *et al.,* 2019). pSOFA is better than PELOD, PELOD-2, PMODS as a predictor of mortality in patients with sepsis (Lalitha *et al.,* 2020b; Mianling *et al.,* 2019; Wulandari *et al.,* 2019).

A similar study showed that pSOFA [(adjusted AUROC 0.892 (range 0.791-0.868)] was statistically significant in assessing mortality outcomes in sepsis patients and even better than PELOD-2 score of ≥8 (AUROC 0.816; 0.777-0.854), qSOFA (AUROC 0.739; 0.695-0.784), and SIRS (AUROC 0.710; 0.664-0.756). The results showed that pSOFA and PELOD-2 were better than severe sepsis criteria to predict mortality. But, the best sensitivity and specificity for PELOD-2 was using a cutpoint score of ≥ 8. A sensitivity of 88.1% and a specificity of 55.7% (Schlapbach *et al.,* 2018).

However, it remains unclear whether pSOFA scores can be applied to assess the prognosis of children with sepsis in developing countries. This study shows that the pSOFA score at day 1 (AUC, 0.937, 95% CI, 0.913 - 0.957) is effective and capable to assess the prognosis of children with sepsis in PICU of a developing country, which is related to the promotion of pSOFA in developing countries. In addition, pSOFA score was better than the performance of other common pediatric organ dysfunction scores (Mianling *et al.,* 2019).

Assessment of organ dysfunction/failure in children uses several scoring systems, including *Pediatric Multiple Organ Dysfunction Score* (P-MODS), *Pediatric Logistic Organ Dysfunction* (PELOD), *Pediatric Logistic Organ Dysfunction-2* (PELOD-2), and the latest consensus the introduction of the *Pediatric Sequential Organ Failure Assessment* (pSOFA) system adapted from the *Sequential Organ Failure Assessment* (SOFA) system with validation results showing that pSOFA gives the same results as other assessment systems (Niederwanger *et al.,* 2020; Qureshi *et al.,* 2007; Wulandari *et al.,* 2019).

Pediatric Sequential Organ Failure Assessment (pSOFA) is the best predictor for prognosis compared to PELOD, PELOD-2, PIM, PIM 2, PIM 3, PMODS, PRISM, PRISM-III, and PRISM-IV. pSOFA was better than other assessment methods if the aim is to get a more accurate screening result for estimating the risk

of death by 10 times more sensitive and specific based on the AUROC Score in table 1. pSOFA had a high AUROC score in 2 studies were 0.94 and 0.93 (Mianling *et al.,* 2019; Wulandari *et al.,* 2019). The AUROC score that is close to a score of 1 indicates that the level of sensitivity and specificity is high so it is more accurate than other tools. Similarly, another retrospective study reported that the pSOFA score were more accurate than SIRS in predicting sepsis mortality in pediatric in PICU (Wu *et al.,* 2019). Another study the pSOFA score, an age-adjusted pediatric version of the adult SOFA score showed that excellent discrimination for in-hospital mortality in a general PICU population and in the subgroup of patients with suspected or confirmed infection (Matics & Sanchez-Pinto, 2017). The advantages of pSOFA are available for free and do not require special biological variables for calculation. In addition, pSOFA can be calculated daily, allowing dynamic assessment of the course of the disease. pSOFA is adapted to use SpO2 instead of PaO2 values, it also does not require arterial blood gas measurements, which are difficult to obtain in children (Mohamed El-Mashad *et al.,* 2020). Below is a description of the clinical and biological variables predicting the prognostic score for sepsis in pediatric (Appendix 2).

Pediatric Sequential Organ Failure Assessment (pSOFA)

Pediatric Sequential Organ Failure Assessment (pSOFA) score is a tool adapted from SOFA in adults. Adaptation used from 2 approaches. First, the cardiovascular and renal variables starting at age from the baseline SOFA score were using a validated cut-off from the PELOD-2 score system (Lalitha *et al.,* 2020a; Leteurtre *et al.,* 2013). Second, the respiratory variable was expanded to include the SpO2 : FiO2 ratio as an alternative to lung injury (Matics & Sanchez-Pinto, 2017). Pediatric SOFA score was shown in (Appendix 3).

Cardiovascular Criteria

Age-adjusted MAP cut-offs for the first score of the PELOD-2 cardiovascular criteria were used to assign a score of 1 in the pSOFA. Scores 2 to 4 remain the same as to the original SOFA criteria (Shime *et al.,* 2017). *Renal criteria* Age-adjusted serum creatinine level cut-offs for the first score of the PELOD-2 renal criteria were used to assign a score of 1 in the pSOFA renal criteria. Scores 2 to 4 were modified by increasing the cut-off values for each score by the same factor as the original SOFA criteria, similar to the approach suggested by other authors (Shime *et al.,* 2017). For this neonatal age group, the cutoff value increase for each score performed as the infant group (1-12 months) given the similarity in the glomerular filtration rate in both age groups (Schwartz *et al.,* 1987).

Respiratory Criteria

The original PaO2:FiO2 ratio cut-off were kept identical to the original score, but the SpO2:FiO2 ratio was used as an alternative surrogate of lung injury. The adaptation proposed by Khemani and colleagues were used to define the SpO2:FiO2 ratio cut-off (Matics & Sanchez-Pinto, 2017).

Coagulation, Hepatic, and Neurologic Criteria

The baseline coagulation and liver criteria were platelet counts and bilirubin level. Glasgow Coma Scale (GCS) criteria for the neurologic outcomes were also kept identical to the original score, but the pediatric version of the scale was used (Reilly *et al.,* 1988). pSOFA score was performed in a similar way to the original SOFA score. The worst variable in each 24-hour period was used to assign a subscore for each system (ranging from 0-4 points). The sum of the 6 criterias in each 24-hour period result pSOFA score

(ranging from 0-24 points; higher scores indicate a worse outcome). If a variable is not measured in a 24-hour period, it was considered to be normal, which is consistent with the original criteria. The identification of a predictor of sepsis in pediatric has limitations as a review creates many variations of the predictors and their reported. In addition, limiting our search strategy to peer-reviewed, original research written in English may have excluded relevant results. Second, it was carried out a review with the inherent weakness of this design that we were not able to know the patient's condition directly. Third, the limitation of our study include the small sample size, although some of the findings of our study may be generalizable to center with low mortality.

5. CONCLUSION

In conclusion, *pediatric SOFA* (pSOFA) is the best predictor for prognosis in pediatric sepsis compared to PELOD, PELOD-2, PIM, PIM 2, PIM 3, PMODS, PRISM, PRISM-III, and PRISM-IV. pSOFA result for estimating the risk of death by 10 times more sensitive and specific. It is better than other tools if the aim is to get a more accurate screening. A strategy to improve the accuracy in assessing the prognosis of septic patients by using the pSOFA score, which can be combined with biomarker that specific in pediatric septic shock.

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Appendix 1 Predictor of Septic Prognosis in Pediatrics

Author, Year	Title	Design	Population	Method	Result
Mianling, Z., Yuge, H., Tufeng, L., Lu, X., Ting, T., Miaofen, L., & Dongqiang, H. (2019).	Performance of the *Pediatric Sequential Organ Failure Assessment* Score in Assessing the Prognosis of Children with Sepsis in A PICU of A Developing Country : A Single-Center Retrospective Observational Study.	Single-center retrospective observational study.	516 children diagnosed with sepsis according to the 2005 International Pediatric Sepsis Consensus Conference	The patients were divided into survivor group and non-survivor group according to the clinical outcome of 28 days after admission. The variables of pSOFA score, PELOD-2 score and P-MODS were collected and scored. Receiver operating characteristic (ROC) curve was plotted; the efficiency of the pSOFA score for predicting death was evaluated by the area under ROC curve (AUC).	ROC curve analysis showed that the AUCs of the pSOFA score, PELOD-2 score and P-MODS predicting the prognosis of children with sepsis in a PICU of a developing country were 0.937, 0.916, and 0.761, respectively (all $P < 0.05$). The pSOFA score is effective and has the ability to assess the prognosis of children with sepsis in a PICU of a developing country.
Niederwanger, C., Varga, T., Hell, T., Stuerzel, D., Prem, J., Gassner, M., Rickmann, F., Schoner, C., Hainz, D., Cortina, G., Hetzer, B., Treml, B., & Bachler, M. (2020).	Comparison of pediatric scoring systems for mortality in septic patients and the impact of missing information on their predictive power: a retrospective analysis.	Retrospective study design	Younger than 18 years old with diagnosed sepsis	This study evaluated and compared the prognostic ability of various common pediatric scoring systems (PRISM, PRISM III, PRISM IV, PIM, PIM2, PIM3, PELOD, PELOD 2) in order to determine which is the most applicable score for pediatric sepsis patients in terms of timing of disease survey and insensitivity to missing data.	PIM scores show comparatively good performance, are stable as far as timing of the disease survey is concerned, and they are also relatively stable in terms of missing parameters. PELOD 2 is best suitable for monitoring clinical course.
Teshager, N. W., Amare, A. T., & Tamirat, K. S. (2020).	Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialised hospital , northwest	A single-centre prospective observational cohort study	A total of 313 children admitted to the ICU	Data were collected using standard case record form, physical examination and patient document review. Clinical characteristics such as systolic blood pressure, pupillary light reflex, oxygen saturation and need for mechanical ventilation (MV) were assessed and documented within	The rate of mortality in the PICU was high, admission over weekends, need for MV, critical illness diagnoses, and higher PIM 2 scores were significant and independent predictors of mortality.

	Ethiopia : a prospective observational cohort study.			the first hour of admission and entered into an electronic application to calculate the modified Pediatric Index of Mortality 2 (PIM 2) Score. We fitted the Cox proportional hazards model to identify predictors of mortality.	
Wulandari, A., & Martuti, S. (2019).	Severe sepsis criteria, PELOD-2, and pSOFA as predictors of mortality in critically ill children with sepsis.	Prospective cohort study was	30 partisipants in pediatric intensive care unit (PICU) and pediatric high care unit (HCU)	All patients who met the systemic inflammatory response syndrome (SIRS) criteria were included in our study. The exclusion criteria were congenital anomalies of heart or kidney, malignancy, or he- matological abnormalities. The data were taken from laboratory and physical examinations by the physicians on duty. The outcome assessed was mortality	Most subjects were treated in the PICU and had a mean length of stay of 8.70 (SD 11.91) days. Severe sepsis and PELOD-2 were not significant predictors of death. However, pSOFA score was a statistically significant predictor of mortality, with odds ratio 10.11 (95%CI 1.054 to 97.002; P=0.039).

Notes. PELOD – Pediatric Logistic Organ Dysfunction. PIM – Pediatric Index of Mortality. PMODS – Pediatric Multiple Organ Dysfunction Score. PRISM – Pediatric Risk of Mortality. pSOFA – Pediatric Sequential Organ Failure Assessment

Appendix 2 Description of Prognosis Score of Septic in Pediatric

Score	Clinical variable	Biological variable
pSOFA	Respiratory PaO2/FiO2 Respiratory SpO2/FiO2 Respiratory support, (yes/no) Coagulation Platelet count,×109/L Hepatic Bilirubin, mg/dl Cardiovascular MAP by age group Dopamine hydrochloride Epinephrine norepinenephrine Dobutamine hydrochloride (any), (yes/no)	-
PELOD	Cardiovascular Heart rate (beats/min) Systolic blood pressure Renal Creatinine Respiratory PaO2 (kPa)/FiO2 ratio PaCO2 (kPa) Mechanical ventilation Hematological White blood cell count (x 109/l) Platelets (x 109/l) Hepatic Aspartate transaminase (IU/l) Prothrombin time (or INR)	Neurological Glasgow coma score Pupillary reactions
PELOD-2	Cardiovascular Lactatemia (mmol/L) Mean arterial pressure Renal Creatinine (pmoL/L) Respiratory PaO2 (mm Hg)/FiO2 PaCO2 (mm Hg) Invasive ventilation Hématologic WBC count (x 10^9L) Platelets (x 10^9L)	Neurological Glasgow Coma Score Pupillary reaction
P-MODS	Lactic acid, (mmol/L) Respiratory PaO2/FiO2 Bilirubina (mol/L or mg/dL) Fibrinogenb (mol/L or mg/dL) BUN (mol/L or mg/dL)	-
PRIMS	Systolic BP (mmHg) Diastolic BP (mmHg) Heart Rate (x/min) Respiratory Rate (x/min) Respiratory PaO2/FiO2 Respiratory PaCO2 PT/PTT Total bilirubin (mg/dl) Potassium (mEq/L) Calsium (mg/dl) Glucose (mg/dl) Bicarbonate (mEq/L)	Neurological Glasgow Coma Score Pupillary reaction

PRISM III	Systolic BP (mmHg) Temperature Heart Rate (x/min) pH Total of CO2 (mmol/L) PCO2 mmHg Arterial PaO2 mmHg Glucose (mmol/L) Potassium (mEq/L) Creatinine (μmol/L) Urea (mmol/L) WBC (Cells/mm^3) Platelet (Cells/mm^3) PT/PPT	Neurological Glasgow Coma Score Pupillary reaction
PRISM IV	Subcategories of neurologic and nonneurologic Pediatric Risk of Mortality scores (PRISM)	Age Admission source Cardiopulmonary arrest within 24 hours before admission Cancer Low-risk systems of primary dysfunction.
PIM	Systolic BP (mmHg) Respiratory PaO2 Respiratory FiO2 Pupillary Reaction Arterial or capillary blood (mmol/l)	Booked admission to ICU after elective surgery, or elective admission to ICU for a procedure such as insertion of a central line or monitoring or review of home ventilation (no=0, yes=1): Underlying conditions [0] None [1] Cardiac arrest preceding ICU admission [2] Severe combined immune deficiency [3] Leukaemia or lymphoma after first induction [4] Spontaneous cerebral haemorrhage [5] Cardiomyopathy or myocarditis [6] Hypoplastic left heart syndrome [7] HIV infection [8] Liver failure is the main reason for ICU admission10 [9] Neuro-degenerative disorder Mechanical ventilation at any time during first hour in ICU (no=0, yes=1) Outcome of ICU admission (discharged alive from ICU=0, died in ICU=1)
PIM 2	Systolic BP (mmHg) Respiratory PaO2/FiO2 Pupillary Reaction Arterial or capillary blood (mmol/l)	Mechanical ventilation (no=0, yes=1) Elective admission to ICU (no=0, yes=1) Recovery from surgery (no=0, yes=1) Admitted following cardiac bypass (no=0, yes=1) High risk diagnosis. [0] None [1] Cardiac arrest preceding ICU admission [2] Severe combined immune deficiency [3] Leukaemia or lymphoma after first induction [4] Spontaneous cerebral haemorrhage

		[5] Cardiomyopathy or myocarditis [6] Hypoplastic left heart syndrome [7] HIV infection [8] Liver failure is the main reason for ICU admission10 [9] Neuro-degenerative disorder Low risk diagnosis. [0] None [1] Asthma is the main reason for ICU admission [2] Bronchiolitis is the main reason for ICU admission [3] Croup is the main reason for ICU admission [4] Obstructive sleep apnoea is the main reason for ICU admission [5] Diabetic keto-acidosis is the main reason for ICU admission
PIM 3	Pupils fixed to light? (Yes/No) Elective admission (Yes/No) Mechanical ventilation in the first hour (Yes/No) Absolute value of base excess (mmol/L) SBP at admission (mm Hg) 100 × Fio2/Pao2 (mm Hg)	Recovery post procedure? Yes, recovery from a bypass cardiac procedure Yes, recovery from a non-bypass cardiac procedure Yes, recovery from a noncardiac procedure Very high-risk diagnosis (Yes/No) High-risk diagnosis (Yes/No) Low-risk diagnosis (Yes/No) Constant

Notes.
PELOD – Pediatric Logistic Organ Dysfunction. PIM – Pediatric Index of Mortality. PMODS – Pediatric Multiple Organ Dysfunction Score. PRISM – Pediatric Risk of Mortality. pSOFA – Pediatric Sequential Organ Failure Assessment

Appendix 3 Pediatric Sequential Organ Failure Assessment (pSOFA) Score

	Score[a]				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory					
PaO2:FiO2 or SpO2:FiO2 [bc]	≥ 400	300 – 399	200 - 299	100 - 199 with respiratory support	< 100 with respiratory support
	≥ 292	264 – 291	221 - 264	148 - 220 with respiratory support	< 148 with respiratory support
Coagulation					
Platelet count, x 10	≥150	100 – 149	50 - 99	20 - 49	<20
Hepatic					
Bilirubin, mg/dl	< 1.2	1.2 - 1.9	2.0 - 5.9	6.0 - 11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or µg/kg/min					
< 1 mo	≥ 46	< 46	Dopamine	Dopamine	Dopamine
1 - 11 mo	≥ 55	< 55	hydrochloride	hydrochloride	hydrochloride >15
12 - 23 mo	≥ 60	< 60	≤ 5 or	>5 or	or epinephrine
24 - 59 mo	≥ 62	< 62	dobutamine	epinephrine ≤0.1	>0.1 or
60 - 143 mo	≥ 65	< 65	hydrochloride	or	norepinephrine
144 - 216 mo	≥ 67	< 67	(any)	norepinephrine	bitartrate >0.1
>216 mo	≥ 70	< 70		bitartrate ≤0.1	
Neurologic					
Glasgow Coma Score	15	13 - 14	10 - 12	6 - 9	< 6
Renal					
Creatinine by age group, mg/dL					
< 1 mo	< 0.8	0.8 - 0.9	1.0 - 1.1	1.2 - 1.5	≥ 1.6
1 - 11 mo	< 0.3	0.3 - 0.4	0.5 - 0.7	0.8 - 1.1	≥ 1.2
12 - 23 mo	< 0.4	0.4 - 0.5	0.6 - 1.0	1.1 - 1.4	≥ 1.5
24 - 59 mo	< 0.6	0.6 - 0.8	0.9 - 1.5	1.6 - 2.2	≥ 2.3
60 - 143 mo	< 0.7	0.7 - 1.0	1.1 - 1.7	1.8 - 2.5	≥ 2.6
144 - 216 mo	< 1.0	1.0 - 1.6	1.7 - 2.8	2.9 - 4.1	≥ 4.2
>216 mo	< 1.2	1.2 - 1.9	2.0 - 3.4	3.5 - 4.9	≥ 5

Notes.

a. Daily pSOFA score was the sum of the 6 subscores (range, 0-24 points; higher scores indicate a worse outcome).
b. PaO2 was measured in millimeters of mercury.
c. Only SpO2 measurements of 97% or lower were used in the calculation.
d. MAP (measured in millimeters of mercury) was used for scores 0 and 1; vasoactive infusion (measured in micrograms per kiligram per minute), for scores 2 to 4. Maximum continuous vasoactive infusion was administered for at least 1 hour.
e. Cut-off for patients older than 18 years (216 months) were identical to the original SOFA score.
f. Glasgow Coma Scale was calculated using the pediatric scale.