**CRITERIA FOR PEDIATRIC SEPSIS – A SYSTEMATIC REVIEW AND META-ANALYSIS BY THE PEDIATRIC SEPSIS DEFINITION TASKFORCE**

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**Key words:** childhood; mortality; infection; sepsis; severe sepsis; septic shock; organ dysfunction; organ failure

**Abstract:**

**Objective:**  To determine the associations of demographic, clinical, laboratory and illness severity variable values on admission in children with infection with 1) development of sepsis, severe sepsis or septic shock in children with infection and 2) multi-organ dysfunction or death.

**Data Sources:** MEDLINE, Embase and the Cochrane Central Register of Controlled Trials from January 1, 2004 and November 16, 2020.

**Study Selection:** Case-control, cohort studies and randomized controlled trials in children 37 weeks to 18 years of age with suspected or confirmed infection which included the terms sepsis, septicemia or septic shock in the title or abstract.

**Data Extraction: S**tudy characteristics, patient demographics, clinical signs, laboratory values and organ dysfunction and illness severity scores were extracted. All analyses were performed using random-effects meta-analysis.

**Data Synthesis:** One hundred and six studies representing 35 countries met the eligibility criteria and 81 studies enrolling 154,474 patients were included in the meta-analysis. In children with infections, level of consciousness and Pediatric Risk of Mortality (PRISM) score were associated with severe sepsis and sepsis respectively. The pooled mortality rates varied between high, upper middle and lower middle-income countries for patients with sepsis, severe sepsis and septic shock (P < 0.0001). Mortality in patients with sepsis, severe sepsis or septic shock was statistically associated with 28 of the 54 variables tested. Chronic conditions, oncologic diagnosis, use of vasoactive/inotropic agents, mechanical ventilation, serum lactate, platelet count, fibrinogen, procalcitonin, multi-organ dysfunction syndrome, Pediatric logistic organ dysfunction score, Pediatric Index of Mortality-3 and PRISM score all demonstrated significant and consistent associations with mortality in greater than four studies.

**Conclusions:** Numerous variables were identified that showed consistent and significant associations with mortality in children with sepsis despite marked heterogeneity in clinical settings and study populations.

1. **BACKGROUND**

 Infections account for 26.5% of the global burden of disease (1) and 25% of deaths in children worldwide (2). However, the clinical manifestations of these infections vary from minimal or absent symptoms to multiorgan failure and death. The concepts of sepsis, severe sepsis and septic shock were developed and refined using different criteria to help identify, treat and study those infections who are at higher risk of significant morbidity and mortality (3,4). However, specific variables identifying children with sepsis and their resulting outcomes have never been rigorously evaluated in a systematic review.

 The 2016 sepsis definition update in adult patients (Sepsis-3) included a systematic review of reported criteria used to identify adults with septic shock (5). This review only assessed hemodynamic criteria and specifically excluded pediatric studies, in addition specific patient populations (such as oncology patients) were excluded. Furthermore, results of adult trials cannot be automatically generalized to children because of differences in epidemiology (6), mortality rates (7), underlying diseases (8), disease-specific outcomes (9,10) and differing responses to therapy (11,12).

 Therefore, the Society of Critical Care Medicine (SCCM) convened the Pediatric Sepsis Definition Taskforce to evaluate, develop and validate criteria for the identification of sepsis in children. As part of this process, the Taskforce conducted a systematic review with explicit goals to determine demographic, clinical and laboratory variables and organ dysfunction/illness severity scores in children with suspected or confirmed infection associated with 1) development of sepsis, severe sepsis or septic shock in children with suspected or confirmed infection; and 2) new or progressive multi-organ dysfunction (NPMODS) or mortality in children with sepsis, severe sepsis or septic shock.

1. **METHODS**

The protocol has been previously published (13) and is summarized below.

**Eligibility criteria**

 Inclusion criteria for studies were: 1) the word “sepsis”, “septic shock” or “septicemia” was present in the title or abstract; 2) publication date between January 1, 2004 and November 16, 2020; 3) NPMODS or mortality was reported as an outcome; 4) case-control study, cohort study (prospective or retrospective), randomized or quasi-randomized trial design and 5) a study population of children ≥ 37 weeks post-gestational age to < 18 years. Studies meeting the following criteria were excluded: 1) less than 50 children with sepsis, septicemia, severe sepsis or septic shock; 2) abstract only publications, case studies, narrative reviews, surveys or study protocols; 3) reported exclusively on adult patients; 4) ineligible medical conditions (e.g. septic arthritis); 5) no comparator group for variable in question; 6) sepsis criteria not specified; 7) article not available; or 8) focused on criteria only available for research (e.g. gene-expression data). Only 17 non-English language articles (0.23%, 17/7502) were identified by the search. As such, the decision was made to exclude non-English language studies.

**Data Sources**

 We identified eligible studies by searching the following databases: MEDLINE (including Epub Ahead of Print), Embase and the Cochrane Central Register of Controlled Trials.

**Study screening and selection**

 The titles, abstracts and full-texts were screened using a previously validated crowdsourcing platform Insight Scope (14). Each title and full-text article was screened by two reviewers for inclusion in the final set of articles for data extraction. At each screening level and for data extraction, conflicts were resolved by a third reviewer.

**Data extraction and management**

 Data from included full-text articles was extracted by two reviewers per citation using a REDcap platform (15) hosted at the Children’s Hospital of Eastern Ontario Clinical Research Unit. Corresponding authors were contacted twice to obtain missing data on identified variables or mortality. The quality of selected articles was assessed using the first four domains of the QUIPS (Quality in Prognostics Studies) tool for assessment of risk of bias in observational studies (16). The overall risk of bias was determined as the highest risk of bias attributed to any criterion. Only unadjusted data were extracted since many studies did not report adjusted data and others did not specify the variables they adjusted for or adjusted for different variables (17). Articles containing variables that were assessed in two or more studies were included in the meta-analysis. The remaining eligible studies are described in the narrative review. Sensitivity and specificity analyses were performed if two studies or more studies used the same threshold for any given variable.

**Definition of variables**

We aimed to identify variables on admission to hospital or PICU for potential use in future pediatric sepsis criteria, as part of the Pediatric Sepsis Definition Taskforce project. The purpose of this systematic review was to assess in a meta-analysis whether a given variable, such as for example arterial hypotension, was associated with outcomes rather than comparing specific definitions of hypotension. Therefore, we collated original data from different studies on variables such as “hypotension” even if they applied different definitions. The same principle applied to all variables investigated. Countries were categorized as low-(LIC), low-middle-(LMIC), upper-middle-(UMIC) and high-income countries (HIC) according to the World Bank classification of 2019-2020 (18).

**Outcomes**

 The primary outcome for the meta-analysis of articles describing children with infection was the development of sepsis, severe sepsis or septic shock. The primary outcome for the meta-analysis of articles describing children with sepsis, severe sepsis or septic shock (henceforth collectively referred to as sepsis) was the development of NPMODS and/or death.

**Data synthesis and analysis**

 Frequencies and descriptive statistics are reported for study demographics and patient characteristics in included studies. Random effects meta-analyses with inverse described in Cochrane Handbook (19).The mean and standard deviation were imputed from the median, interquartile range or range (minimum and maximum) and sample size (20). Statistical heterogeneity was assessed using I2 statistic and visual inspection of the forest plots. DerSimonian-Laird random-effects models were employed for all comparisons and Stata (StataCorp, Release 16.1. College Station, TX) for data analyses (21). All laboratory values were converted to conventional units. Baseline sepsis, severe sepsis and septic shock rates between HIC, UMIC and LMIC were compared using Kruskal-Wallis tests weighted for study sample sizes.

**3. RESULTS**

*Overview of included studies*

The search yielded 12,343 articles of which 969 underwent full-text review for eligibility. Of these, 863 were excluded (see Figure 1). One hundred and six articles were retained for the systematic review, and 81 articles were used in the meta-analysis. Study characteristics are summarized in Table 1. The majority of studies were conducted at a single site (80/106, 75.5%) and studies included patients from 35 countries. These countries represented all seven regions from the World Bank list of economies with 46.2% (49/106) being from HICs, 30.2% (32/106) from UMICs, 22.6% (24/106) from LMICs, and one study from a LIC. The majority of studies were conducted in the PICU setting (89/106, 84.0%). The patient characteristics for included studies are shown in Table 2. More than half the patients were male (pooled estimate 55.7%, 95% CI: 54.8, 56.6). The majority of studies were of PICU patients (70.8%, 75/106) followed by those from the Emergency Department (10.4%, 11/106).

The most commonly used definition of sepsis was the Goldstein criteria (69.8%, 74/106) (3). The mortality endpoint in included studies was unspecified (n=17 studies) or reported at 72-hours (n=1), PICU discharge (n=14), 28 or 30-days (n=31) or hospital discharge (n=20). In the 107 included studies, the pooled mortality rate using a random-effects model for patients with sepsis was 10.9% (n = 47 studies; 95% CI, 8.9-13.2), for severe sepsis patients was 23.0% (n = 26 studies; 95% CI, 19.6-26.9) and for septic shock patients was 36.8% (n = 28 studies; 95% CI, 29.4-44.9). The pooled mortality rates varied between HIC, UMIC and LMIC locations for sepsis, severe sepsis and septic shock patients (P < 0.0001, see Figure 2).

The studies included in the meta-analysis, their overall risk of bias and the narrative review are detailed in Supplementary Tables 1 and 2 respectively. The variables assessed in the meta-analysis are listed in Supplementary Table 1 and those discussed in the narrative review are summarized in Supplementary Table 2. Forest plots for variables with significant findings are shown in Supplementary Figures 1-8 and associations of these variables with the outcomes of sepsis and mortality are summarized in Table 3.

*Variables associated with sepsis, severe sepsis, septic shock*

Sixteen studies on 9,732 patients provided data for the meta-analysis of the association of 16 variables with the primary outcome of sepsis, severe sepsis, septic shock. Our meta-analysis did not demonstrate an association between age, age groups, gender or malnutrition (22-26) and sepsis, severe sepsis or septic shock. Sepsis among infected children was not associated with pooled estimates of hemoglobin (27-29), C-reactive protein (30,31) or procalcitonin (32,33). Severe sepsis and sepsis among infected children were associated with decreased level of consciousness in (30,31,34,35) and higher PRISM scores (36,37) respectively (Supplementary Figures 3 and 8).

*Variables associated with NPMODS and mortality*

Seventy-one studies (146,182 patients) provided data for the meta-analysis of the association of 52 variables with the primary outcome of mortality. One study reported separately on two populations which were therefore reported as two studies in the meta-analysis (38). Only one study reported NPMODS as an outcome and two reported a composite outcome of NPMODS and death. Meta-analysis with NPMODS as the outcome was not possible as none of these studies assessed the same variables.

The evidence does not support an association between age, age groups or gender with mortality. In addition, no association was noted with race (38,39), obesity (40-42) or malnutrition (22-26) and mortality but only a small number of studies assessed these variables. Pooled estimates supported an increased odds of mortality in patients with severe acute malnutrition (23,43,44), chronic conditions (23,25,45-53), and oncologic conditions (23,38,50,54-57) (Supplementary Figure 1).

*Clinical variables*

Among children with sepsis, pooled estimates provide strong evidence for increased mortality in patients with hypotension (49,50,58,59), use of vasoactive agents/inotropes (23-25,35,43,44,47,52,53,58,60-69), increased vasoactive inotropic score (54,56,68,70-72), decreased level of consciousness (58,59,67), decreased Glasgow Coma Scale (56,70,73) and mechanical ventilation (23,24,35,36,43-47,49,52-54,56,58-62,65-69,71-78) (Supplementary Figure 3). There were no mortality difference in mean heart rate (50,56,58,71,74,79), median mean blood pressure (56,71) and systolic blood pressure (50,58,67,74,79), but the reported values did not account for the ages of included patients. Additionally, non-survivors and survivors had similar central venous pressures (54,56,71) and arterial oxygen saturations (50,58).

*Laboratory variables*

Pooled estimates provided strong support for a difference in the following laboratory measures between non-survivors and survivors: serum pH (56,58,72,73), lactate (46,53,54,56,60-62,65,68,71-74,79-82), serum base deficit (62,71,73,74,83,84), urea (58,74,80,85), creatinine (56,58,71,74,80,82,84,85), platelets (44,46,53,56,58,62,71,75,80,82-84,86,87) and fibrinogen (62,80,83,84,86) potassium (62,71,74), albumin (56,74,82), procalcitonin (27,35,46,74,82,84,88-90) and alanine aminotransferase (58,74,80) (Supplementary Figures 2, 4, 5 and 6). Pooled estimates did not support a difference in mean glucose (53,68,71,72,74), total bilirubin (56,58,74,80,84,85), WBC (35,46,53,56,58,62,71,73-75,80,82,84,86,88), hemoglobin (35,46,53,71,82,84), INR (62,80), PT(56,71,74,80,91,91), aPTT (62,71,80,91,91) and BNP (54,66,74) between non-survivors and survivors.

*Illness severity and organ dysfunction scores*

Our meta-analysis provided strong support for greater organ dysfunction in non-survivors compared to survivors as shown by the pooled estimates for renal dysfunction (53,64,67,70), MODS (25,38,44,53,69,70,92,93), number of organ dysfunctions (36,43,64,82), PELOD (36,38,40,43,47,53,56,60,65,72,84), PELOD-2 (84,85,94), pSOFA (53,58,70,94), SOFA (84,85,94), PRISM (24,40,46,54,56,60-62,64,68,70-73,75,80,83,84,87), PIM-2 (77,84) and PIM-3 (38,61,65,84) (Supplementary Figures 7 and 8).

*Narrative review*

 In patients with septic shock, those with hematopoetic cell transplants had increased odds of mortality (OR 4.74; 95% CI, 2.56, 8.77) (95) and those with progressively higher LODS and AVPU scores demonstrated increasing positive predictive values for early mortality from 40% to 60% and 39.3% to 50% respectively (96). In one study, the Tp-e interval/QT on an ECG was an independent predictor of mortality in patients with septic shock (97). Laboratory values that showed an association with mortality in single studies included red cell distribution width elevation (98), anti-thrombin III levels below 41.5% (< 1 year) and 67.5% (≥ 1 year) (91), 25-hydroxy vitamin < 50 nmol/L (99), baseline cortisol cut-off of 20 µg/dL and post ACTH stimulation level of ≤ 9 µg/dL (100), lower serum zinc levels (101), lower HDL, LDL and cholesterol levels (102) and lower total T3 and T4, and free T3 and T4 hormone levels (103).

 Several studies assessed the association of serum troponin and mortality in sepsis. Two studies provided incomplete data (66,74), another reported an association with a cut-off of > 1 ng/dL (104) and one study found higher levels of troponin in non-survivors compared to survivors (71). Two studies provided differing thresholds of CRP and procalcitonin levels (81.9 nmol/dL and 43 ng/mL) and (154.3 nmol/dL and 19.1 ng/mL) for developing septic shock in patients with meningococcemia (105) and sepsis (106) respectively. Serum lactate levels were studied using three criteria. Serum lactate to albumin ratio > 1.17 was associated with increased mortality (107), a level of > 3 mmol/L with increased risk of sepsis (108) and lack of lactate clearance (decrease of ≤10%) or normalization (< 2 mmol/L) was associated with persistent MODS (109). Finally, several studies assessed thresholds for hemodynamic variables. A VIS of > 20 was associated with increased mortality (110), another suggested time dependant cut-offs for shock index values from 0 to 6 hours post admission (111) and two studies each found an association of a decreased LVEF (45% and 55%) with mortality (112,113).

**4. DISCUSSION**

 Our systematic review and meta-analysis evaluated over 50 variables for their association with sepsis in children with infection and with mortality in children who already had sepsis. We found evidence of increased odds of mortality for septic patients with severe acute malnutrition, chronic conditions, oncologic disorders, hypotension, use of inotropes, mechanical ventilation, decreased level of consciousness and lower GCS. In addition, we found a significant difference in vasoactive-inotropic scores, serum base excess, pH, lactate, platelets, fibrinogen, urea, creatinine, albumin, potassium, ALT, and procalcitonin between non-survivors and survivors. All measures of organ dysfunction and illness severity in sepsis showed significant differences between those who survived and those who died.

 Our study evaluated data from 35 countries in seven geographic regions and all income levels of World Bank Income Classification (18). This is an important consideration given that up to 85% of all sepsis cases and sepsis related deaths occur in lower- and middle-income countries (2). However, although 18 studies were included from LIC and LMIC countries, these represented only 1.8% (2,784/154,474) of the patients analyzed. The potential biases that may be introduced include distinct causes of sepsis (114), limited access to and availability of treatments (115) and higher mortality rates (2) in patients with sepsis from LMIC/LIC versus UMIC/HIC locations. It is possible that a sub-group analysis of the assessed variables in LMIC/LIC countries may have yielded differential results which will need to be accounted for in the data validation phase of the Pediatric Sepsis Definition Taskforce.

 For continuous variables such as vasoactive-inotropic scores and laboratory values, we were not able to determine thresholds for the development of sepsis or for mortality due to lack of data. However, we determined overall means for survivors and non-survivors for variables with a significant mean difference which may provide initial thresholds to be explored in the data analysis phase of the Pediatric Sepsis Definition Taskforce project.

 It could be argued that determination of the association of certain variables with mortality in septic children using pre-established definitions of sepsis may appear to be a self-confirming exercise. However, even though variables such as serum lactate were included in the 2001 Consensus Conference definition (116) and Bone criteria (117), their inclusion was the result of a consensus process and was never formally validated. Furthermore, several of the variables assessed including serum lactate are not included in the Goldstein criteria or ICD-9 codes which were collectively used in 78% of studies and 92.3% of patients.

 This review had several limitations. The first is that several variables in the meta-analysis demonstrated significant heterogeneity. However, since the purpose of this review was to identify potential variables for use in an updated definition of pediatric sepsis rather than draw conclusions regarding a treatment effect, the actual effect size and its associated I2 value may be less relevant. Secondly, our pragmatic approach resulted in the inclusion of studies with different definitions of sepsis. Although this may have limited our ability to find associations of some variables with our outcomes of interest, it may also have contributed to the robustness of the associations for other variables. Thirdly, all included studies were observational and therefore subject to confounding with regards to the outcomes of interest.

This systematic review is the first study to rigorously assess the association of individual variables with development of sepsis in children with infections and the odds of mortality in children with sepsis, severe sepsis and septic shock. The included studies were from economically diverse regions of the world, populations with diverse underlying conditions and varying definitions of sepsis. Despite the clinical heterogeneity and limited number of studies for some variables, strong associations with the outcomes of interest were seen for many of the variables assessed, supporting the value of including these variables in the database validation phase of the Pediatric Sepsis Definition Taskforce.

**List of Abbreviations:**

ESCIM European Society of Intensive Care Medicine

ESPNIC European Society of Pediatric and Neonatal Intensive Care

MODS Multi-Organ Dysfunction Syndrome

OR Odds ratio

PELOD Pediatric Logistic Organ Dysfunction score

PICU Pediatric Intensive Care Unit

PIM Pediatric Index of Mortality

PRISM Pediatric Risk of Mortality

SOFA Sequential (Sepsis-related) Organ Failure Assessment

pSOFA pediatric Sequential (Sepsis-related) Organ Failure Assessment

SSC Surviving Sepsis Campaign

SCCM Society of Critical Care Medicine

SIRS Systemic Inflammatory Response Syndrome

SOFA Sequential (Sepsis-related) Organ Failure Assessment

VIS Vasopressor Inotrope Score

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References

 1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.

 2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.

 3. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.

 4. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med 2020;21:e52-e106.

 5. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.

 6. Agyeman PKA, Schlapbach LJ, Giannoni E, et al. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. Lancet Child Adolesc Health 2017;1:124-33.

 7. Volakli EA, Sdougka M, Drossou-Agakidou V, et al. Short-term and long-term mortality following pediatric intensive care. Pediatr Int 2012;54:248-55.

 8. Pollack MM, Holubkov R, Funai T, et al. Simultaneous Prediction of New Morbidity, Mortality, and Survival Without New Morbidity From Pediatric Intensive Care: A New Paradigm for Outcomes Assessment. Crit Care Med 2015;43:1699-709.

 9. Alberico AM, Ward JD, Choi SC, et al. Outcome after severe head injury. Relationship to mass lesions, diffuse injury, and ICP course in pediatric and adult patients. J Neurosurg 1987;67:648-56.

 10. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015;191:1147-57.

 11. Choong K, Bohn D, Fraser DD, et al. Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial. Am J Respir Crit Care Med 2009;180:632-9.

 12. Lauzier F, Levy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Med 2006;32:1782-9.

 13. Menon K, Schlapbach LJ, Akech S, et al. Pediatric Sepsis Definition-A Systematic Review Protocol by the Pediatric Sepsis Definition Taskforce. Crit Care Explor 2020;2:e0123.

 14. Nama N, Sampson M, Barrowman N, et al. Crowdsourcing the Citation Screening Process for Systematic Reviews: Validation Study. J Med Internet Res 2019;21:e12953.

 15. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

 16. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;%19;158:280-6.

 17. Voils CI, Crandell JL, Chang Y, et al. Combining adjusted and unadjusted findings in mixed research synthesis. J Eval Clin Pract 2011;17:429-34.

 18. World Bank Economies. World Bank 2019.

 19. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. Second edition ed. 2020.

 20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.

 21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

 22. Branco RG, Garcia PC, Piva JP, et al. Glucose level and risk of mortality in pediatric septic shock. Pediatr Crit Care Med 2005;6:470-2.

 23. Jabornisky R, Saenz SS, Capocasa P, et al. Epidemiological study of pediatric severe sepsis in Argentina. Arch Argent Pediatr 2019;117:S135-S156.

 24. Kaur G, Vinayak N, Mittal K, et al. Clinical outcome and predictors of mortality in children with sepsis, severe sepsis, and septic shock from Rohtak, Haryana: A prospective observational study. Indian J Crit Care Med 2014;18:437-41.

 25. Khan MR, Maheshwari PK, Masood K, et al. Epidemiology and outcome of sepsis in a tertiary care PICU of Pakistan. Indian J Pediatr 2012;79:1454-8.

 26. Villegas, D. and Echandia, C. A. Factors associated with mortality through sepsis syndrome in children 31 days to 14 years of age. Colombia Medica 41[4], 349-357. 2010.
Ref Type: Journal (Full)

 27. Sakyi SA, Enimil A, Adu DK, et al. Individual and combined bioscore model of presepsin, procalcitonin, and high sensitive C - reactive protein as biomarkers for early diagnosis of paediatric sepsis. Heliyon 2020;6:e04841.

 28. Wiens MO, Larson CP, Kumbakumba E, et al. Application of Sepsis Definitions to Pediatric Patients Admitted With Suspected Infections in Uganda. Pediatr Crit Care Med 2016;17:400-5.

 29. Yang J, Ma Y, Mao M, et al. Application of regression model combined with computer technology in the construction of early warning model of sepsis infection in children. J Infect Public Health 2020;13:253-9.

 30. Santolaya ME, Alvarez AM, Aviles CL, et al. Predictors of severe sepsis not clinically apparent during the first twenty-four hours of hospitalization in children with cancer, neutropenia, and fever: a prospective, multicenter trial. Pediatr Infect Dis J 2008;27:538-43.

 31. Wang Y, Lin X, Yue H, et al. Evaluation of systemic inflammatory response syndrome-negative sepsis from a Chinese regional pediatric network. BMC Pediatr 2019;19:11-1364.

 32. Alejandre C, Guitart C, Balaguer M, et al. Use of procalcitonin and C-reactive protein in the diagnosis of bacterial infection in infants with severe bronchiolitis. Eur J Pediatr 2020;10-03790.

 33. Smok B, Domagalski K, PawÅ‚owska M. Diagnostic and Prognostic Value of IL-6 and sTREM-1 in SIRS and Sepsis in Children. Mediators Inflamm 2020;2020:8201585. doi: 10.1155/2020/8201585. eCollection;%2020.:8201585.

 34. Chisti MJ, Salam MA, Bardhan PK, et al. Severe Sepsis in Severely Malnourished Young Bangladeshi Children with Pneumonia: A Retrospective Case Control Study. PLoS One 2015;10:e0139966.

 35. Shah S, Kaul A, Jadhav Y, Shiwarkar G. Clinical outcome of severe sepsis and septic shock in critically ill children. Trop Doct 2020;50:186-90.

 36. de Souza DC, Shieh HH, Barreira ER, et al. Epidemiology of Sepsis in Children Admitted to PICUs in South America. Pediatr Crit Care Med 2016;17:727-34.

 37. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr 2017;171:e172352.

 38. Thakkar RK, Weiss SL, Fitzgerald JC, et al. Risk Factors for Mortality in Pediatric Postsurgical versus Medical Severe Sepsis. J Surg Res 2019;242:100-110. doi: 10.1016/j.jss.2019.04.011. Epub;%2019 May 7.:100-10.

 39. Markovitz BP, Goodman DM, Watson RS, et al. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? Pediatr Crit Care Med 2005;6:270-4.

 40. Ibrahiem SK, Galal YS, Youssef MR, et al. Prognostic markers among Egyptian children with sepsis in the Intensive Care Units, Cairo University Hospitals. Allergol Immunopathol (Madr) 2016;44:46-53.

 41. Peterson LS, GÃ¡llego SrC, Segaloff HE, et al. Outcomes and Resource Use Among Overweight and Obese Children With Sepsis in the Pediatric Intensive Care Unit. J Intensive Care Med 2020;35:472-7.

 42. Ross PA, Klein MJ, Nguyen T, et al. Body Habitus and Risk of Mortality in Pediatric Sepsis and Septic Shock: A Retrospective Cohort Study. J Pediatr 2019;210:178-183.e2. doi: 10.1016/j.jpeds.2019.03.027. Epub;%2019 Apr 26.:178-83.

 43. Baranwal AK, Deepthi G, Rohit MK, et al. Longitudinal Study of CPK-MB and Echocardiographic Measures of Myocardial Dysfunction in Pediatric Sepsis: Are Patients with Shock Different from Those without? Indian J Crit Care Med 2020;24:109-15.

 44. Shah S, Deshmukh CT, Tullu MS. The predictors of outcome and progression of pediatric sepsis and septic shock: A prospective observational study from western India. J Postgrad Med 2020;66:67-72.

 45. Ames SG, Davis BS, Angus DC, et al. Hospital Variation in Risk-Adjusted Pediatric Sepsis Mortality. Pediatr Crit Care Med 2018;19:390-6.

 46. Isguder R, Ceylan G, Agin H, et al. Increased mean platelet volume in children with sepsis as a predictor of mortality. Turk J Pediatr 2016;58:503-11.

 47. Lanziotti VS, Pavoa P, Prata-Barbosa A, et al. Patterns of C-reactive protein ratio response to antibiotics in pediatric sepsis: A prospective cohort study. J Crit Care 2018;44:217-222. doi: 10.1016/j.jcrc.2017.11.018. Epub;%2017 Nov 11.:217-22.

 48. Prout AJ, Talisa VB, Carcillo JA, et al. Children with Chronic Disease Bear the Highest Burden of Pediatric Sepsis. J Pediatr 2018;199:194-199.e1. doi: 10.1016/j.jpeds.2018.03.056. Epub;%2018 May 9.:194-9.

 49. Schlapbach LJ, MacLaren G, Festa M, et al. Prediction of pediatric sepsis mortality within 1 h of intensive care admission. Intensive Care Med 2017;43:1085-96.

 50. Scott HF, Brou L, Deakyne SJ, et al. Association Between Early Lactate Levels and 30-Day Mortality in Clinically Suspected Sepsis in Children. JAMA Pediatr 2017;171:249-55.

 51. Shime N, Kawasaki T, Saito O, et al. Incidence and risk factors for mortality in paediatric severe sepsis: results from the national paediatric intensive care registry in Japan. Intensive Care Med 2012;38:1191-7.

 52. Tonial CT, Costa CAD, Andrades GRH, et al. Performance of prognostic markers in pediatric sepsis. J Pediatr (Rio J) 2020;10.

 53. Vila-Perez D., Jordan I, Esteban E, et al. Prognostic factors in pediatric sepsis study, from the Spanish Society of Pediatric Intensive Care. Pediatr Infect Dis J 2014;33:152-7.

 54. Choi SJ, Ha EJ, Jhang WK, Park SJ. Elevated central venous pressure is associated with increased mortality in pediatric septic shock patients. BMC Pediatr 2018;18:58-1059.

 55. Dagher GA, Safa R, Hajjar K, et al. Characteristics and Outcomes of Pediatric Septic Patients With Cancer: A Retrospective Cohort Study. J Emerg Med 2019;57:216-26.

 56. Nazir, M., Wani, W., Dar, S. A., Mir, I., Charoo, B. A., Ahmad, Q. I., and Wajid, S. Lactate clearance prognosticates outcome in pediatric septic shock during first 24h of intensive care unit admission. Journal of the Intensive Care Society 20[4], 290-298. 2019.
Ref Type: Journal (Full)

 57. Pound CM, Johnston DL, Armstrong R, et al. The morbidity and mortality of pediatric oncology patients presenting to the intensive care unit with septic shock. Pediatr Blood Cancer 2008;51:584-8.

 58. Jaiswal P, Dewan P, Gomber S, et al. Early lactate measurements for predicting in-hospital mortality in paediatric sepsis. J Paediatr Child Health 2020;56:1570-6.

 59. Peters C, Murthy S, Brant R, et al. Mortality Risk Using a Pediatric Quick Sequential (Sepsis-Related) Organ Failure Assessment Varies With Vital Sign Thresholds. Pediatr Crit Care Med 2018;19:e394-e402.

 60. Alam A, Gupta S. Lactate Measurements and Their Association With Mortality in Pediatric Severe Sepsis in India: Evidence That 6-Hour Level Performs Best. J Intensive Care Med 2020;885066620903231.

 61. Boeddha NP, Schlapbach LJ, Driessen GJ, et al. Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS). Crit Care 2018;22:143-2052.

 62. Couto-Alves A, Wright VJ, Perumal K, et al. A new scoring system derived from base excess and platelet count at presentation predicts mortality in paediatric meningococcal sepsis. Crit Care 2013;17:R68.

 63. Carvalho MV, Maluf MA, Catani R, et al. Cytokines and pediatric open heart surgery with cardiopulmonary bypass. Cardiol Young 2001;11:36-43.

 64. Fiser RT, West NK, Bush AJ, et al. Outcome of severe sepsis in pediatric oncology patients. Pediatr Crit Care Med 2005;6:531-6.

 65. Gorgis N, Asselin JM, Fontana C, et al. Evaluation of the Association of Early Elevated Lactate With Outcomes in Children With Severe Sepsis or Septic Shock. Pediatr Emerg Care 2019;35:661-5.

 66. Li J, Ning B, Wang Y, et al. The prognostic value of left ventricular systolic function and cardiac biomarkers in pediatric severe sepsis. Medicine (Baltimore) 2019;98:e15070.

 67. Sarmin M, Afroze F, Sharifuzzaman, et al. Predictor of Death in Diarrheal Children Under 5 Years of Age Having Severe Sepsis in an Urban Critical Care Ward in Bangladesh. Glob Pediatr Health 2019;6:2333794X19862716. doi: 10.1177/2333794X19862716. eCollection;%2019.:2333794X19862716.

 68. Verhoeven JJ, den BM, Hokken-Koelega AC, et al. Pathophysiological aspects of hyperglycemia in children with meningococcal sepsis and septic shock: a prospective, observational cohort study. Crit Care 2011;15:R44.

 69. Wang C, Cui Y, Miao H, et al. Circulating Vitronectin Predicts Liver Injury and Mortality in Children With Sepsis: A Prospective Observational Study. Clin Appl Thromb Hemost 2020;26:1076029620935201. doi: 10.1177/1076029620935201.:1076029620935201.

 70. Angurana SK, Bansal A, Muralidharan J, et al. Cytokine Levels in Critically Ill Children With Severe Sepsis and Their Relation With the Severity of Illness and Mortality. J Intensive Care Med 2020;885066620912989.

 71. El-Zayat RS, Shalaby AG. Mitral Annular Plane Systolic Excursion as a Predictor of Mortality in Children With Septic Shock. Pediatr Crit Care Med 2018;19:e486-e494.

 72. Sachdev A, Raheja K, Gupta N, Chugh P. Association of Urinary Albumin:Creatinine Ratio with Outcome of Children with Sepsis. Indian J Crit Care Med 2020;24:465-72.

 73. Choudhary R, Sitaraman S, Choudhary A. Lactate clearance as the predictor of outcome in pediatric septic shock. J Emerg Trauma Shock 2017;10:55-9.

 74. Chen M, Lu X, Hu L, et al. Development and validation of a mortality risk model for pediatric sepsis. Medicine (Baltimore) 2017;96:e6923.

 75. Choi SJ, Ha E, Jhang WK, Park SJ. Platelet indices as predictive markers of prognosis in pediatric septic shock patients. Iranian Journal of Pediatrics 2017;27:e2712.

 76. da Silva ED, Koch Nogueira PC, Russo Zamataro TM, et al. Risk factors for death in children and adolescents with cancer and sepsis/septic shock. J Pediatr Hematol Oncol 2008;30:513-8.

 77. Goonasekera CDA, Carcillo JA, Deep A. Oxygen Delivery and Oxygen Consumption in Pediatric Fluid Refractory Septic Shock During the First 42 h of Therapy and Their Relationship to 28-Day Outcome. Front Pediatr 2018;6:314. doi: 10.3389/fped.2018.00314. eCollection;%2018.:314.

 78. Ostrowski JA, MacLaren G, Alexander J, et al. The burden of invasive infections in critically ill Indigenous children in Australia. Med J Aust 2017;206:78-84.

 79. Rousseaux J, Grandbastien B, Dorkenoo A, et al. Prognostic value of shock index in children with septic shock. Pediatr Emerg Care 2013;29:1055-9.

 80. Tang X, Shao L, Dou J, et al. Fibrinogen as a Prognostic Predictor in Pediatric Patients with Sepsis: A Database Study. Mediators Inflamm 2020;2020:9153620.:9153620.

 81. Tonial CT, Costa CAD, Andrades GRH, et al. Prediction of Poor Outcomes for Septic Children According to Ferritin Levels in a Middle-Income Setting. Pediatr Crit Care Med 2020;21:e259-e266.

 82. Xie X, Li M, Xiong TT, et al. Nested case-control study of multiple serological indexes and Brighton pediatric early warming score in predicting death of children with sepsis. World J Clin Cases 2019;7:431-40.

 83. Maat, M., Buysse, C. M. P., Emonts, M., Spanjaard, L., Joosten, K. F. M., De Groot, R., and Hazelzet, J. A. Improved survival of children with sepsis and purpura: effects of age, gender, and era. Critical Care 11[5], 1-10. 10-18-2007.
Ref Type: Journal (Full)

 84. Niederwanger C, Varga T, Hell T, et al. Comparison of pediatric scoring systems for mortality in septic patients and the impact of missing information on their predictive power: a retrospective analysis. PeerJ 2020;8:e9993.:e9993.

 85. Zhong M, Huang Y, Li T, et al. Day-1 PELOD-2 and day-1 "quick" PELOD-2 scores in children with sepsis in the PICU. J Pediatr (Rio J) 2020;96:660-5.

 86. Niederwanger C, Bachler M, Hell T, et al. Inflammatory and coagulatory parameters linked to survival in critically ill children with sepsis. Ann Intensive Care 2018;8:111-0457.

 87. Sayed SZ, Mahmoud MM, Moness HM, Mousa SO. Admission platelet count and indices as predictors of outcome in children with severe Sepsis: a prospective hospital-based study. BMC Pediatr 2020;19;20:387-02278.

 88. Lawang SA, Jayaganda DD. White Blood Cell, Procalcitonin, C-Reactive Protein and TNF-alpha as Prognostic Factors in Pediatric Sepsis. Indian Journal of Public Health Research and Development 2019;10:708-13.

 89. Liu GB, Cui XQ, Wang ZB, et al. Detection of Serum Procalcitonin and Hypersensitive C-Reative Protein in Patients with Pneumonia and Sepsis. Journal of Biological Regulators and Homeostatic Agents 2018;32:1165-9.

 90. Wu Q, Nie J, Wu FX, et al. Prognostic Value of High-Sensitivity C-Reactive Protein, Procalcitonin and Pancreatic Stone Protein in Pediatric Sepsis. Med Sci Monit 2017;23:1533-1539. doi: 10.12659/msm.900856.:1533-9.

 91. Niederwanger C, Hell T, Hofer S, et al. Antithrombin deficiency is associated with mortality and impaired organ function in septic pediatric patients: a retrospective study. PeerJ 2018;6:e5538. doi: 10.7717/peerj.5538. eCollection;%2018.:e5538.

 92. Jaramillo-Bustamante JC, MarÃ­n-Agudelo A, FernÃ¡ndez-Laverde M, BareÃ±o-Silva J. Epidemiology of sepsis in pediatric intensive care units: first Colombian multicenter study. Pediatr Crit Care Med 2012;13:501-8.

 93. Xiao C, Wang S, Fang F, et al. Epidemiology of Pediatric Severe Sepsis in Main PICU Centers in Southwest China. Pediatr Crit Care Med 2019;20:1118-25.

 94. Mianling Z, Yuge H, Tufeng L, et al. 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. Iranian Journal of Pediatrics 2019;29:e89024.

 95. Lindell RB, Gertz SJ, Rowan CM, et al. High Levels of Morbidity and Mortality Among Pediatric Hematopoietic Cell Transplant Recipients With Severe Sepsis: Insights From the Sepsis PRevalence, OUtcomes, and Therapies International Point Prevalence Study. Pediatr Crit Care Med 2017;18:1114-25.

 96. Kortz TB, Sawe HR, Murray B, et al. Clinical Presentation and Outcomes among Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania. Front Pediatr 2017;5:278. doi: 10.3389/fped.2017.00278. eCollection;%2017.:278.

 97. Ozdemir R, Isguder R, Kucuk M, et al. A Valuable Tool in Predicting Poor Outcome due to Sepsis in Pediatric Intensive Care Unit: Tp-e/QT Ratio. J Trop Pediatr 2016;62:377-84.

 98. Khanbabaee G, Hashemi SM, Salarian S, et al. Red Cell Distribution Width Elevation and Sepsis in Pediatric Critically Ill Patients. Archives of Pediatric Infectious Diseases 2010;6:e12210.

 99. Onwuneme C, Carroll A, Doherty D, et al. Inadequate vitamin D levels are associated with culture positive sepsis and poor outcomes in paediatric intensive care. Acta Paediatr 2015;104:e433-e438.

 100. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. Crit Care Med 2005;33:855-9.

 101. Saleh NY, bo El Fotoh WMM. Low serum zinc level: The relationship with severe pneumonia and survival in critically ill children. Int J Clin Pract 2018;72:e13211.

 102. Vermont CL, den BM, KÃ¢keci N, et al. Serum lipids and disease severity in children with severe meningococcal sepsis. Crit Care Med 2005;33:1610-5.

 103. Yildizdas D, Yapicioglu H, Celik U, et al. Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. Intensive Care Med 2008;34:511-7.

 104. Oliveira NS, Silva VR, Castelo JS, et al. Serum level of cardiac troponin I in pediatric patients with sepsis or septic shock. Pediatr Crit Care Med 2008;9:414-7.

 105. Carrol ED, Newland P, Thomson AP, Hart CA. Prognostic value of procalcitonin in children with meningococcal sepsis. Crit Care Med 2005;33:224-5.

 106. Rey C, Los AM, Concha A, et al. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. Intensive Care Med 2007;33:477-84.

 107. Moustafa, A. A., Antonios, A. M., Abdellatif, E. M., and Hussain, A. H. Association of lactate/albumin ratio level to organ failure and mortality in severe sepsis in a pediatric intensive care unit in Egypt. The Turkish Journal of Pediatrics 60[6], 691-701. 12-24-2017.

 108. Reed L, Carroll J, Cummings A, et al. Serum lactate as a screening tool and predictor of outcome in pediatric patients presenting to the emergency department with suspected infection. Pediatr Emerg Care 2013;29:787-91.

 109. Scott HF, Brou L, Deakyne SJ, et al. Lactate Clearance and Normalization and Prolonged Organ Dysfunction in Pediatric Sepsis. J Pediatr 2016;170:149-55.

 110. Haque A, Siddiqui NR, Munir O, et al. Association between vasoactive-inotropic score and mortality in pediatric septic shock. Indian Pediatr 2015;52:311-3.

 111. Gupta S, Alam A. Shock Index-A Useful Noninvasive Marker Associated With Age-Specific Early Mortality in Children With Severe Sepsis and Septic Shock: Age-Specific Shock Index Cut-Offs. J Intensive Care Med 2020;35:984-91.

 112. Lautz AJ, Wong HR, Ryan TD, Statile CJ. Myocardial Dysfunction Is Independently Associated With Mortality in Pediatric Septic Shock. Crit Care Explor 2020;2:e0231.

 113. Sankar J, Das RR, Jain A, et al. Prevalence and outcome of diastolic dysfunction in children with fluid refractory septic shock--a prospective observational study. Pediatr Crit Care Med 2014;15:e370-e378.

 114. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-95.

 115. Wiens MO, Kumbakumba E, Kissoon N, et al. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. Clin Epidemiol 2012;4:319-25. doi: 10.2147/CLEP.S35693. Epub;%2012 Nov 22.:319-25.

 116. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29:530-8.

 117. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.