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PRIMARY OUTCOME MEASURES IN PEDIATRIC SEPTIC SHOCK: SYSTEMATIC REVIEW

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Abstract

Introduction: *Sepsis is a major cause of mortality in pediatric populations, with 22 cases per 100,000 live births in infants and 2,202 cases per 100,000 live births in neonates, causing an annual burden of 1.2 million cases. There is currently no consensus regarding the most appropriate to measure the primary outcome of pediatric septic shock.*

Objective: *The aim of this study was to determine the primary outcome that should be assessed in pediatric patients who experience sepsis shock*

Methods: *Based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), we searched literature from several databases (PubMed, ScienceDirect, and Web of Science) following PRISMA guidelines. The following keywords are used: ((Primary) AND (Outcome) AND (Measure) OR (Indicator) AND (Pediatric) OR (Childern) AND (Septic) AND (Shock)). Manual searches are also conducted to get relevant articles that meet the mentioned criteria. Data were extracted based on author, year, study design, sample size, results and discussion.*

Results: *In this systematic review, we found a total of five studies, with three types of prospective studies and two retrospective studies. A total of 5.164 cases were involved in the study, with a range years 2014 to 2023. Of the five studies, all discussed that mortality was the primary outcome measured in pediatric patients with septic shock. Other indicators that can be measured as outcomes in patients are length of hospitalization, clearance from lactic acid, and occurrence of multiple organ disfunction.*

Conclusion: *In pediatric patients with sepsis shock there are several primary outcomes that can be assessed. Some literature suggests that mortality is a major outcome to be considered.*

Keywords: *Outcome; Septic Shock; Pediatric*

INTRODUCTION

Sepsis is the primary cause of death among children, with the burden being greatest in nations with the fewest resources to treat it. In 2017, sepsis is recognized as a significant global health issue. The global incidence of pediatric sepsis is estimated to be 22 cases per 100,000 children annually, whereas neonatal sepsis affects around 2,202 instances. Consequently, the total number of pediatric sepsis cases per year amounts to approximately 1.2 million. In high-income nations, sepsis affects around 4% of hospitalized patients below the age of 18, and approximately 8% of patients admitted to pediatric intensive care units.[1]

Children with sepsis have a mortality rate between 4% and 50%, depending on disease severity, risk factors, and geographic location[2]. A local study reported that in Dr. Cipto RS Mangunkusumo[3] In 2011, the primary etiology of sepsis in children was found to be associated with various organ systems, including the respiratory system, central nervous system, urinary system, and gastrointestinal system. A significant number of infants diagnosed with sepsis and refractory shock with Multiple Organ Dysfunction Syndrome (MODS) unfortunately succumb to mortality during the initial 48-72 hours of receiving medical intervention. Given the high incidence of this condition, urgent interventions are needed as well as new treatment designs with collaborative efforts to improve our understanding of sepsis.[4]

Complex pathogenesis is one of the hallmarks of sepsis. It can present with a variety of clinical symptoms and lack of specificity. Hence, it is not feasible to provide a concise and definitive description. Hence, the conceptualization of sepsis has undergone modifications throughout history, with diverse definitions and terminology employed in studies published until the late 1980s, including sepsis, septicaemia, general infection, and sepsis syndrome. Consequently, comparing findings across various studies has proven to be a tough endeavor.[5]

Childhood mortality resulting from infectious illnesses and septic shock is a complex phenomenon influenced by a combination of host-related, agent-related, and environmental factors. In industrialized countries, the death rate from septic shock is found to be higher in individuals with certain host features, including of chronic disorders such as neoplastic, immunological, and hematological conditions, as well as specific infectious agent characteristics. On the other hand, it is important to note that in low- and middle-income nations, various factors contribute to mortality rates. Numerous studies conducted in both developed and developing countries have shown evidence that mortality resulting from septic shock is linked to inadequate healthcare provision, encompassing delayed diagnosis and treatment, as well as nonadherence to treatment protocols.[5–7]

In a retrospective observational study conducted within the emergency department and critical care unit of two academic pediatric facilities, Weiss et al. discovered a substantial mortality rate (49%) within the first week following the identification of pediatric sepsis. This study examines the characteristics of children who died from sepsis within three days of its onset. The findings show that younger children have a greater likelihood of developing community-acquired sepsis.[8] Due to delays in diagnosis and medical intervention, neonates may die from refractory shock. In a different investigation, Cvetkovic et al. found that a mortality rate of 26% occurred in children who developed sepsis before their admission to the Pediatric Intensive Care Unit (PICU). In addition, it was shown that 50% of children referred for intensive care due to severe sepsis experienced death within the first 24-hour period.[8]

Clinical research is essential to support progress and improvement in the intervention of pediatric patients with septic shock.[9] Survival is becoming a key indicator as a significant outcome by medical professionals, researchers in the context of critical illnesses. Nevertheless, the use of death as the primary outcome measure in clinical studies for pediatric patients with septic shock may not always be feasible, given the fluctuating mortality rates and limited patient population. [10,11] As a result, several studies employ primary outcome measures, such as the duration of vasoactive-free hemodynamic stability and the presence of organ failure, to evaluate the effectiveness of therapies for septic shock in pediatric patients. At now, a consensus has not been reached about the optimal and feasible outcome measure for intervention trials in the context of pediatric septic shock. Hence, there is a need for a comprehensive study that examines the key outcome measure in pediatric septic shock.

METHODS

1. Eligibility criteria

The following are the inclusion criteria for this study:

- Published in English and accessible in its entirety.
- Issued between January 20, 2013 and 2023.
- The studies employed are cohort, case-control, case-series, cross-sectional, and randomized controlled trials (RCTs).
- The research examines the primary outcome measure in pediatric septic shock.

2. Guideline

In this investigation, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As depicted in the flowchart in Figure 1, we included five corresponding studies in our review.

3. Search strategy

Following PRISMA guidelines, two researchers (XX and XX) independently conducted a search for relevant articles in multiple databases (PubMed, ScienceDirect, and Web of Science) on August 17, 2023. ((Primary) AND (Outcome) AND (Measure) OR (Indicator) AND (Pediatric) OR (Children) AND (Septic) AND (Shock)) are used as keywords. Additionally, manual searches are conducted to obtain articles that satisfy the specified criteria. Discrepancies are resolved through consensus with the third author (XX).

Based on the author, year, study design, sample size, results, and discussion, data were extracted. Primary outcomes are the factors measured to determine the primary outcome of patients in the pediatric population with septic shock.

RESULT

Study characteristics

In this systematic review, we found a total of five studies, with three types of prospective studies and two retrospective studies. A total of 5164 cases were involved in the study. With an age range from 1 month to 15 years. Studies come from various countries including Brazil, India, Utah, and the USA. With a range of research years, namely 2014 to 2023. All studies addressed the measurement of primary outcomes in pediatric patients with septic shock.

Primary Outcome in Pediatric Shock Septic

Of the five studies, all discussed that mortality was the primary outcome measured in pediatric patients who experienced septic shock. Other indicators that can be measured as primary outcomes in patients are length of hospitalization, clearance from lactic acid, occurrence of multiple organ disfunction.

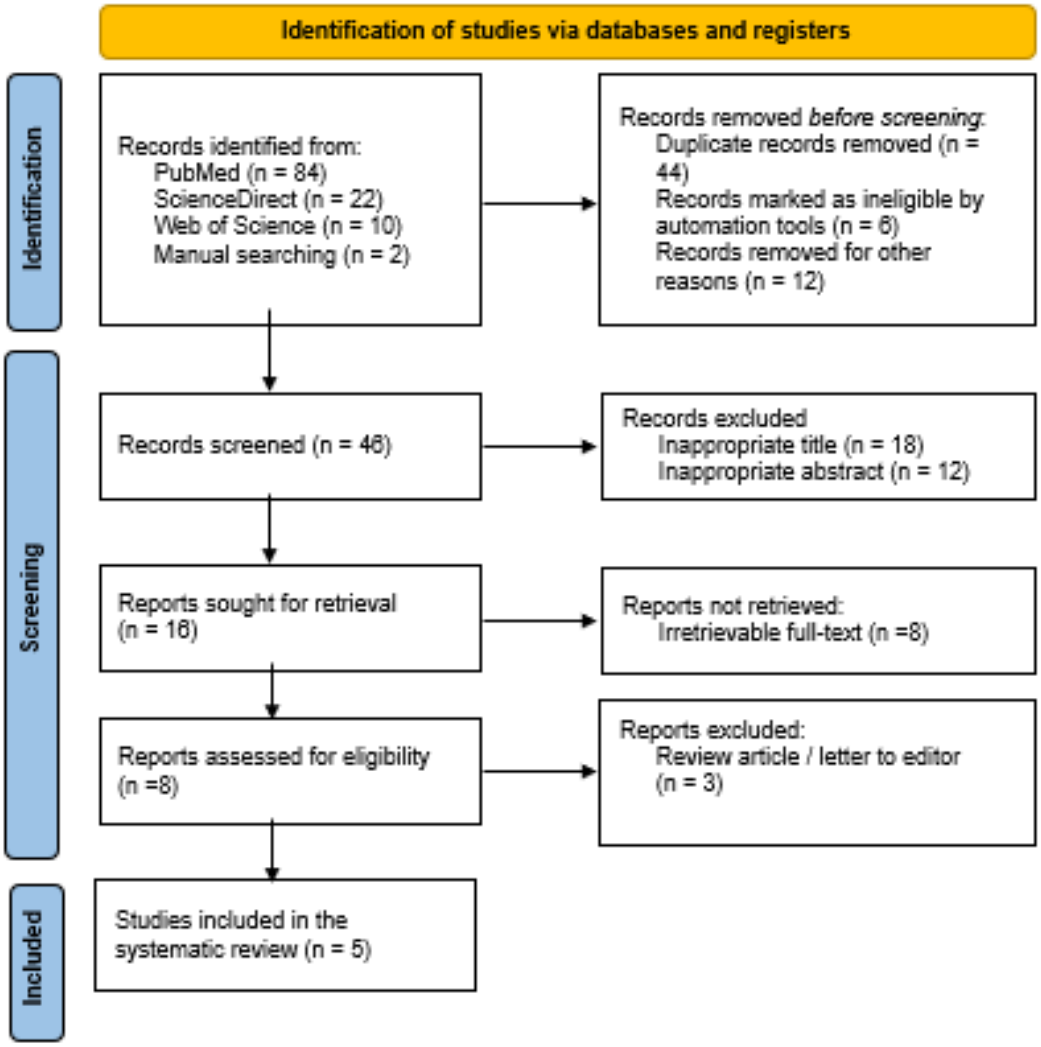

Figure 1. Flowchart PRISMA

Table 1. Characteristic Studies

No	Author	Study Design	Sample size	Age	Results	Discussion
1.	Kaur, et al., 2014[12]	Prospective observational study	50 patients	18 ± 6, 60 months	• Mortality was not significantly predicted by any factor individually, including age (OR [95% CI: 0.96 [0.91-1.01], P = 0.17), • duration of PICU stay (OR [1.18 [0.99-1.25], P = 0.054) • time lag to PICU transfer (OR: 1.02 [0.93-1.12], P = 0.63). • Organ dysfunction prevalence (OR 0.03 [0.01-0.53], P =0.08)	No statistically significant correlation was observed between any specific factor, including the time delay in transferring to the pediatric intensive care unit (PICU), the length of stay in the PICU, the occurrence of multiorgan failure, or the Pediatric Risk of death (PRISM) score upon admission, and the mortality rate among children diagnosed with sepsis, severe sepsis, and septic shock.
2	Choudhary, et al., 2017[13]	Prospective observational study	713	55.1±50.5 months	• Nonsurvivors had significantly higher admission lactate levels than survivors, with a 4 mmol/L level best predicting mortality. Survivors had significantly higher mean lactate clearance, with a 10% rate at 24 hours having a 78.7% sensitivity, 72.2% specificity, and 83.1% positive predictive value for mortality. Failure to achieve this clearance was associated with an increased risk of mortality.	Lactate levels have the potential to serve as a prognostic indicator for the outcome of septic shock in pediatric patients. The prediction of hospital mortality in these patients can be made based on a lactate clearance threshold of 10% during a 24-hour period.
3	Ames, et al., 2016[14]	Retrospective cohort	321	65 (13–156) months	• The main objective of the study was to assess the occurrence of new or worsening multiple system organ dysfunction syndrome (NP-MODS) as the major result, while mortality served as the secondary endpoint.	The study findings indicate that children diagnosed with septic shock who received treatment within one hour at a children's hospital emergency department exhibited significantly higher levels of illness severity compared to those who received treatment at a later time. However, there was no observed increase in their likelihood of developing NP-MODS (non-pulmonary multiple organ dysfunction syndrome) or mortality.
4	Mullan, et al., 2023[15]	Retrospective cohort	3969	5.8 (2.3–12.3) years	• The parameters assessed in pediatric patients with septic shock encompass 30-day mortality, as well as the need for intubation and non-invasive positive pressure ventilation (NIPPV).	In this database on pediatric sepsis, quicker ED IVF bolus administration rates were associated with increased mortality, intubation, and NIPPV probabilities. To assess the reproducibility of these associations, controlled experiments are necessary.
5	Ventura, et al.,[16] 2015	Prospective RCT	120	1 month to 15 years	• The primary outcome was death within 28 days of inclusion from any cause. Secondary outcomes included HAI, the need for other vasoactive medications, and the multiple organ dysfunction score.	The primary outcome was a comparison dopamine and epinephrine effects on 28-day mortality in severe sepsis patients; examining healthcare-associated infection, medication requirements, and multiple organ dysfunction scores.

DISCUSSION

The most frequently reported outcome measure is the death rate. Mortality may be a viable outcome measure in developing nations due to its high frequency and low cost of measurement. Despite this, a number of studies have uncovered significant limitations associated with using mortality as the primary outcome measure. The first is that mortality is typically overestimated during study design and sample size determination. Second, the anticipated decline in mortality is frequently so optimistic that observed mortality trends may not be statistically significant. In addition, it is crucial to take into account the limitations of potential fatalities other than those described in the study as significant outcomes. This is because not all sepsis interventions are expected to decrease mortality. Thirdly, a focus on mortality implies that interventions that do not reduce mortality are not clinically significant and, consequently, do not account for important outcomes such as Health-Related Quality of Life (HRQL) and long-term morbidity.

Short-term mortality is often overlooked in pediatric sepsis, especially in children with chronic diseases. Other primary outcome measurements include physiological markers like recovery time and the emergence of new or progressive MODS. A recent study found 30% of pediatric septic shock patients developed new or progressive MODS, highlighting the potential value of organ dysfunction as an outcome measure.

Several randomized controlled trials (RCTs) in pediatric intensive care have shown improved physiological outcomes without significant improvements in clinical outcomes. Consequently, it is not optimal to use these metrics alone as the principal outcome. Although duration of mechanical ventilation, length of stay in the pediatric intensive care unit, and length of hospital stay are frequently measured, they are not used as primary outcome measures.[17]

A systematic review of primary outcome measures in clinical trials of pediatric septic shock reveals that the use of mortality alone has significant limitations, and long-term outcomes should be investigated. Therefore, a standardized method for evaluating trial results is essential. The Core Outcome Set (COS), which is defined as a set of minimum outcomes that must be consistently measured and reported in clinical trials for a particular clinical area, is gaining popularity as a solution to this issue.[18]

The American College of Critical Care Medicine's Surviving Paediatric Sepsis Guidelines emphasize early resuscitation techniques for pediatric patients with septic shock. They recommend aggressive fluid resuscitation with repeated intravenous fluid boluses, potentially up to 200 mL/kg. However, excessive fluid resuscitation is associated with increased morbidity and mortality, leading to debates on its primary outcome.[1]

Elevated serum lactate levels in patients with septic shock reflect anaerobic metabolism associated with cellular hypoxia and are regarded as an important marker of tissue perfusion disorders. Observational studies conducted on adults and children have demonstrated a correlation between lactate and the severity of shock and prognosis in sepsis. Although the sensitivity and specificity of a single lactate concentration as a marker of tissue hypoperfusion have been debated, its usefulness as a biomarker has been established. The serial measurement or clearance of lactate clearance (LC) over time is a more accurate predictor of organ failure and mortality, according to studies. In addition, adult studies have established lactate and LC as diagnostic, prognostic, and therapeutic markers of global tissue hypoxia in sepsis and septic shock; however, the literature on their potential prognostic function in pediatric septic shock is minimal. Moreover, there are no data comparing LC at different intervals during pediatric septic shock resuscitation.[19,20]

Other studies indicate that lactate clearance is a significant predictor of mortality in children with sepsis. In a research, the lactate levels of critically ill infants were analyzed. Due to the fact that lactic clearance reflects variations in lactate metabolism, it is a more accurate predictor of mortality in children with sepsis than lactate clearance alone. Patients with sepsis who respond to treatment have increased lactic clearance because pyruvate dehydrogenase converts accumulated lactate to pyruvic acid, which is then converted to acetic acid and enters the Krebs cycle. Lactate clearance is decreased in sepsis patients who do not respond to treatment; however, long-term lactate accumulation in the body can contribute to tissue hypoxia.[21]

Conclusion

In pediatric patients with sepsis shock there are several primary outcomes that can be assessed. Some literature suggests that mortality is a major outcome to be considered in patients.

References

[1]. Parker MJ, Thabane L, Fox-robichaud A, Liaw P, Choong K. A trial to determine whether septic shock- reversal is quicker in pediatric patients randomized to an early goal-directed fluid-sparing strategy versus usual care (SQUEEZE): study protocol for a pilot randomized controlled trial. Trials. 2016;1–13.

[2]. Bansude A, Sanjay N, Kulkarni K, Deshpande D. Study of Clinicopathological Profile and Outcome of Patients with Septic Shock in PICU of Tertiary Care Hospital. International Journal of Pediatric Research. 2023 Feb 25;9(1):111.

[3]. Dewi Ratih Priyantiningsih author. Karakteristik sepsis di pediatric intensive care unit RS dr. Cipto Mangunkusumo = Characteristics of sepsis in the pediatric intensive care unit of dr. Cipto Mangunkusumo hospital [Internet]. Universitas Indonesia; 2016 [cited 2023 Aug 17]. Available from: https://lib.ui.ac.id

[4]. Wooldridge G, Murthy S, Kissoon N. Core outcome set in paediatric sepsis in income countries : a study protocol. 2020;1–5.
[5]. Souza DC de, Machado FR. Advances in Pediatric Septic Shock: Epidemiology of Pediatric Septic Shock. J Pediatr Intensive Care [Internet]. 2019 Mar [cited 2023 Aug 17];8(1):3. Available from: /pmc/articles/PMC6506671/
[6]. Wiens MO, Kumbakumba E, Kissoon N, Ansermino JM, Ndamira A, Larson CP. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. Clin Epidemiol [Internet]. 2012 Nov 21 [cited 2023 Aug 17];4(1):319. Available from: /pmc/articles/PMC3514048/
[7]. Mathias B, Mira JC, Larson SD. Pediatric Sepsis. Curr Opin Pediatr [Internet]. 2016 Jun 1 [cited 2023 Aug 17];28(3):380. Available from: /pmc/articles/PMC4913352/
[8]. Cvetkovic M, Lutman D, Ramnarayan P, Pathan N, Inwald DP, Peters MJ. Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. Pediatr Crit Care Med [Internet]. 2015 Jun 21 [cited 2023 Aug 17];16(5):410–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25739013/
[9]. Zimmerman JJ, Anand KJS, Meert KL, Willson DF, Newth CJL, Harrison R, et al. Research as a standard of care in PICU. Pediatr Crit Care Med [Internet]. 2016 Jan 1 [cited 2023 Aug 17];17(1):e13. Available from: /pmc/articles/PMC5003779/
[10]. Menon K, McNally JD, Zimmerman JJ, Agus MSD, O'Hearn K, Watson RS, et al. Primary Outcome Measures in Pediatric Septic Shock Trials: A Systematic Review. Pediatr Crit Care Med [Internet]. 2017 Mar 1 [cited 2023 Aug 17];18(3):e146. Available from: /pmc/articles/PMC5336483/
[11]. Zimmerman JJ, Banks R, Berg RA, Zuppa A, Newth CJ, Wessel D, et al. Critical Illness Factors Associated With Long-Term Mortality and Health Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. Crit Care Med [Internet]. 2020 Mar 1 [cited 2023 Aug 17];48(3):319. Available from: /pmc/articles/PMC7089387/
[12]. Kaur G, Vinayak N, Mittal K, Kaushik JS, Aamir M. Clinical outcome and predictors of mortality in children with sepsis, severe sepsis, and septic shock from Rohtak, Haryana: A prospective observational study. Indian Journal of Critical Care Medicine. 2014;18(7):437–41.
[13]. Choudhary R, Sitaraman S, Choudhary A. Lactate clearance as the predictor of outcome in pediatric septic shock. J Emerg Trauma Shock. 2017 Apr 1;10(2):55–9.
[14]. Ames SG, Workman JK, Olson JA, Kent Korgenski E, Masotti S, Knackstedt ED, et al. Infectious etiologies and patient outcomes in pediatric septic shock. J Pediatric Infect Dis Soc. 2017;6(1):80–6.
[15]. Mullan PC, Pruitt CM, Levasseur KA, Macias CG, Paul R, Depinet H, et al. Intravenous Fluid Bolus Rates Associated with Outcomes in Pediatric Sepsis: A Multi-Center Analysis. Open Access Emergency Medicine. 2022;14:375–84.
[16]. Ventura AMC, Shieh HH, Bousso A, Góes PF, Fernandes IDCFO, De Souza DC, et al. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. Crit Care Med. 2015;43(11):2292–302.
[17]. Menon K, Mcnally JD, Zimmerman JJ, Agus MSD, Hearn KO, Watson RS, et al. Primary Outcome Measures in Pediatric Septic Shock Trials : A Systematic Review *. 2017;18(3).
[18]. Pomerantz WJ, Torrey SB, Kaplan SL. Septic shock in children : Rapid recognition and initial resuscitation (first hour). 2023;
[19]. Ames SG, Workman JK, Olson JA, Kent Korgenski E, Masotti S, Knackstedt ED, et al. Infectious etiologies and patient outcomes in pediatric septic shock. J Pediatric Infect Dis Soc. 2017;6(1):80–6.
[20]. Nazir M, Wani W, Dar SA, Mir IH, Charoo BA, Ahmad QI, et al. Lactate clearance prognosticates outcome in pediatric septic shock during first 24 h of intensive care unit admission. J Intensive Care Soc. 2019;20(4):290–8.
[21]. Saputra DK, Runtunuwu AL, Tatura SNN, Manoppo JICh, Lolombulan JH. Lactate clearance and mortality in pediatric sepsis. Paediatr Indones. 2016;56(4):215