DOI: https://doi.org/10.53555/h2w52p26 Publication URL: https://nnpub.org/index.php/MHS/article/view/1893

PRIMARY OUTCOME MEASURES IN PEDIATRIC SEPTIC SHOCK TRIALS : A SYSTEMATIC REVIEW

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Abstract

Background: *Septic is a significant global health concern for children, with about 1.2 million cases each year and varying mortality rates up to 50%. Clinical research in pediatric septic shock faces challenges in choosing appropriate outcome measures beyond mortality due to diverse mortality rates and patient populations. As a result, there's a need for comprehensive research to determine the optimal primary outcome measure for intervention trials in pediatric septic shock cases.*

Purpose: *This study was aimed for an extensive investigation aimed at identifying the primary outcome measure for pediatric septic shock cases.*

Result*: We compiled 17 articles from PubMed, Springer Nature, SAGE Pub, and Google Scholar. Ultimately, we included 5 articles that met the criteria.*

Conclusion: *Collectively, these studies emphasize the multifaceted nature of childhood stunting, necessitating comprehensive strategies that encompass education, nutrition, and healthcare to combat its prevalence. The presented studies on pediatric sepsis management provide insights into tailored approaches, emphasizing lactate clearance, Shock Index (SI), Restricted Lactate Solution (RLS), and Hydrocortisone, Ascorbic Acid, and Thiamine (HAT) therapy as potential measures for improving patient outcomes. Despite limitations, these insights contribute to informed clinical decisions and advancements in pediatric sepsis management.*

INTRODUCTION

Sepsis stands as a major contributor to illness, death, and healthcare utilization among children on a global scale. Worldwide, there are approximately 22 instances of childhood sepsis per 100,000 person-years and 2,202 cases of neonatal sepsis per 100,000 live births, resulting in a total of around 1.2 million instances of childhood sepsis each year. It's noteworthy that over 4% of all hospitalized children under 18 years old, as well as approximately 8% of patients admitted to Pediatric Intensive Care Units (PICUs) in high-income countries, are affected by sepsis. The mortality rate for children with sepsis varies, ranging from 4% to potentially as high as 50%, contingent upon factors such as the severity of the illness, risk elements, and geographical location. Most of the children who do not survive sepsis experience unmanageable shock and/or multiple organ dysfunction syndrome, with a significant number of fatalities occurring within the initial 48 to 72 hours of treatment.[2]

Clinical research plays a vital role in advancing and enhancing the treatment of pediatric patients dealing with septic shock. Medical professionals and researchers consider survival as a pivotal benchmark when addressing critical illnesses. Nonetheless, relying solely on mortality as the primary measure of success in clinical studies involving pediatric patients with septic shock might encounter challenges due to variable mortality rates and a restricted patient pool. Studies opt for alternative primary outcome measures like assessing the duration of vasoactive-free hemodynamic stability and monitoring the presence of organ failure. These measures help gauge the efficacy of therapeutic approaches for septic shock in pediatric cases. [3,4] Presently, a consensus remains elusive regarding the most suitable and practical outcome measure for intervention trials related to pediatric septic shock. Therefore, there is a clear need for an extensive investigation aimed at identifying the primary outcome measure for pediatric septic shock cases.

METHODS

Protocol

By adhering to the guidelines outlined in the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), the researcher of this study ensured its alignment with the necessary standards. This was carried out to guarantee the accuracy of the conclusions drawn from the investigation.

Criteria for Eligibility

For the purpose of this systematic review, the writers compare and evaluate written articles related to risk factors of stunting in toddlers, specifically. Throughout the entirety of this writing, the main objective is to consistently highlight the significance of the risk factors that have been identified.

The extraction of data was performed by considering the author, year, study design, sample size, results, and discussion. Primary outcomes refer to the variables that were assessed to establish the main result for pediatric patients experiencing septic shock.

For researchers to participate in the study, they were required to accomplish the following conditions: The paper should be written in English and should focus on determining the risk factors of stunting in toddlers. Published article of related studies must be required to meet these following conditions, in order to be included: The papers under study encompass those published after 2018 but prior to the timeframe deemed relevant by this systematic review. Studies falling into categories such as editorials, submissions lacking a DOI, already published review articles, and entries essentially mirroring already-published journal papers were not permitted as examples.

Search Strategy

Researchers independently conducted a search for relevant articles in multiple databases (PubMed, Springer Nature 1, SAGE Pub 2, and Google Scholar1) on August 26th, 2023 using keywords Primary Outcome Measures in Pediatric Septic Shock Trials in PubMed, Springer Nature, SAGE Pub, and Google Scholar. Keywords format were as following ((("primary"[MeSH Subheading] AND "outcome"[All Fields] AND "septic"[All Fields]) AND "shock"[All Fields]) AND ("children"[All Fields] OR "pediatric"[All Fields]) AND ("septic, shock"[MeSH Terms] OR ("primary"[All Fields] AND "outcome"[All Fields]) OR "septic trial"[All Fields]. Additionally, manual searches are conducted to obtain articles that satisfy the specified criteria.

Data retrieval

Upon reviewing the abstracts and titles of each study, the authors conducted an assessment to ascertain the fulfillment of the inclusion criteria. Subsequently, the authors made choices regarding the prior research they aimed to incorporate as references in their article, and accordingly, they selected those studies. Upon evaluating multiple diverse studies that consistently indicated a shared trend, this overarching observation was made. Notably, all submissions were required to be composed in English and were expected to be original and previously unpublished.

The systematic review exclusively considered papers that met all the specified inclusion criteria. This focused approach narrowed down the results to those directly relevant to the search. Conclusions from studies failing to meet our criteria were disregarded. Subsequently, the research findings underwent meticulous analysis. Through the conducted inquiry for this study's objectives, various information facets were revealed, including names, authors, publication dates, geographical locations, study methodologies, and parameters.

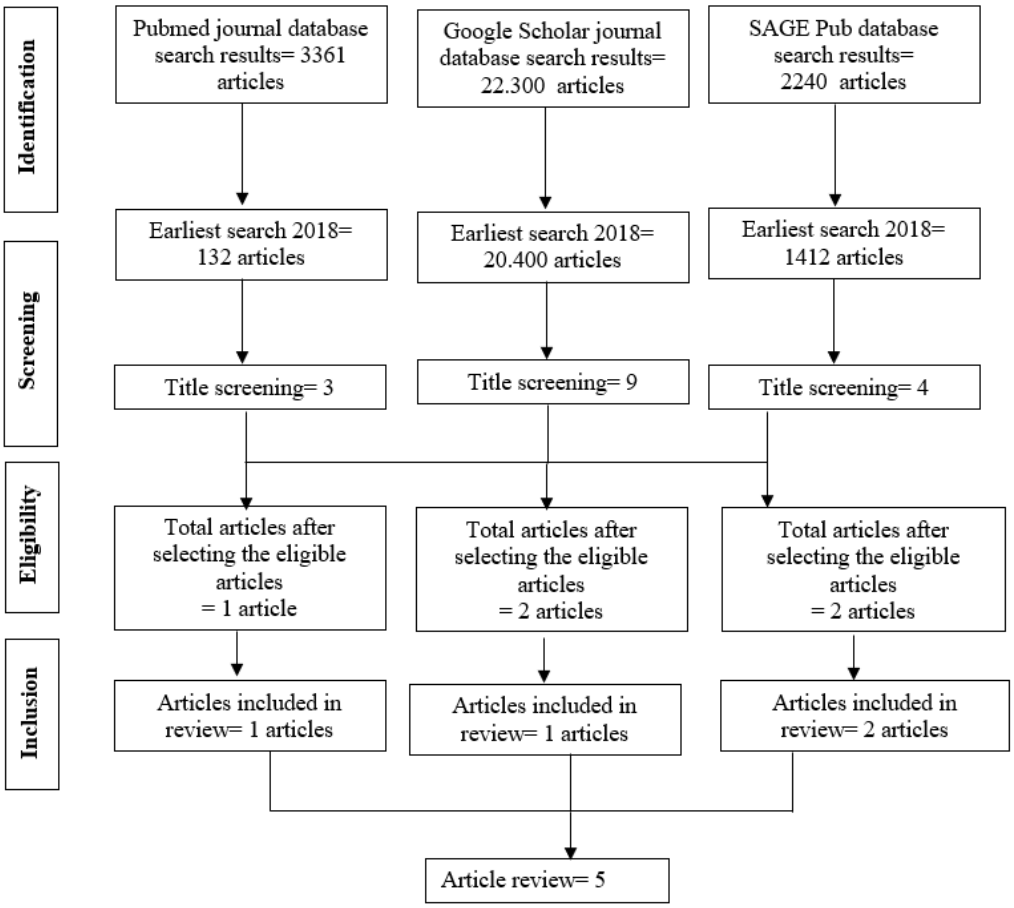

Figure 1. Article search flowchart

Quality Assessment and Data Synthesis

Author assessed research aligned with the publication's title and abstract to determine which studies merited more extensive investigation. The next step involves evaluating all eligible articles according to pre-established review criteria. Following this, we will determine the articles to be included in the review based on the uncovered outcomes. These criteria facilitate the selection process for the subsequent assessment of papers. The initial explorations undertaken and the distinct characteristics that deemed particular studies appropriate for incorporation into the review are under discussion within this context.

RESULT

Lactate levels were evaluated as predictive indicators of mortality in pediatric patients experiencing shock. Despite the straightforward measurement of the Delta Shock Index (DSI), there is a noticeable lack of research exploring its potential benefits. Wati et al.[5] (2023) in the following study, collected 33 subjects (84.61%) with dengue shock syndrome (DSS), while six (15.38%) experienced septic shock. Out of the 33 with DSS, 21 had compensated DSS, and the remaining 12 had decompensated DSS, two of whom died. Comparing the survival groups, the one that survived exhibited a lower shock index than the non-surviving group, which is connected to patient outcomes. Given that the data didn't exhibit the same variance, the repeated measures test used the Greenhouse-Geisser value due to sphericity test results. This value for the shock index associated with outcomes was 0.034 ($p < 0.05$). The Spearman correlation test, chosen due to non-normal data distribution, revealed a weak positive correlation ($r = +0.351$, $p = 0.028$) between lactate clearance and delta shock index. Multiple regression analysis indicated that the correlation between lactate clearance and delta shock index was not significant ($p = 0.071$). Examining shock index using repeated measurement analysis, lactate clearance below 30% surpassed that of lactate clearance equal to or above 30%. The Greenhouse-Geisser value for the shock index associated with lactate clearance was 0.437 (significant if $p < 0.05$). This indicates a weak positive correlation between lactate clearance and DSI. There were significant differences in the decrease of shock index over time between survivors and non-survivors.[5]

Association of shock index (SI) from 0 to 6 hours with early mortality in severe sepsis/septic shock and to explore its age-specific cut-off values was investigated in a prospective study. Children under 14 years old who were admitted to an emergency department at a tertiary care hospital due to severe sepsis or septic shock were categorized into three groups: group 1 (1 month to under 1 year), group 2 (1 to under 6 years), and group 3 (6 to 12 years). The shock index (SI), calculated as the heart rate divided by the systolic blood pressure, was measured at admission (designated as X0) and then hourly for up to 6 hours (X1-6). The primary outcome was defined as death within 48 hours of admission. Receiver operating characteristic (ROC) curves were constructed for SI at different time intervals (0-6 hours). The optimal cut-off

values for SI 0 and SI 6, maximizing both sensitivity and specificity, were determined, and positive and negative predictive values (PPV, NPV) were computed. [5]

Between 2015 and 2016, a total of 120 children were enrolled in the study to analyze the association of shock index (SI) from 0 to 6 hours with early mortality in severe sepsis/septic shock and to explore its age-specific cut-off values. Upon admission, 56.7% of the children had septic shock. Early mortality was observed in 50% of cases. Among the hourly shock indices (SI 0-6), all were found to be higher among non-survivors in group 2 ($P < .03$) and group 3 ($P < .001$). In group 1, the SI after 2 hours was elevated among non-survivors (P for 2-6: < .02). ROC curve analysis revealed that the area under the curve (AUC) for SI at 0 hours was 0.72 (95% CI 0.5-0.9), 0.66 (CI 0.5-0.8), and 0.77 (CI 0.6-0.9) for the three respective groups. For SI at 6 hours, the AUC was 0.8 (CI 0.6-1), 0.75 (CI 0.6-0.9), and 0.8 (CI 0.7-1) for the three groups. The determined cut-off values for SI 0 and SI 6, along with their corresponding sensitivity, specificity, PPV, and NPV, were as follows: Group 1: SI 0 cut-off: 1.98 (sensitivity 77; specificity 75; PPV 67; NPV 83), SI 6 cut-off: 1.66 (sensitivity 85; specificity 80; PPV 73; NPV 89) Group 2: SI 0 cut-off: 1.50 (sensitivity 65; specificity 65; PPV 68; NPV 63), SI 6 cut-off: 1.36 (sensitivity 73; specificity 70; PPV 73; NPV 70) Group 3: SI 0 cut-off: 1.25 (sensitivity 90; specificity 67; PPV 77; NPV 83), SI 6 cut-off: 1.30 (sensitivity 74; specificity 73; PPV 78; NPV 69) An improvement in SI over the span of 6 hours was linked to a better outcome. Children with higher SI values at both time points had a higher mortality rate compared to those with SI scores below the determined cut-offs ($P = .001$).[6]

Wald et al[7] (2020) carried out a retrospective cohort study that utilized propensity score matching for patients diagnosed with septic shock and admitted to our pediatric Intensive Care Unit (PICU) during the period spanning January 2014 to February 2019. Patients categorized as having septic shock met the criteria of suspected or confirmed infection and the necessity for vasoactive infusions within 24 hours of admission. Stress-dose hydrocortisone therapy, referred to as "hydrocortisone only," and HAT (Hydrocortisone–Ascorbic Acid–Thiamine) therapy were administered based on the clinical judgment of the attending physicians. The adoption of HAT therapy commenced in May 2017. This therapy protocol included intravenous ascorbic acid (30 mg/kg/dose administered every 6 hours for 4 days, up to a maximum of 1,500 mg/dose), intravenous hydrocortisone (50 mg/m2/d divided into intervals of every 6 hours), and intravenous thiamine (4 mg/kg/d for 4 days, up to a maximum of 200 mg/dose). Patients were categorized as receiving these therapies if they were initiated within 24 hours of vasoactive treatment commencement.

The study encompassed a total of 557 patients, among whom 64 (11.5%) succumbed within 30 days after their admission to the Pediatric Intensive Care Unit (PICU). Patients initiated vasoactive infusions at a median interval of 0.5 hours (with an interquartile range of 20.4 to 6 hours) from their admission to the PICU. Among those who underwent HAT therapy, intravenous ascorbic acid was administered with a median delay of 12 hours (interquartile range, 6–19 hours) following PICU admission. Propensity score matching yielded a reduction in standardized differences among the treatment groups. Patients who received HAT therapy exhibited significantly lower 30-day mortality rates compared to matched control individuals and matched patients receiving hydrocortisone-only treatment ($P < 0.03$). No disparities were observed in terms of vasoactive inotrope-free days or hospital-free days.[7]

In the sensitivity analysis employing inverse probability treatment weighting over a specified time period, patients with septic shock who underwent HAT therapy once again displayed lower 30-day mortality rates when contrasted with untreated control individuals ($P = 0.006$) and hydrocortisone-only patients ($P = 0.014$). In the Cox regression analysis, HAT therapy was found to be independently associated with a lower hazard ratio for mortality (0.3; 95% confidence interval, 0.1–0.9). [7]

In a retrospective study, Lee et al.[8] (2020) conducted an analysis involving pediatric patients with refractory septic shock who were admitted to a pediatric intensive care unit (PICU). The study focused on monitoring their hemodynamic status using a pulse index continuous cardiac output (PiCCO) system. Over the initial 72 hours following admission to the PICU, serial hemodynamic measurements, such as cardiac index (CI), systemic vascular resistance index (SVRI), and vasoactive-inotropic score (VIS), were collected. Within this context, a new parameter termed vascular reactivity index (VRI) was defined as the ratio of SVRI to VIS. The objective of the study was to assess the potential of VRI in predicting mortality among children grappling with refractory septic shock. [8]

Throughout the study duration, a total of 11,832 patients were admitted to our Pediatric Intensive Care Unit (PICU), and within this cohort, 2,699 patients (22.8%) received a diagnosis of sepsis. Among these septic patients, 520 individuals (19.2%) were diagnosed with septic shock. Out of those individuals who had septic shock, 39 patients were specifically identified as having persistent catecholamine-resistant shock, which led to the insertion of a PiCCO device for invasive hemodynamic monitoring. After excluding 6 patients due to missing data, a total of 33 patients were included in the study. The age of these children was found to be 12.2 ± 4.3 years, and among them, 72.7% had confirmed microbiological infections. The bloodstream was identified as the most common site of infection, with gram-negative bacteria being the predominant pathogens. Within this group, 15 cases (45%) managed to survive, while 18 cases (55%) unfortunately resulted in mortality within a span of 28 days. [8]

Dopamine and epinephrine emerged as the two most frequently employed initial vasoactive-inotropic agents in both the group of patients who survived and the group who did not. Concerning the initial cardiac characteristics observed after the setup of the PiCCO device, it was observed that the mortality group exhibited a higher vasoactive-inotropic score (VIS) but a lower mean arterial pressure compared to the survival group ($P < .05$). [8]

During the initial 72 hours following admission to the Pediatric Intensive Care Unit (PICU), we meticulously documented sequential hemodynamic data, encompassing Cardiac Index (CI), Systemic Vascular Resistance Index (SVRI), Vasoactive-Inotropic Score (VIS), and Vascular Reactivity Index (VRI). Within this context, Stroke Volume Variation (a parameter denoting preload) was found to be higher in the mortality group compared to the survival group ($P < .05$). Conversely, SVRI (a parameter reflecting afterload) was lower in the mortality group than in the survival group ($P < .05$).

Notably, no substantial differences were observed between the survival and mortality groups regarding PiCCO parameters such as Cardiac Output (CO) and cardiac contractility. [8]

To identify the independent predictors of 28-day mortality within the initial 72 hours, we introduced factors such as age, sex, Pediatric Risk of Mortality score, and initial hemodynamics (including heart rate, Systolic Blood Pressure [SBP], CI, Global End-Diastolic Volume Index [GEDVI], Extravascular Lung Water Index [EVLWI], Intrathoracic Blood Volume Index [ITBVI], and VRI) into a multivariate logistic regression model. Results revealed that VRI independently predicted 28-day mortality during this period. [8]

Throughout the study, Cardiac Index data were assessed at 6-hour intervals subsequent to the establishment of the PiCCO device, demonstrating no significant distinctions between the survival and mortality groups. Based on the Receiver Operating Characteristic (ROC) analysis, the serial VRI values within 6-hour intervals. The mean Area Under the Curve (AUC) during the initial 72 hours stood at 0.8, with VRI values consistently lower in the mortality group compared to the survival group during the 0 to 48-hour period. The highest AUC of 0.85 occurred for the initial VRI value (0 hours) within the first 72 hours (Figure 3A). Optimal cutoff values for VRI, indicating the likelihood of mortality, progressively increased from over 30 initially (0-12 hours) to over 60 at 30 to 48 hours. Intriguingly, none of the children with VRI levels below 21 within the 0 to 24-hour interval and levels below 29 within the 24 to 48-hour interval survived, even after aggressive resuscitation efforts within the PICU. Conversely, children with VRI levels exceeding 80 within the 0 to 24-hour interval and surpassing 100 within the 24 to 48-hour interval exhibited a notably higher probability of survival. [8]

Trepatchayakorn et al.[9](2021) objective was to provide a comprehensive assessment of the utilization of balanced salt solution in pediatric populations affected by sepsis, in contrast to the usage of normal saline. The main focus of the study was to analyze and compare the acid-base balance status subsequent to fluid bolus therapy involving distinct types of crystalloid fluids. Additionally, a secondary aim of the research was to make comparisons regarding various other outcomes observed in the Pediatric Intensive Care Unit (PICU).

Throughout the designated study period, a total of 42 patients with pediatric septic shock were enrolled, with 57.1% being males and 42.9% being females. The participants had a median age of 29 months, a median weight of 13 kg, a Pediatric Logistic Organ Dysfunction II (PELODS-II) score of 5 points, a Pediatric Risk of Mortality III (PRISM-III) score of 4 points, and a maximal vasopressor-inotropic score (VIS) of 10 points. The median time span from diagnosis to administration of antibiotics was 60 minutes, and the median fluid dosage amounted to 30 mL/kg. No discernible disparities were observed among the three groups in terms of arterial pH, base excess, serum lactate, central venous saturation (ScvO2), lactate clearance, or alterations in base excess over the course of time. [9]

The present study did not show any difference regarding serum sodium level, chloride level, potassium level, ionized calcium level, ionized magnesium level, or change in serum chloride level (Δ[Cl−]) at any points of measurement. No difference could be observed regarding cumulative fluid after fluid bolus therapy. Other renal outcomes also did not differ significantly among the groups. No association was found among types of fluid and abnormal coagulation study, serious bleeding, or requirement for blood product transfusion. In the present study, different types of fluid bolus therapy did not correlate with any of the PICU outcomes. In subgroup analysis of participants who received fluid bolus therapy at large dose equal to or larger than 30 mL/kg, there was a significant decrease in urinary neutrophil gelatinase-associated lipocalin (uNGAL) level after 2 h of fluid bolus therapy in Ringer lactate solution (RLS) group. [9]

Author	Origin	Method	Sample Size	Result
Wati et al.[5], 2023.	Denpasar, Indonesia.	Prospective cohort study.	There were 39 subjects obtained in this study, with 34 subjects surviving and 5 subjects not surviving.	The median lactate clearance was 28.5 (-95 - 77.7), with a median DSI of 0.45 (0.04-1.3). There were significant differences in the decrease of shock index over time (p = 0.034). The correlation test results showed a weak positive between lactate clearance with DSI (r = +0.351) and p = 0.028. Multivariate analysis test results obtained a value of â 0.002 with p = 0.071.
Gupta, S., & Alam, A.[6], 2018.	King George's Medical University Hospital is a large, multispeciality, 3000-bed tertiary care teaching hospital in North India.	Prospective observational study.	133 children met the inclusion criteria. Out of 133, 6 did not give consent, 2 had incomplete data, and 5 were not validated by senior resident.	From 2015 to 2016, 120 children were recruited. Septic shock was present at admission in 56.7% children. Early mortality was 50%. All hourly shock indices (SI 0-6) were higher among nonsurvivors in group 2 (P .03) and group 3 (P < .001). In group 1, SI after 2 hours was higher in nonsurvivors (P 2-6: .02). Area under receiver operating characteristic curves (95% CI) for SI at 0 hour was 0.72 (0.5-0.9), 0.66 (0.5-0.8), and 0.77 (0.6-0.9) and at 6 hours was 0.8 (0.6-1), 0.75 (0.6-0.9), and 0.8 (0.7-1) in 3 groups. The cut-off values of SI 0 (sensitivity; specificity; PPV; NPV) in 3 groups: 1.98 (77; 75; 67; 83), 1.50 (65; 65; 68; 63), and 1.25 (90; 67; 77; 83) and SI6: 1.66 (85; 80; 73; 89), 1.36 (73; 70; 73; 70), and 1.30 (74; 73; 78; 69). Improvement of SI over 6 hours was associated with better outcome. Children

				with higher SI at both time points had higher mortality than those with SI score below the cut-offs (P ¼ .001).
Wald et al. [7],2019.	Chicago, Illinois.	Prospective, propensity score–matched cohort study.	There were 557 patients included, and 64 (11.5%) died within 30 days of PICU admission.	Patients were started on vasoactive infusions a median of 0.5 hours (interquartile range, 20.4 to 6 h) from PICU admission, and those treated with HAT therapy received i.v. ascorbic acid a median of 12 hours (interquartile range, 6–19 h) after PICU admission. Propensity score matching reduced the standardized differences between the treatment groups, as seen in Figure 1A. Patients who received HAT therapy had significantly lower 30-day mortality than matched control individuals and matched hydrocortisone-only patients (P<0.03). There were no differences in vasoactive inotrope-free days or hospital-free days. In the sensitivity analysis, using inverse probability treatment weighting with a time epoch, 30-day mortality was again lower in patients with septic shock who received HAT therapy compared with untreated control individuals (P=0.006) and hydrocortisone-only patients (P=0.014). In the Cox regression analysis, HAT therapy was independently associated with a lower hazard ratio for death (0.3; 95% confidence interval, 0.1–0.9).
Lee et al,[8] 2022.	Division of Pediatric Critical Care Medicine, Department of Pediatrics, Chang Gung Memorial Hospital at Linko, No. 5, Fu-Hsin Street, Kweishan, Taoyuan.	Retrospective observational cohort study.	76,165 children aged under 5 years were included in this study.	Thirty-three children with refractory septic shock were enrolled. The SVRI was lower in the mortality group compared to the survival group (P < .05). The average area under the receiver operating characteristic curve of VRI within the first 72 hours was 0.8 and the serial values of VRI were significantly lower in the mortality group during the period from 0 to 48 hours (P < .05). However, there were no significant differences in serial CI values between the survival and mortality groups.
Trepatchayakorn et al,[9] 2021.	The study included pediatric patients admitted to King Chulalongkorn Memorial Hospital, Bangkok, Thailand.	Randomized control trial.	Forty-two patients were included in the study. Median age was 29 mo and, weight 13 kg.	The present study did not show any difference regarding serum sodium level, chloride level, potassium level, ionized calcium level, ionized magnesium level, or change in serum chloride level (Δ[Cl−]) at any points of measurement. No difference could be observed regarding cumulative fluid after fluid bolus therapy. Other renal outcomes also did not differ significantly among the groups. No association was found among types of fluid and abnormal coagulation study, serious bleeding, or requirement for blood product transfusion. In the present study, different types of fluid bolus therapy did not correlate with any of the PICU outcomes. In subgroup analysis of participants who received fluid bolus therapy at large dose equal to or larger than 30 mL/kg, there was a significant decrease in urinary neutrophil gelatinase-associated lipocalin (uNGAL) level after 2 h of fluid bolus therapy in Ringer lactate solution (RLS) group.

DISCUSSION

The incidence of severe sepsis and septic shock in pediatric patients exhibits variability. Wati et al.,[5] studied sepsis prevalence and characteristics at Prof Dr. I.G.N.G Ngoerah Hospital Denpasar's PICU in 2018. Among 17 diagnosed septic shock cases, infants under two years were prominent. Survivors averaged a 5-day stay, contrasting with non-survivors' 2-day duration. The median PIM-2-based mortality risk was 1.2% (0.4-7.9) for survivors and 10.2% (5.3-41.8) for nonsurvivors, aligning with a 12.8% mortality rate.

Lactate clearance outperforms initial levels in sepsis prognosis. This study's median pre-resuscitation lactate was 4.1 (2-13.4) mmol/L, with 3.4 ± 1.6 mmol/L at the 6th hour. Median lactate clearance was 28.57%. Compensated DSS subjects had 29.04%, decompensated DSS had 7.8%, and septic shock patients had 27.82%. Saputra et al.,13 found survivors had 58.48% lactate clearance, compared to 18.2% in nonsurvivors, where high clearance within six hours correlated with reduced pediatric sepsis mortality (OR 0.49; p <0.01).[5]

Nazir et al.,[10] discovered that a 10% lactate clearance at the 6th hour following admission yielded 0.948 sensitivity and 0.571 specificity in predicting sepsis mortality. A 20% clearance at 24 hours offered 0.922 sensitivity and 0.629 specificity, with lower clearance associating with higher mortality. A Vietnam study noted increased lactate in dengue patients' ICU treatment's early stages linked with adverse outcomes, recurrent shock, and respiratory distress. Hyperlactatemia causes include liver dysfunction, associated with reduced liver lactate clearance. In dengue patients, shock levels' lactate ranged from 2.2 mmol/L (no shock) to 4.1 mmol/L (recurrent shock).[11]

Shock index norms for different age groups are 0.8 - 2.3 (1 year), 0.7 - 1.22 (1-6 years), and 0.5 - 1.2 (6-12 years). This study's median DSI was 0.45 (0.04 - 1.3). The mean was 0.48 (0.04 - 1.1) in survivors and 0.36 (0.15 - 1.3) in nonsurvivors. Improved DSI after resuscitation correlates with survival. Though inconsistency exists across ages, shock index changes in the first 6 hours post-diagnosis relate to mortality.[5]

The study spanned a year to investigate the link between Shock Index (SI) at 0 to 6 hours and its variations within the first 6 hours with early mortality in severe sepsis/septic shock, also identifying age-specific cut-off values. Age-specific SI was significantly higher in nonsurvivors from 0 to 6 hours across various age groups. This aligned with a study in children that associated higher SI with death at multiple time points but found a significant risk only at 0 and 6 hours when adjusting for age. Other studies reported associations between higher SI values and early death within 48 hours.[6]

Receiver Operating Characteristic (ROC) curve analysis revealed SI's fair-to-good predictive value for early mortality, which improved to good after 6 hours. Contrary to some child studies, this work presented relatively higher AUROC values. Age-specific SI cut-off values were identified, varying across age groups, distinguishing children at risk of early death. SI's sensitivity and specificity were promising, and its likelihood ratios showed potential in predicting mortality. [6]

Positive predictive values for SI scores above cut-off values demonstrated the likelihood of death, while negative predictive values indicated the likelihood of survival. The association between SI change from 0 to 6 hours and mortality was explored, revealing that children with consistently lower SI had significantly lower mortality rates. Notably, this study contributes to understanding the association of SI with early mortality in children with severe sepsis/septic shock and introduces age-specific cut-off values, improving prognostication and therapeutic escalation decisions.[6]

In retrospective study using propensity score matching, we found that children with septic shock who received HAT (Hydrocortisone, Ascorbic Acid, and Thiamine) therapy had reduced mortality compared to those who received hydrocortisone only or no adjunctive therapy. This study is the first of its kind to investigate the clinical outcomes linked to HAT therapy in pediatric septic shock patients.[7] The observed reduction in mortality seems primarily linked to a decrease in early deaths. Research has indicated that a significant portion of pediatric septic shock patients experience early death due to refractory shock. The findings suggest that HAT therapy potentially lessens the occurrence and duration of refractory shock, thus leading to a decrease in early fatalities. This could explain the improved survival rate without a simultaneous increase in vasoactive-free days. Once the initial shock phase is resolved, the need for vasoactive support diminishes substantially in survivors.[7]

Wald et al.[7] proposed that the positive impact of HAT therapy results from the combination of intravenous ascorbic acid administration and the synergistic effects of hydrocortisone and thiamine. Critically ill patients with sepsis often suffer from reduced ascorbic acid levels, which is linked to unfavorable outcomes. Intravenous ascorbic acid administration elevates both plasma and cellular levels, potentially mitigating the pathological changes that occur during sepsis, thereby improving clinical outcomes. Thiamine, an energy production pathway cofactor, also plays a role by preventing the formation of renal oxalate crystals that can arise from high-dose ascorbic acid treatment.

The occurrence of in-hospital mortality rates due to septic shock is notably high, particularly in children experiencing persistent catecholamine-resistant shock. A significant phenomenon in such cases is vasoplegia, characterized by reduced responsiveness of blood vessels to vasopressors. This study aimed to quantify vasoplegia using the Vascular Reactivity Index (VRI) as an objective measure and assess its ability to predict mortality in children with persistent catecholamine-resistant shock. The findings indicated that VRI was a strong predictor of mortality (average AUC > 0.8), with significantly lower VRI values observed in the mortality group compared to survivors. This suggests that children with lower VRI may exhibit more severe vasoplegia and heightened mortality risk in septic shock scenarios.[8]

Vasoplegia's physiological basis is rooted in Systemic Vascular Resistance (SVR), which reflects the contractile activity of vascular smooth muscle cells. Desensitization of receptors such as angiotensin type 1 and the reduction of vasopressin levels contribute to vascular hyporesponsiveness in septic shock. While vasoplegia provides insights into vascular diameter under specific pressures, it may not encompass dynamic hemodynamic changes. Serial monitoring of hemodynamic parameters is essential to predict clinical outcomes and guide appropriate treatments. VRI offers objective values based on vasoplegia principles and dynamic data on vascular reactivity progression in pediatric septic shock cases.[8]

Among survivors, VRI values demonstrated an increasing trend after resuscitation within the initial 48 hours of PICU admission. However, consistently lower values after resuscitation correlated with a higher mortality rate in this group. The study proposed two VRI cutoff levels every 6 hours to identify points of heightened survival likelihood (sensitivity: 100%) and increased mortality risk (specificity: 100%). Clinicians should closely evaluate cases falling within the indeterminate VRI zone and be vigilant about decreasing VRI values after resuscitation.[8]

The outcomes observed in the current study regarding resuscitation fluid choice did not reveal significant differences among the groups. However, the Restricted Lactate Solution (RLS) group displayed several potential advantages. Firstly,

there was a tendency toward a reduction in urinary NGAL levels after a 2-hour fluid bolus compared to the other groups. Secondly, the RLS group showed a trend toward more negative Δ[Cl−] at 2 hours, potentially attributed to higher chloride content in normal saline solution (NSS) and Sterofundin compared to RLS. The outcomes observed in the current study did not reveal significant differences among the groups. However, the Restricted Lactate Solution (RLS) group displayed several potential advantages. Firstly, there was a tendency toward a reduction in urinary NGAL levels after a 2-hour fluid bolus compared to the other groups. Secondly, the RLS group showed a trend toward more negative Δ[Cl−] at 2 hours, potentially attributed to higher chloride content in normal saline solution (NSS) and Sterofundin compared to RLS.

When analyzing data from participants who received a large dose of fluid bolus therapy, a statistically significant decrease in uNGAL levels at 2 hours was observed in the RLS group. Additionally, this group exhibited trends toward improved lactate clearance at 24 hours and more negative Δ[Cl−] at 2 hours, although these trends did not reach statistical significance. Overall, the present study's findings suggest potential benefits of using RLS over NSS and Sterofundin in the resuscitation of children with septic shock. These results align with data from the adult population and recommendations from the Surviving Sepsis Campaign in 2016. Retrospective studies in pediatric sepsis have also indicated similar conclusions. The current study contributes prospective randomized controlled trial data to this specific pediatric sepsis population, further reinforcing these recommendations and enhancing the existing evidence base. However, it's important to note that the study has limitations, such as its small sample size, the use of small fluid bolus doses, and the focus on laboratory biomarkers rather than clinical outcomes.

CONCLUSION

In conclusion, the presented studies shed light on various aspects of pediatric sepsis and septic shock management. The variability in the incidence of severe sepsis and septic shock among pediatric patients highlights the need for tailored approaches. Lactate clearance emerges as a robust predictor of prognosis, with higher clearance associated with improved outcomes. The Shock Index (SI) proves to be a valuable tool for early mortality prediction, with age-specific cut-off values enhancing its accuracy. Additionally, the study on resuscitation fluid choice indicates potential benefits of Restricted Lactate Solution (RLS) over traditional options, emphasizing the importance of fluid composition.

Furthermore, the investigation into vasoplegia and the Vascular Reactivity Index (VRI) reveals its significance in understanding vascular dynamics and mortality prediction in children with persistent catecholamine-resistant shock. The integration of Hydrocortisone, Ascorbic Acid, and Thiamine (HAT) therapy emerges as a promising approach in reducing mortality among pediatric septic shock patients, potentially by mitigating early refractory shock-associated deaths.

Despite these valuable findings, the studies also acknowledge limitations, including sample size constraints, focus on laboratory markers rather than clinical outcomes, and the need for further validation. Collectively, these insights contribute to advancing our understanding of pediatric sepsis management, highlighting potential strategies to enhance patient outcomes and informing clinical decisions.

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