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The Efficacy of Epinephrine versus Norepinephrine on the Outcome of Children with Septic Shock

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ABSTRACT

Background: Severe sepsis and septic shock remain significant causes of death and morbidity in critically-ill kids, with the majority of deaths occurring in settings lacking intensive care facilities. Pediatric septic shock is described as sepsis with cardiovascular dysfunction, which may occur without hypotension, in contrast to adult definitions. Optimal vasoactive therapy in pediatric septic shock remains debated, with limited evidence comparing epinephrine and norepinephrine. **Aim of the study:** This prospective observational research aimed to compare the clinical outcomes of epinephrine versus norepinephrine in pediatric septic shock. **Methodology:** A total of 68 kids admitted to the Pediatric Intensive Care Unit (PICU) at Menoufia University Hospital and Shebin El Koum Teaching Hospital with septic shock were enrolled and separated into two groups depending on the vasoactive agent administered. Group A: 34 kids with septic shock who will receive adrenaline. Group B: 34 kids with septic shock who will receive noradrenaline.

Results: Demographic and baseline hemodynamic parameters were comparable between groups. Norepinephrine recipients required significantly higher drug doses (7.79 ± 1.64 vs. 0.20 ± 0.05 μg/kg/min, $p < 0.001$) and greater fluid resuscitation volumes (51.73 ± 5.66 vs. 40.00 mL/kg, $p < 0.001$) than those receiving epinephrine. The norepinephrine group also demonstrated a higher need for mechanical ventilation (97.1% vs. 58.8%, $p < 0.001$) and longer ventilation duration (6.50 ± 2.78 vs. 3.41 ± 3.58 days, $p < 0.001$). PICU length of stay was significantly shorter in the epinephrine group (3.65 ± 3.78 vs. 6.97 ± 2.85 days, $p < 0.001$). Although survival differences were not statistically significant, epinephrine was related to a higher survival rate (97.1% vs. 85.3%). The norepinephrine group had a significantly higher need for mechanical ventilation and a longer duration of ventilation than the epinephrine group ($p < 0.001$). PRISM and PRISM III scores were significantly lower in the epinephrine group, indicating reduced illness severity. Mortality predictors included lower mean blood pressure, prolonged capillary refill time, elevated CRP and creatinine, metabolic acidosis, hyperkalemia, higher vasoactive requirements, and greater fluid volumes.

Conclusion: Findings showed that epinephrine was associated with improved clinical outcomes in pediatric septic shock, particularly regarding ventilation needs and PICU stay. Larger multicenter trials are warranted to confirm these results and guide practice.

Keywords: Pediatric septic shock, Epinephrine, Norepinephrine, Vasoactive agents, PRISM score.

INTRODUCTION

Severe sepsis and septic shock are significant contributors to death and morbidity in critically sick pediatric patients. The majority of sepsis-related fatalities worldwide transpire in regions lacking critical care centers, and numerous cases could be averted with straightforward interventions as advised by the World Health Organization's Integrated Management of Childhood Illnesses guidelines [(1)].

Septic shock in children is characterized by the presence of sepsis accompanied by indicators of cardiovascular organ dysfunction, which does not always include hypotension, whereas adult septic shock requires the presence of hypotension. Furthermore, indicators of organ dysfunction are contingent upon age-specific thresholds for breathing rate, heart rate, and white blood cell count, which vary across several pediatric age groups [(2)]. The Surviving Sepsis Campaign Guidelines [(3)] stipulate that the management of septic shock necessitates immediate antibiotic therapy, vigorous fluid resuscitation, and vasoactive support, specifically noradrenaline (NA) and dobutamine as 1st-line agents, tailored to the hemodynamic condition.

Norepinephrine (NE), a highly effective vasoconstrictor, is predominantly utilized to counteract hypotension in adults experiencing septic shock, with a mean dosage varying from 0.2 to 1.3 microgram per kilogram per minute**.** While it is advised to limit administration to 0.6l g/kg per minute to prevent arrhythmias, larger doses of NA have occasionally been utilized in adults. The hemodynamic profile of septic shock in kids is believed to vary from that in adults [(4)].

The American College of Critical Care Medicine endorses dopamine as the primary vasopressor and norepinephrine in cases of warm hyperdynamic shock unresponsive to dopamine. Nonetheless, certain committee members advocate for the utilization of norepinephrine as a primary treatment for fluid-refractory hypotensive hyperdynamic shock. Despite the utilization of NA, no research has explicitly shown its application in pediatric cases with septic shock [(5)].

Epinephrine is the sole vasoactive drug authorized for peripheral administration, however numerous practitioners may opt to inject norepinephrine peripherally when central venous access is unavailable and severe tachycardia prevents the utilization of epinephrine. The available data about the safety of peripheral administration of vasoactive medicines in kids is scarce, and doctors should strive to secure central venous access at the earliest opportunity**.** Due to the

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lack of robust evidence comparing norepinephrine and epinephrine in pediatric patients with fluid-refractory shock, the selection of the agent is contingent upon the clinician's preference, institutional policy and physiological evaluation. Epinephrine is frequently employed to address shock linked to a diminished cardiac output, whilst norepinephrine is typically utilized to treat shock characterized by vasodilation and reduced systemic vascular resistance. The former classification of shock into 'warm shock' and 'cold shock' is now obsolete due to inadequate association between cardiac index, clinical evaluation and systemic vascular resistance as determined by sophisticated monitoring [6]. So, this research aimed to compare the effects of epinephrine versus norepinephrine on the outcomes of children with septic shock.

PATIENTS AND METHODS

Study design and setting: Prospective observational research has been carried out on 68 kids with septic shock who were admitted to the emergency department in Menoufia University Hospital and Shebin El Koum Teaching Hospital. The children were divided into 2 equal groups (34 children each).

Sample size: In order to ensure that our estimate was both reliable and accurate, the sample size has been determined through the following formula as follows [7]: $n = [z^2 * p * (1 - p) / e^2] / [1 + (z^2 * p * (1 - p) / (e^2 * N))]$. Where: z = 1.96 for a confidence level (α) of ninety-five percent, p = proportion (expressed as a decimal), N = population size, e = margin of error. The sample size (with finite population correction) was equal to 68. The patient children were divided into 2 groups:

- **Group A (34):** 34 kids with septic shock who will receive adrenaline.
- **Group B (34):** 34 kids with septic shock who will receive noradrenaline.

Inclusion criteria: Both sexes. Children aged from one month to eighteen years. Children who were admitted with septic shock or developed septic shock. Children of parents who approved to participate in the study.

Exclusion criteria: If child stay in the emergency department after diagnosis of septic shock was < 24 hrs. Children presenting with cardiogenic shock and known cardiac dysfunction. Parents who refused the research.

All children were subjected to the following:

Full history taking including age, sex and cause of admission. General examination including vital signs including heart rate, respiratory rate, temperature, and blood pressure measurements, capillary refill and urine output. Anthropometric measurements include weight (kg), height (cm) and BMI. Need for mechanical ventilation, weaning from mechanical ventilation, length of stay in PICU and survival rate. Complete local physical examination of all body systems including cardiac, chest, abdominal and CNS examinations.

Mortality scoring systems: The Pediatric Risk of Mortality (PRISM) score is a validated severity-of-illness and mortality prediction tool used in pediatric intensive care units (PICUs). It is derived from physiological and laboratory parameters collected during a defined period after admission, commonly the first 24 hours. Parameters include vital signs (heart rate, blood pressure & temperature), neurologic status, and laboratory values (such as arterial blood gases, electrolytes & coagulation profile). Higher scores indicate greater severity of illness and a higher predicted risk of mortality.

- Pediatric risk of mortality (PRISM) scoring, use of dopamine or norepinephrine (24 hrs).
- Pediatric Risk of mortality (PRISM) III score was applied in the first 24 hrs of emergency department (ED) admission to predict outcome and severity of illness.

Laboratory investigations:

- All patients underwent a complete blood count (CBC) using an automated hematology analyzer (cells/μL for white blood cell count [WBC], g/dL for hemoglobin, and $\times 10^9$/L for platelet count).
- Inflammatory markers have been determined, including C-reactive protein (CRP) determined by immunoturbidimetric assay (mg/L) and erythrocyte sedimentation rate (ESR) assessed by the Westergren method (mm/hour).
- Microbiological cultures including blood, sputum, broncho-alveolar lavage, cerebrospinal fluid (CSF), urine, stool, and wound swabs were performed when clinically indicated, using standard aerobic and anaerobic culture techniques (qualitative growth in colony-forming units [CFU]/mL).
- Kidney and liver function tests were performed using an automated chemistry analyzer, including serum blood urea nitrogen (BUN) (mg/dl), creatinine (mg/dl), aspartate aminotransferase (AST) (U/L), alanine aminotransferase (ALT) (U/L), and bilirubin both total and direct fractions (mg/dl). Random blood sugar was measured using the glucose oxidase method (mg/dl). Arterial blood gases (ABG) have been examined using a blood gas analyzer (pH units, mmHg for PaO_2 and $PaCO_2$, mmol/L for HCO_3^-).
- Serum electrolytes, including sodium (Na^+) (mmol/L), potassium (K^+) (mmol/L), and calcium (Ca^{2+}) (mg/dl or mmol/L) were determined using ion-selective electrode (ISE) methodology. These measurements provided a comprehensive biochemical, hematological, and microbiological profile to guide diagnosis, monitor disease progression and evaluate treatment response. Follow up the result of the cases at the end of PICU stay regarding length of stay (LOS) and need for mechanical ventilation as well as survival and death rates.

Statistical analysis

The gathered data were analyzed, encoded, and organized utilizing the Statistical Package for Social Sciences (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Information was given and appropriate analysis was conducted based on the type of data acquired for each parameter. The Shapiro-Wilk test has been conducted to assess the normality of the data distribution. The Student's t test has been utilized to evaluate the statistical significance of the variance between the means of two research groups. The Mann-Whitney U test has been applied to evaluate the statistical significance of the distinction in a non-parametric variable between two research groups. The Chi-Square test was utilized to analyze the association between two categorical variables. A p-value was deemed significant if it was ≤ 0.05 at a ninety-five percent confidence interval.

Ethical approval: A written consent has been gathered from each parent/caregiver of the subjects after explaining to them the aim of the study. The Local Ethics Committee of the Menoufia University approved the study protocol with approval number (7/2023PEDI 22). The study followed The Declaration of Helsinki through its execution.

RESULTS

The current research involved 68 pediatric patients diagnosed with septic shock, who were admitted to the pediatric intensive care unit (PICU). The cases were separated into two groups depending on the vasoactive medication they received: one group received epinephrine, and the other group received norepinephrine. According to the demographic data of the study groups, there were insignificant variances amongst the epinephrine and norepinephrine groups in terms of age, gender distribution or anthropometric measurements. The mean age in the epinephrine group was 9.59 ± 4.61 years, compared to 9.09 ± 4.96 years in the norepinephrine group (p = 0.777). The gender distribution was identical, with both groups having 47.1% females and 52.9% males (p = 1.000). Additionally, the mean weight and height were comparable among both groups, with insignificant variance detected (p = 0.676 for weight and p = 0.941 for height). BMI also showed insignificant variance among the groups (p = 0.645). Regarding vital signs, there was insignificant variance between the study groups in terms of mean blood pressure (MBP). The epinephrine group had a mean MBP of 62.17 ± 1.59 mmHg, while the norepinephrine group had a mean MBP of 60.24 ± 3.94 mmHg (p = 0.345). Similarly, in terms of heart rate (HR), insignificant variance has been detected among the groups, with the epinephrine group having a mean HR of 122.62 ± 15.56 bpm, and the norepinephrine group having a mean HR of 119.76 ± 16.27 bpm (p = 0.463). The mean respiratory rates for Epinephrine and Norepinephrine were 17.52 ± 2.79 and 16.68 ± 2.70 respectively with a t-statistic of 1.265 and a p-value of 0.210. Similarly, the temperature data showed mean values of 36.95 ± 0.46 °C for epinephrine and 36.83 ± 0.53 °C for NE with a p-value of 0.299.

Table (1): Demographic and clinical data of study groups

		Epinephrine (n=34)	Norepinephrine (n=34)	Test, p-value
Age (years)	Mean ± SD	9.59 ± 4.61	9.09 ± 4.96	t: 0.288 p=0.777
	Median (Range)	11.00 (3.00-17.00)	8.00 (1.00-17.00)	
Gender	Female	16 (47.1%)	16 (47.1%)	X^2: 0.000 p=1.000
	Male	18 (52.9%)	18 (52.9%)	
Weight (kg)	Mean ± SD	33.62 ± 16.43	31.91 ± 16.80	t: 0.423 p=0.676
	Median (Range)	30.00 (14.00-58.00)	24.00 (10.00-57.00)	
Height (cm)	Mean ± SD	134.22 ± 25.16	131.38 ± 29.17	t: 0.080 p=0.941
	Median (Range)	143.99 (94.61-168.00)	128.27 (73.66-172.72)	
BMI (kg/m²)	Mean ± SD	17.27 ± 2.95	16.98 ± 2.49	t: 0.466 p=0.645
	Median (Range)	15.33 (14.19-22.94)	15.66 (14.19-22.27)	
HR (bpm)	Mean ± SD	122.62 ± 15.56	119.76 ± 16.27	t: 0.739 p=0.463
	Median (Range)	125.50 (90.00-146.00)	122.50 (91.00-145.00)	
MBP (mmHg)	Mean ± SD	62.17 ± 1.59	60.24 ± 3.94	Z: 0.624 p=0.253
	Median (Range)	62.45 (59.00-65.59)	60.61 (40.00-64.71)	
Capillary Refill Time (s)	Mean ± SD	3.38 ± 0.49	3.62 ± 0.49	Z: 1.668 p=0.055
	Median (Range)	3.00 (3.00-4.00)	4.00 (3.00-4.00)	
Respiratory rate (breaths/min)	Mean ± SD	17.52 ± 2.79	16.68 ± 2.70	1.265, p=0.210
	Median (Range)	17.30 (11.30)	16.72 (9.95)	
Temperature (°C)	Mean ± SD	36.95 ± 0.46	36.83 ± 0.53	1.046, p=0.299
	Median (Range)	36.99 (2.09)	36.81 (2.19)	

t: Student t test, Z: Mann Whitney test, * for significant p value (<0.05).

Regarding baseline laboratory investigations, there were insignificant variances among the epinephrine and norepinephrine groups across all parameters.

The mean white blood cell (WBC) count was similar between the groups, with 19.30 ± 1.43 in the epinephrine group and 19.43 ± 1.42 in the norepinephrine group (p = 0.714). Hemoglobin levels and platelet counts were also comparable, with a statistically insignificant variances detected (p = 0.196 and p = 0.992, respectively). The mean C-reactive protein (CRP) concentrations were slightly higher in the epinephrine group (132.00 ± 15.37 mg/L) compared to the norepinephrine group (126.70 ± 28.45 mg/L), but this variance was insignificant (p = 0.606). Blood culture results showed no significant difference, with 29.4% of cases in the epinephrine group and 35.3% in the norepinephrine group having positive cultures (p = 0.795).

Additionally, insignificant variances were observed in other parameters such as creatinine, AST,

ALT & bilirubin or random blood sugar (RBS) levels. According to the baseline arterial blood gas results, there were insignificant variances among both study groups. According to the baseline serum electrolytes, there were insignificant variances between the epinephrine and norepinephrine groups.

Table (2): Baseline laboratory investigations in study groups

		Epinephrine (n=34)	Norepinephrine (n=34)	Test, p-value
WBC (10^9/L)	Mean ± SD	19.30 ± 1.43	19.43 ± 1.42	t: 0.368, p=0.714
Hemoglobin (g/dL)	Mean ± SD	9.69 ± 0.37	9.81 ± 0.33	t: 1.305, p=0.196
Platelet Count (10^9/L)	Mean ± SD	187.24 ± 33.68	186.33 ± 36.68	t: 0.011, p=0.992
CRP (mg/L)	Mean ± SD	132.00 ± 15.37	126.70 ± 28.45	Z: 0.521 p=0.606
Blood Culture	Negative	24 (70.6%)	22 (64.7%)	X^2: 0.067 p=0.795
	Positive	10 (29.4%)	12 (35.3%)	
Creatinine (mg/dL)	Mean ± SD	0.72 ± 0.13	0.82 ± 0.14	Z: -0.429 p=0.672
AST (U/L)	Mean ± SD	115.70 ± 22.56	115.82 ± 22.59	t: 0.023, p=0.982
ALT (U/L)	Mean ± SD	86.15 ± 9.40	88.29 ± 10.39	t: 0.059, p=0.953
Bilirubin (mg/dL)	Mean ± SD	0.79 ± 0.17	0.76 ± 0.13	Z: 0.889 p=0.358
RBS (mg/dL)	Mean ± SD	143.15 ± 5.17	143.26 ± 6.59	Z: 0.178 p=0.864
pH	Mean ± SD	7.40 ± 0.05	7.37 ± 0.06	Z: 1.834 p=0.066
	Median (Range)	7.40 (7.19-7.45)	7.39 (7.24-7.45)	
pCO2 (mmHg)	Mean ± SD	40.88 ± 3.14	43.53 ± 3.96	Z: 0.184, p=0.859
	Median (Range)	41.02 (35.00-45.00)	44.00 (37.10-49.33)	
pO2 (mmHg)	Mean ± SD	88.74 ± 4.86	81.88 ± 5.92	t: 0.044, p=0.965
	Median (Range)	89.12 (80.50-98.15)	83.05 (71.27-89.90)	
HCO3 (mmol/L)	Mean ± SD	18.55 ± 1.40	17.04 ± 2.29	Z: 0.350, p=0.731
Sodium (Na+, mmol/L)	Mean ± SD	139.78 ± 2.96	139.69 ± 3.96	Z: 0.117 p=0.912
Potassium (K+, mmol/L)	Mean ± SD	4.36 ± 0.56	4.52 ± 0.85	Z: 0.644, p=0.524
Ionized Calcium(mg/dL)	Mean ± SD	0.96 ± 0.02	1.02 ± 0.03	Z: 248 p=0.865

Z: Mann Whitney test, * for significant p value (<0.05).

There was a significant variance between the study groups with regard to both vasoactive medication dose and fluid resuscitation. The norepinephrine group required a significantly higher dose of vasoactive medications (7.79 ± 1.64 µg/kg/min) compared to the epinephrine group (0.20 ± 0.05 µg/kg/min), with a highly significant p-value (p < 0.001). Furthermore, the fluid resuscitation volume was significantly greater in the norepinephrine group (51.73 ± 5.66 mL/kg) than the fixed volume of 40.00 mL/kg in the epinephrine group (p < 0.001) (Table 3 and figures 1 & 2).

Table (3): Vasoactive medication dose and fluid resuscitation in study groups

		Epinephrine (n=34)	Norepinephrine (n=34)	Test, p-value
Vasoactive Medication Dose (µg/kg/min)	Mean ± SD	0.20 ± 0.05	7.79 ± 1.64	Z: 7.089 p<0.001*
	Median (Range)	0.20 (0.11-0.29)	8.48 (5.01-9.91)	
Fluid Resuscitation rate (mL/kg)	Mean ± SD	40.00 ± 0.00	51.73 ± 5.66	Z: 7.089 p<0.001*
	Median (Range)	40.00 (40.00-40.00)	52.77 (40.96-59.78)	

Z: Mann Whitney test, * for significant p value (<0.05)

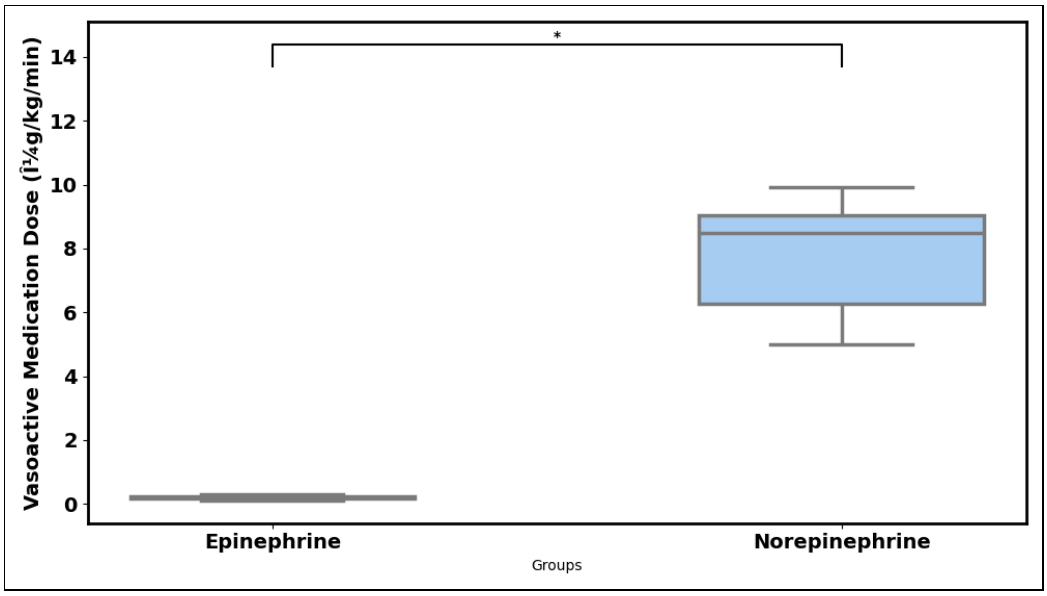

Figure (1): Vasoactive medication dose in study groups in study groups.

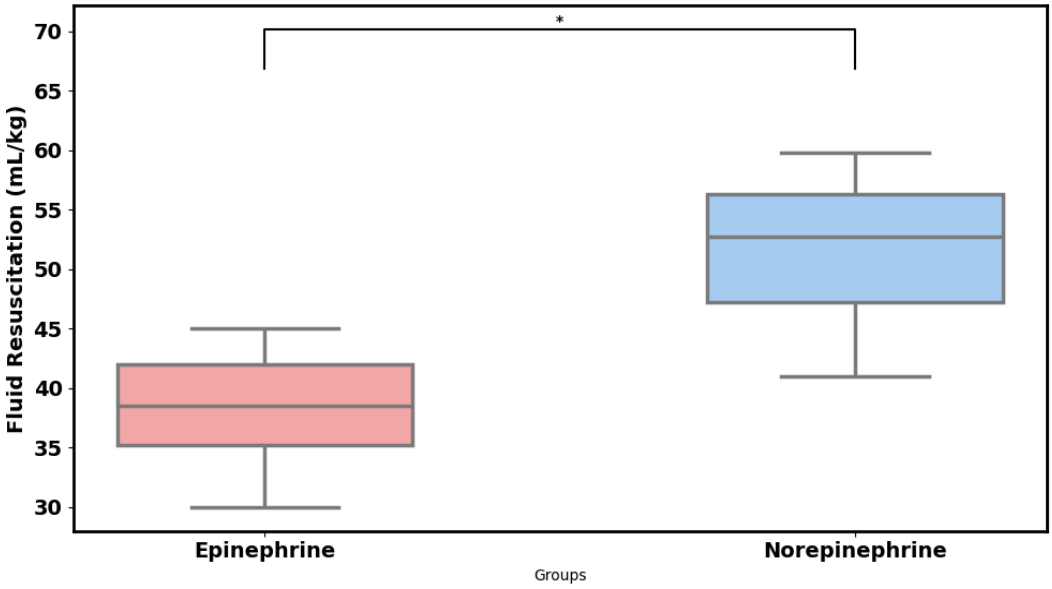

Figure (2): Fluid resuscitation in study groups.

Regarding mechanical ventilation data, there was a significant distinction among the epinephrine and norepinephrine groups. The need for mechanical ventilation was much greater in the norepinephrine group (97.1%) than in the epinephrine group (58.8%) ($p < 0.001$). Additionally, the length of mechanical ventilation was significantly extended in the norepinephrine group, with a mean of 6.50 ± 2.78 days, in comparison with 3.41 ± 3.58 days in the epinephrine group ($p < 0.001$) (table 4 and figures 3 & 4).

Table (4): Mechanical ventilation related data in study groups

		Epinephrine (n=34)	Norepinephrine (n=34)	Test, p-value
Need for Mechanical Ventilation (%)	n (%)	20 (58.8%)	33 (97.1%)	X^2: 12.317 p<0.001*
Length of Mechanical Ventilation (days)	Mean ± SD	3.41 ± 3.58	6.50 ± 2.78	Z: 3.526 p<0.001*
	Median (Range)	3.00 (0.00-10.00)	6.00 (0.00-10.00)	

X2: Chi square test, Z: Mann Whitney test, * for significant p value (<0.05).

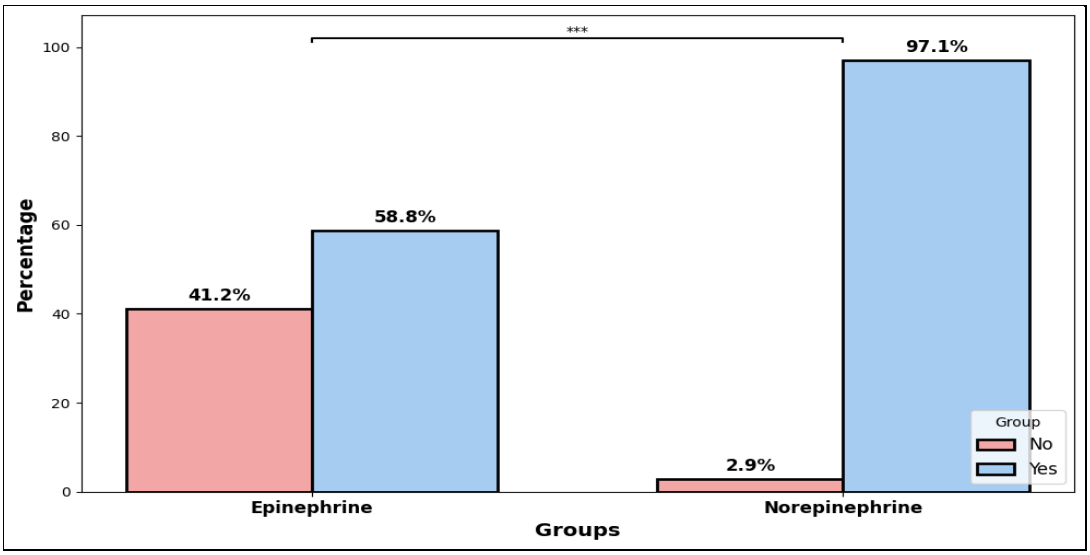

Figure (3): Need of mechanical ventilation in study groups.

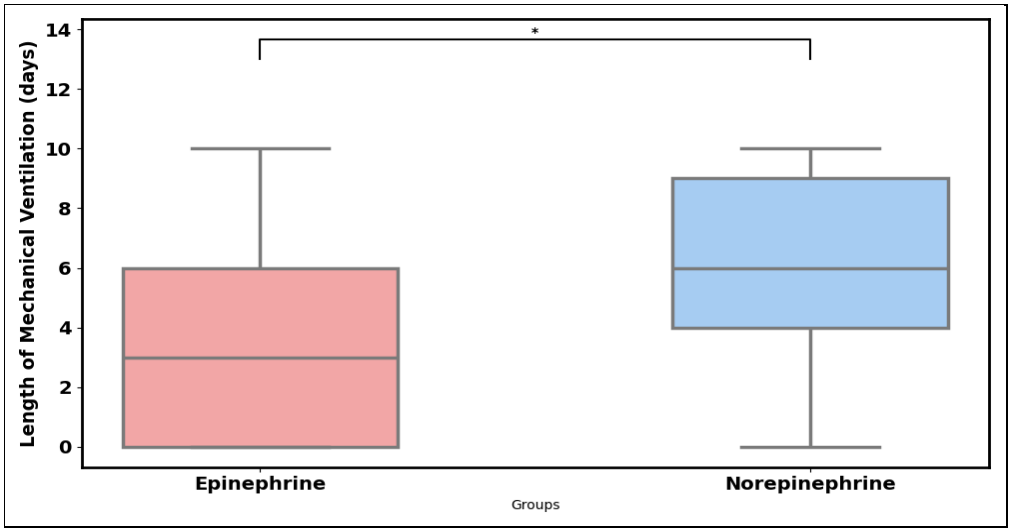

Figure (4): Comparison amid examined groups with regard to length of mechanical ventilation.

In terms of outcome and prognosis, there was a significant variance in the length of stay (LOS) in the PICU among both groups. The NE group had a longer mean LOS of 6.97 ± 2.85 days than 3.65 ± 3.78 days in the epinephrine group ($p < 0.001$). However, the epinephrine group demonstrated better results, with a higher survival rate of 97.1% compared to 85.3% in the NE group ($p = 0.200$). Regarding mechanical ventilation, there was a significant distinction between the epinephrine and NE groups. The need for mechanical ventilation was much greater in the NE group (97.1%) compared to the epinephrine group (58.8%) (P-value under 0.001). Additionally, the length of mechanical ventilation was significantly extended in the NE group, with a mean of 6.50 ± 2.78 days, compared to 3.41 ± 3.58 days in the epinephrine group (p-value under 0.001).

Table (5): Outcome and prognosis in study groups

		Group Epinephrine (n=34)	**Group Norepinephrine (n=34)**	**Test, p-value**
Length of Stay (LOS) in PICU (days)	Mean ± SD	3.65 ± 3.78	6.97 ± 2.85	Z: 3.539 p<0.001*
	Median (Range)	3.50 (0.00-11.00)	7.00 (0.00-11.00)	
Survival Rates (%)	n (%)	33 (97.1%)	29 (85.3%)	X^2: 1.645 p=0.200
Need for Mechanical Ventilation (%)	n (%)	20 (58.8%)	33 (97.1%)	X^2: 12.317 p<0.001*
Length of Mechanical Ventilation (days)	Mean ± SD	3.41 ± 3.58	6.50 ± 2.78	Z: 3.526 p<0.001*
	Median (Range)	3.00 (0.00-10.00)	6.00 (0.00-10.00)	

X^2: Chi square test, Z: Mann Whitney test, * for significant p value (<0.05)

Regarding organ dysfunction and assessment scores, there were significant variances between the epinephrine and norepinephrine groups. The PRISM score, which evaluates the severity of illness, was significantly reduced in the epinephrine group, with a mean of 16.43 ± 5.02 compared to 19.13 ± 5.25 in the norepinephrine group (p = 0.016). Similarly, the PRISM III score was also lower in the epinephrine group (15.81 ± 5.02) compared to the norepinephrine group (18.63 ± 5.21), with a significant variance (p = 0.019) (table 6, figures 5,6).

Table (6): Organ Dysfunction and assessment scores

		Group Epinephrine (n=34)	Group Norepinephrine (n=34)	Test, p-value
PRISM Score	Mean ± SD	16.43 ± 5.02	19.13 ± 5.25	Z: 2.416, p=0.016*
	Median (Range)	14.00 (10.00-29.71)	19.27 (10.00-30.75)	
PRISM III Score	Mean ± SD	15.81 ± 5.02	18.63 ± 5.21	Z: 2.343, p=0.019*
	Median (Range)	14.00 (9.00-28.71)	18.27 (9.29-29.75)	

Z: Mann Whitney test, * for significant p value (<0.05).

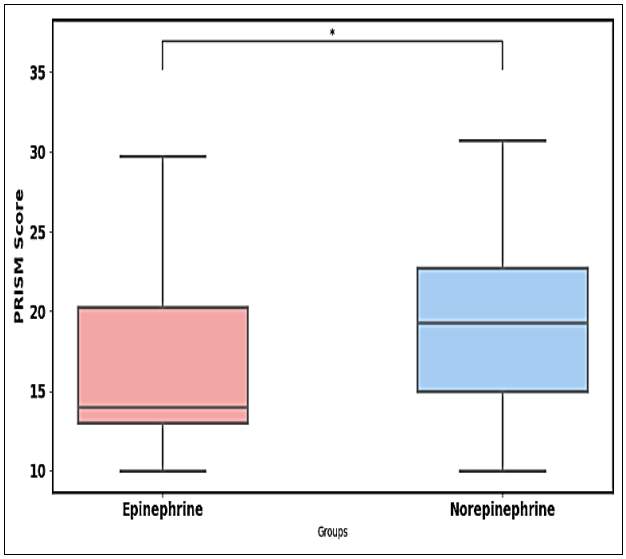

Figure (5): Comparison between studied groups according to PRISM score.

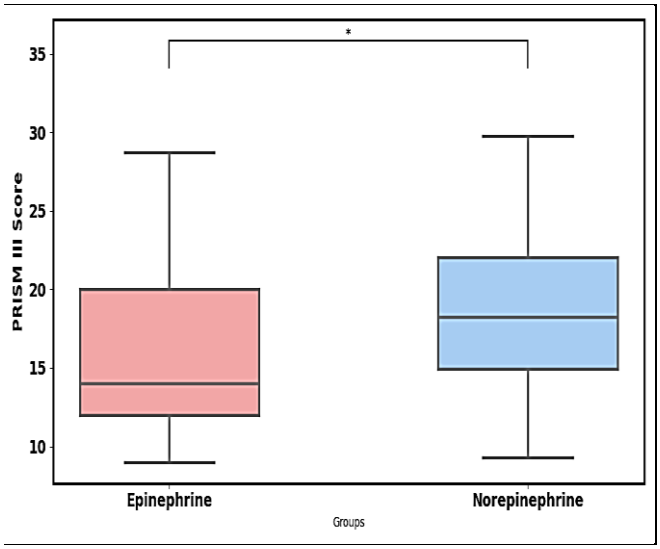

Figure (6): Comparison between studied groups with regard to PRISM III score.

The comparison between survived and non-survived subjects revealed significant differences in several clinical parameters. Non-survived subjects had significantly lower mean blood pressure (**p** -value under 0.001) and extended capillary refill time (p = 0.011) indicating poorer circulation.

They also exhibited higher C-reactive protein levels (**p** -value under 0.001) reflecting greater inflammation and higher creatinine levels (p = 0.028) suggesting worse kidney function. In terms of respiratory and metabolic status, non-survived subjects had worse blood gas values with lower pH (**p** -value under 0.001), greater pCO_2 (p < 0.001), lower pO_2 (**p** -value under 0.001) and lower bicarbonate levels (**p** -value under 0.001).

Additionally, non-survived subjects had significantly higher potassium levels (**p** -value under 0.001) and required greater doses of vasoactive medication (**p** -value under 0.001) and more fluid resuscitation (**p** -value under 0.001).

PRISM and PRISM III scores were significantly higher in non-survived subjects (p -value under 0.001) indicating greater disease severity.

Table (7): Comparison among survived and non-survived subjects

		Died	Survived	Test Result
		n=6	n=62	
Age (years)	Mean ± SD	8.50 ± 5.47	9.42 ± 4.73	p=0.588
Sex	Female	4(66.7%)	28(45.2%)	p=0.562
	Male	2(33.3%)	34(54.8%)	
Weight (kg)	Mean ± SD	33.17 ± 19.45	32.73 ± 16.38	p=0.761
Height (cm)	Mean ± SD	128.11 ± 34.80	133.26 ± 26.52	p=0.634
BMI (kg/m2)	Mean ± SD	18.16 ± 3.01	17.02 ± 2.68	p=0.324
HR (bpm)	Mean ± SD	114.17 ± 10.91	121.87 ± 16.17	p=0.180
MBP (mmHg)	Mean ± SD	55.46 ± 7.61	61.76 ± 1.57	p<0.001*
Capillary Refill Time (s)	Mean ± SD	4.00 ± 0.00	3.45 ± 0.50	p=0.011*
WBC (10^9/L)	Mean ± SD	19.39 ± 1.41	19.36 ± 1.43	p=0.795
Hemoglobin (g/dL)	Mean ± SD	9.71 ± 0.22	9.75 ± 0.36	p=0.745
Platelet Count (10^9/L)	Mean ± SD	177.60 ± 17.86	187.12 ± 37.70	p=0.456
CRP (mg/L)	Mean ± SD	160.56 ± 20.08	129.30 ± 11.60	p<0.001*
Creatinine (mg/dL)	Mean ± SD	0.87 ± 0.10	0.76 ± 0.16	p=0.028*
AST (U/L)	Mean ± SD	110.34 ± 14.77	116.29 ± 23.03	p=0.539
ALT (U/L)	Mean ± SD	89.15 ± 6.13	88.13 ± 10.66	p=0.787
Bilirubin (mg/dL)	Mean ± SD	0.82 ± 0.13	0.85 ± 0.21	p=0.774
RBS (mg/dL)	Mean ± SD	161.17 ± 5.58	141.40 ± 5.06	p=0.482
pH	Mean ± SD	7.30 ± 0.09	7.44 ± 0.08	p<0.001*
pCO2 (mmHg)	Mean ± SD	44.80 ± 0.27	40.55 ± 3.01	p<0.001*
pO2 (mmHg)	Mean ± SD	81.58 ± 0.92	89.46 ± 4.41	p<0.001*
HCO3 (mmol/L)	Mean ± SD	16.13 ± 1.66	18.85 ± 1.12	p<0.001*
Sodium (Na+, mmol/L)	Mean ± SD	138.71 ± 1.93	139.97 ± 3.03	p=0.430
Potassium (K+, mmol/L)	Mean ± SD	5.53 ± 0.83	4.29 ± 0.41	p<0.001*
Ionised Calcium	Mean ± SD	1.04 ± 0.14	1.01 ± 0.10	p=0.957
Blood Culture	Negative	6(100.0%)	40(64.5%)	p=0.188
	Positive	0(0.0%)	22(35.5%)	
Vasoactive Medication Dose (g/kg/min)	Mean ± SD	8.20 ± 3.88	3.59 ± 3.79	p<0.001*
Fluid Resuscitation (mL/kg)	Mean ± SD	56.63 ± 5.72	43.89 ± 7.88	p<0.001*
Length of Mechanical Ventilation (days)	Mean ± SD	5.17 ± 4.07	4.94 ± 3.52	p=0.930
Length of Stay (LOS) in PICU (days)	Mean ± SD	5.50 ± 4.23	5.29 ± 3.71	p=0.930
PRISM Score	Mean ± SD	27.92 ± 2.26	16.80 ± 4.37	p<0.001*
PRISM III Score	Mean ± SD	27.47 ± 2.08	16.25 ± 4.43	p<0.001*

* For significant p value (<0.05).

DISCUSSION

Septic shock continues to rank among the primary contributors to death and morbidity in pediatric intensive care units globally. Defined by uncorrected hypotension following adequate fluid administration, the condition demands immediate cardiovascular stabilization through vasoactive medications [8]. First-line therapies typically involve epinephrine and norepinephrine, but uncertainty persists regarding the preferred agent in pediatric cohorts [9].

Epinephrine stimulates both α- and β-adrenergic receptors, yielding simultaneous vasoconstrictive and inotropic responses that can elevate cardiac output and enhance tissue perfusion. Norepinephrine, by contrast, predominantly activates α-adrenergic receptors, resulting in strong vasoconstriction while exerting minimal effects on myocardial contractility. Despite both medications raising systemic arterial pressure, their divergent pharmacodynamics may differentially affect downstream endpoints including regional perfusion, ventilatory support needs, and duration of PICU admission [10].

The current research aimed to assess the consequences of initiating therapy with epinephrine compared to norepinephrine on the clinical course of children with septic shock. Both the epinephrine and norepinephrine cohorts exhibited comparable demographic and anthropometric variables with no statistically significant deviations in sex distribution, age, height, weight, or body mass index. The evident uniformity of these baseline metrics reduced the likelihood of confounding biases and permitted a more robust assessment of the therapeutic endpoints. A parallel demographic equivalence was noted by **Annane *et al.*** [11] randomized trial assessing pediatric septic patients, thereby reinforcing the replicability of our results.

No material variation in heart rate, mean arterial pressure, or capillary refill time characterized the baseline recordings of either group. The congruence of these hemodynamic indices supports the interpretation that any subsequent variation in clinical outcomes can reasonably be ascribed to the pharmacodynamic properties of epinephrine and norepinephrine rather than pre-treatment hemodynamic imbalances. These observations corroborate the earlier work of **Ramaswamy *et al.*** [12] who documented congruent baseline hemodynamic conditions in a pediatric shock comparison trial. Our results, however, diverge from those of **Ventura *et al.*** [13] who identified baseline discrepancies in capillary refill time among treatment groups in their cohort. **Banothu *et al.*** [14] compared norepinephrine plus dobutamine to epinephrine as the first choice in fluid-refractory cold septic shock in children. Their findings indicated that hemodynamic parameters, heart rate, capillary refill time, and mean arterial pressure, improved in the norepinephrine plus dobutamine cohort at several intervals from one to seventy-two hours after initiation. **Ruslan *et al.*** [15] evaluated norepinephrine's efficacy and safety in septic shock. They found no statistical difference in the proportion of patients reaching the target mean arterial pressure when norepinephrine was compared with other vasopressors.

In the present investigation, we noted a markedly higher requirement for vasoactive agents in the norepinephrine cohort, with a mean dose of 7.79 ± 1.64 microgram per kilogram per minute, compared to 0.20 ± 0.05 microgram per kilogram per minute in the epinephrine arm ($p<0.001$). **Garegrat *et al.*** [16] documented that 23.8% of neonates in the noradrenaline arm required additional vasopressors, versus 38.1% in the adrenaline group ($p=0.53$). **Banothu *et al.*** [14] found an increased necessity for supplementary agents in the epinephrine-treated children compared to those receiving combination therapy.

In our analysis, the fluid resuscitation volume required by the norepinephrine group was significantly higher, at 51.73 ± 5.66 mL/kg compared to 6.89 ± 4.38 days ($p < 0.001$), a finding that reinforces epinephrine's efficacious impact on overall clinical recovery. The cumulative requirement for vasoactive drugs, represented as noradrenaline equivalent doses, was also lower in the epinephrine cohort, indicating a potentially better titration profile in the context of pediatric septic shock.

While the observational nature of our data precludes definitive causality, the consistency of epinephrine's beneficial effects on both inotropic support and respiratory management aligns with its pharmacological profile, which balances neurohormonal modulation while delivering sufficient myocardial contractility at moderate dosing. Moreover, recent cohort and registry analyses of pediatric septic shock support a trend favoring the α-adrenergic potency of epinephrine in achieving earlier shock resolution without collateral detrimental effects on respiratory mechanics. Future prospective trials should consider multicenter designs that power for clinically relevant outcomes, ideally stratifying by shock etiology and pre-existing cardiopulmonary disease. Such heterogeneity may unveil subgroup-specific interactions and refine guidance on the most judicious use of catecholamines across the pediatric septic shock spectrum.

The mean for PICU length of stay was 6.97 ± 2.85 days ($p < 0.001$). Conversely, **Ventura *et al.*** [13] found insignificant variance in PICU length of stay between dopamine and epinephrine groups, suggesting that variation in illness severity, underlying comorbidities, or institutional management protocols may underlie the conflicting findings. **Garegrat *et al.*** [16] reported a median (SD) PICU stay of 6 (SD) days for the norepinephrine cohort and 10 (SD) days for the epinephrine cohort ($p = 0.045$). **Kohn-Loncarica *et al.*** [17] found that median total hospital stay was 11 days in the epinephrine cohort and 13 days in the dopamine cohort ($p = 0.554$), while median PICU duration was 4 days (range 0 to 81 days) in each cohort ($p = 0.748$).

Our data indicated a trend toward better survival in the epinephrine group (97.1%) versus the norepinephrine group (85.3%, p = 0.200), although this did not reach statistical significance. **Garegrat *et al.*** [16] found comparable mortality rates in the norepinephrine and epinephrine groups (28.6% vs. 33.6%, p = 0.77). Within-hospital mortality was 28.6% (6 of 21) for the norepinephrine group and 33.3% (7 of 21) for the epinephrine group (p = 0.58). Two systematic reviews examining clinical outcomes in adult populations have demonstrated an association between syndromes of early vasoactive pharmacotherapy and reduced mortality at 28 days **as showed by Chen *et al.*** [18] and **Cheng *et al.*** [19]**. Banothu *et al.*** [14] however, did not replicate this mortality benefit in a cohort of infants, reporting 28-day mortality rates of 23.5% and 39.3% for a first-line dual infused strategy of norepinephrine and dobutamine versus single agent epinephrine, a difference not achieving statistical significance.

Although very high cumulative norepinephrine doses of 4.7 µg/kg/min were tolerated in adult cohorts, permitting a 33% survival at 30 days. Data vital for the neonate population, including delineating the exposure-to-outcome relationship and refining optimal dosing strategies, remain scant [20].

One of the most striking results in our research was the significant difference in mechanical ventilation requirements between the two groups. Patients treated with norepinephrine exhibited a significantly higher need for mechanical ventilation (97.1% vs. 58.8%, p < 0.001) and an extended duration of ventilatory support (6.50 ± 2.78 days vs. 3.41 ± 3.58 days, p < 0.001) than the epinephrine group.

These findings contrast with those reported by **De Backer *et al.*** [21] in their adult septic shock study, which found insignificant variance in ventilation duration between norepinephrine and epinephrine groups. However, our results are consistent with recent pediatric-specific research by **Iramain *et al.*** [22] who reported lower ventilation requirements with epinephrine use in kids with septic shock.

Kohn-Loncarica *et al.* [17] reported that the rate of invasive mechanical ventilation was 38.8% for epinephrine against 40.6% for dopamine (p-value equal 0.84), with a median of 4 days for the epinephrine group and 5.5 for the dopamine group (p-value equal 0.104) in kids with fluid-refractory septic shock. The reduced need for mechanical ventilation in the epinephrine group could be attributed to epinephrine's bronchodilatory effects via beta-2 adrenergic receptor stimulation, which may improve respiratory mechanics and gas exchange. Additionally, epinephrine's stronger inotropic effects might result in better cardiac output and tissue perfusion, potentially reducing respiratory muscle fatigue and respiratory failure [23]**.** These pharmacological differences may explain why epinephrine-treated patients demonstrated better respiratory outcomes compared to those receiving norepinephrine.

In the present investigation, the severity-of-illness scores measured by PRISM and PRISM III were both significantly lower in the epinephrine group than in the norepinephrine group (PRISM: 16.43 ± 5.02 vs. 19.13 ± 5.25, p = 0.016; PRISM III: 15.81 ± 5.02 vs. 18.63 ± 5.21, p = 0.019) suggesting that epinephrine may be linked to milder clinical presentation and potentially more favorable outcomes in pediatric septic shock.

Consistent with these findings, **Kohn-Loncarica *et al.*** [17] reported reduced organ dysfunction scores among pediatric patients treated with epinephrine. Conversely, **Ventura *et al.*** [13] could not demonstrate a significant difference in PRISM scores when comparing cohort subsets exposed to differing vasoactive therapies. This finding underscores the multifaceted nature of vasoactive management in pediatric septic shock and suggests the necessity for additional controlled studies to discern outcome-related thresholds of therapy.

When comparing our cohort of survivors and non-survivors, we identified an ensemble of mortality predictors that reached statistical significance: Lower mean arterial blood pressure, prolonged capillary refill, elevated CRP and creatinine, deteriorated arterial blood gas indices (lower pH, elevated pCO_2, reduced pO_2, and lower bicarbonate), elevated potassium, increasing dosage of vasoactive infusions, and higher PRISM and PRISM III scores. **Garegrat *et al.*** [16] similarly observed that initial demographic, clinical, and hemodynamic variables were statistically indistinguishable between neonates who survived the septic course and those who did not. Our data suggest a potential clinical preference for epinephrine relative to norepinephrine in pediatric septic shock.

Administration of epinephrine is related to reduced reliance on mechanical ventilation, a shortened pediatric intensive care unit length of stay, and, on an exploratory basis, improved survival. The agent's dual alpha and beta receptor activation may confer broader hemodynamic stabilization at lower dosing than norepinephrine, which exerts predominant alpha-adrenergic vasoconstriction. These observations are congruent with the 2020 Surviving Sepsis Campaign guidelines [4]**,** which advocate for epinephrine as the initial vasoactive agent in the context of cold shock, a hemodynamic profile notably prevalent in pediatric patients, while norepinephrine is reserved for the warm shock phenotype. Our findings indicate that epinephrine could confer advantages that extend beyond the management of cold shock, highlighting the need for additional scrutiny.

LIMITATIONS

A few limitations must be acknowledged. The observational framework of the analysis prevents attribution of effect to intervention. A modest cohort size may have restricted the power to observe variances in rarer endpoints, especially mortality. Finally, results

drawn from a single tertiary pediatric center may not extend without qualification to other hospitals or demographic groups. Subsequent investigations should consist of larger, multicenter, randomized controlled trials in pediatric septic shock that juxtapose epinephrine and norepinephrine, stratified by cold or warm shock, and that track outcomes extending beyond pediatric intensive care unit discharge. Further exploration of the timing and sequencing of vasoactive agents, in conjunction with additional therapeutic modalities, is warranted to inform the refinement of clinical protocols.

CONCLUSION

In conclusion, our study showed that epinephrine may be related to better clinical results than norepinephrine in pediatric septic shock, particularly in terms of reducing mechanical ventilation requirements and shortening the PICU length of stay. These findings contribute to the ongoing discussion about optimal vasoactive therapy in pediatric septic shock and highlight the need for further research to establish evidence-based guidelines for this vulnerable population.

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