Research Article

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Septic Shock And Multiple Organ Dysfunction Syndrome: A Observational Study From Amazon Region

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ABSTRACT

Objectives: *To evaluate the risk factors and mortality associated with septic shock and multiple organ dysfunction syndrome (MODS), and to examine associations with unfavorable outcomes among pediatric patients from the Brazilian Amazon.*

Design: *A matched nested case-control, observational, single-center study was conducted between January 1, 2016, and December 31, 2019.*

Patients: *All children admitted to the pediatric intensive care unit (PICU) with sepsis, as defined in the inclusion criteria, were included.*

Interventions: *The selected cases consisted of patients with septic shock with MODS, while the control group consisted of children who were randomly chosen (1:2 ratio) among patients admitted to the PICU, matched for age and sex. Qualified students collected the data while being "blinded" to the research hypotheses.*

Measurements and Main Results: *There was an association between septic shock with MODS and pH, sodium bicarbonate and base excess, hypernatremia, hypocalcemia, and hyperchloremia. In patients with septic shock with or without MODS, hypocalcemia, hyperchloremia, hypomagnesemia, hypokalemia, and hypophosphatemia were associated with mortality. We also observed an association between acute respiratory distress symptoms, elevated anion gap, and hyperlactatemia in patients with septic shock and non-surviving MODS. Infections by gram-negative organisms, changes in coagulation markers, inadequate nutritional status, pulmonar impairment requiring invasive support, and the presence of acute respiratory distress syndrome were associated with an increased risk of septic shock with MODS and mortality.*

Conclusions: *In our study, septic shock with MODS associated with death affected male infants with previous comorbidities, hospitalized for clinical reasons, and coming from other services. The main factors associated with a higher risk of septic shock with MODS in this study were the origin of outside facilities.*

Keywords

Sepsis, Shock, Pediatrics, Intensive Care Units (ICU), Multiple Organ Failure.

Introduction

Sepsis is a potentially fatal multi-organ failure caused by the body's unregulated response to an infectious process. It is a leading cause of mortality in critically ill children and a common indication for

admission to the pediatric intensive care unit (PICU) However, its appropriate management remains a challenge, both in developing and developed countries [1-2].

Prognostic markers in sepsis help identify patients at increased risk of death, select the most appropriate therapies, in certain situations, and guide the response to treatment over time. They have also led to improvements in sepsis mortality over the last decade, especially among previously healthy children [3-6]. Based on the available literature, it is challenging to assess clinically relevant risk factors and outcomes of septic shock with multiple organ dysfunction syndrome (MODS) in low- and middle-income settings, especially in the Brazilian Amazon with its vulnerable economic, geographic, and health care access. The purpose of the present study was to evaluate the risk factors and mortality in a relevant sample of pediatric patients with septic shock with MODS from the Brazilian Amazon and to examine their associations with unfavorable outcomes.

Materials and Methods

Study and Data Collection

A matched nested case-control, observational, single-center study investigating pediatric septic shock with MODS was conducted between January 1, 2016 and December 31, 2019. The PICU at the hospital from the Fundação Santa Casa de Misericórdia do Pará is a 20- bed quaternary care medical-surgical ICU, catering to approximately 400 annual admissions. The study was approved by the Institutional Research Ethics Committee (No. 3.164.138). CAAE: 02152818.5.0000.5171. All researchers were instructed to inform patients with the standardized patient information sheet about their right to refuse participation. Before initiating the survey, some specialists were requested to provide educational lectures to the participants from the PICU. During the study, the coordinator and physicians in charge were responsible for validating the collected data and checking for any suspicious erros or missing values. Children were retrospectively followed up from the date of hospital admission until PICU discharge, death, or 28th day of hospitalization, whichever occurred first. Laboratory results were recorded at admission and on the most critical days until the 28th day of hospitalization, before PICU discharge. A collaborating researcher independently reviewed the data.

All children admitted to the PICU with a diagnosis of sepsis were included in the study. We excluded patients who received palliative care at the end of life, those prescribed with antibiotics supposedly and/or proven to be effective against the infectious process in question for more than 48 hours before admission, those with a previously diagnosed immunocompromised status, and those with a length of stay of more than 90 days or less than 24 hours of hospitalization. For patients readmitted to the PICU, only the first hospitalization in the unit was considered.

The selected cases consisted of patients with septic shock with MODS, while the control group consisted of children who were randomly chosen (1:2 ratio) among patients admitted to the PICU, matched for age and sex. Qualified students were trained in data collection but were "blinded" to the research hypotheses. Following the diagnostic criteria, septic shock was defined as suspected or proven infection caused by any pathogen presenting with tachycardia and hypothermia (≤35.0°C) or hyperthermia (≥38.5°C), or an abnormal WBC count with acute circulatory failure, characterized by persistent hypotension (<2 standard deviations for the standard age range and/or poor peripheral perfusion [absent peripheral pulses or capillary refilling time >3s] in the absence of clinical dehydration) despite adequate volumetric resuscitation and otherwise unexplained by other causes [7]. On the other hand, MODS was defined as the simultaneous occurrence of two organ dysfunctions. Following previously published criteria, the presence of new or progressive MODS was evaluated for 14 days following the diagnosis of severe sepsis [8].

Variable and Outcome Measures

Baseline information, including sex, age, weight, medical or surgical admission, definition of severe sepsis and septic shock, length of PICU stay, complex chronic condition according to Feudtner and co-workers (2014) [9], Pediatric Index of Mortality 3 (PIM 3) [10], Pediatric Risk of Mortality IV (PRISM IV) [11], Pediatric Logistic Organ Dysfunction 2 (PELOD 2) [12], and dates of admission and discharge, clinical manifestations, microbiological and laboratory findings, and outcome (death), were recorded using standardized data collection forms. All tests were performed according to the manufacturers' instructions. The reference ranges were defined according to age and sex. In addition to the epidemiological data, we evaluated the clinical course, associated diagnosis of MODS, ventilator settings, arterial gasometry (blood gases were measured at admission, and their most critical values during the clinical course were recorded), strong ion GAP, anion gap, use and duration of invasive mechanical ventilation, vasoactive drug use, ventilator-free days [13], and development of acute respiratory distress syndrome (ARDS) [14].

Nutritional status on admission was determined using the body mass index (BMI) Zscore, which incorporated the most relevant growth standards and references. The Z-scores were calculated using the World Health Organization AnthroPlus® software, and subjects were categorized as underweight (BMI Z-score < -2), normal weight (BMI Z-score ≥ -2 and ≤ 1), overweight (BMI Z-score > 1 and ≤ 2), or obese (BMI Z-score > 2) [15]. The primary outcome variable was the presence of septic shock with MODS, while the secondary outcome was mortality on the 28th day.

Statistical Analysis

Statistical analyses were performed using Minitab 14.0 (Minitab, LLC, Pennsylvania, USA). Categorical variables were expressed as n (%), while continuous variables were expressed as mean (SD) or median (interquartile range [IQR]), depending on whether the data were parametric or nonparametric, respectively. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Student's t-test was used for parametric analysis, and the

Mann-Whitney U test was used for the nonparametric continuous variables. Binary logistic regression was used to assess the risk factors for septic shock and mortality adjusted for PELOD 2 in both analyses. Cumulative survival was estimated using the Kaplan-Meier method. Statistical significance was defined as a p-value of less than 0.05.

Results

Demographics and Clinical Characteristics

During the study period, 1.216 patients were admitted, and 863 (71%) patients were eligible for inclusion. Fifty-three patients were excluded because of incomplete data. After performing paired randomization by age and sex, 616 patients (71.4%) were included in the final analysis. Among them, 65 were removed from the study because of the use of an effective antimicrobial for an infectious condition for more than 48 h (n = 23), length of stay in the intensive care unit for less than 24 h or greater than 90 days (n = 17), more than one admission to the unit (n = 10), immunocompromised status (n = 17), and end-of-life care (n = 8). The case group (G1) included 153 patients, while there were 306 patients in the control group (G0), with 69 (45.1%) and 53 (17.1%) deaths in each group, respectively (Figure 1).

The median age of the patients was 46.9 months, and the majority of them were male (362, 58.8%). The main reasons for hospitalization were the presence of clinical illnesses (440 cases, 71.4%) and comorbidities (418 cases, 67.9%). The most common diagnosis at admission was infection (344 patients, 55.8%). Community infection was the most predominant, seen in 200 cases (58.1%). The focus of infection in this series was pulmonary (200 cases, 32.5%) and abdominal (58 cases, 9.4%). However, among those with confirmed infection, gram-negative bacteria (64 cases, 56.7%], such as Klebsiella pneumoniae (22, 29.7%) and Pseudomonas aeruginosa (17, 13.5%), accounted for most cases (Table 1).

Sepsis was diagnosed in 310 patients. Precisely, 153 (49.3%) had septic shock and MODS, 73 (23.6%) had septic shock without MODS, and 84 (27.1%) had severe sepsis/sepsis. Vasoactive and ventilatory support was required in 412 patients (66.9%).

Risk Factors For Septic Shock and Mods

Malnourished children from external servisse in both groups, there was a higher frequency of infants and males (G1 with 56.9% vs. 45.1%, p = 0.0591, and G0 with 63.4% vs. 59.5%, p = 0.475,

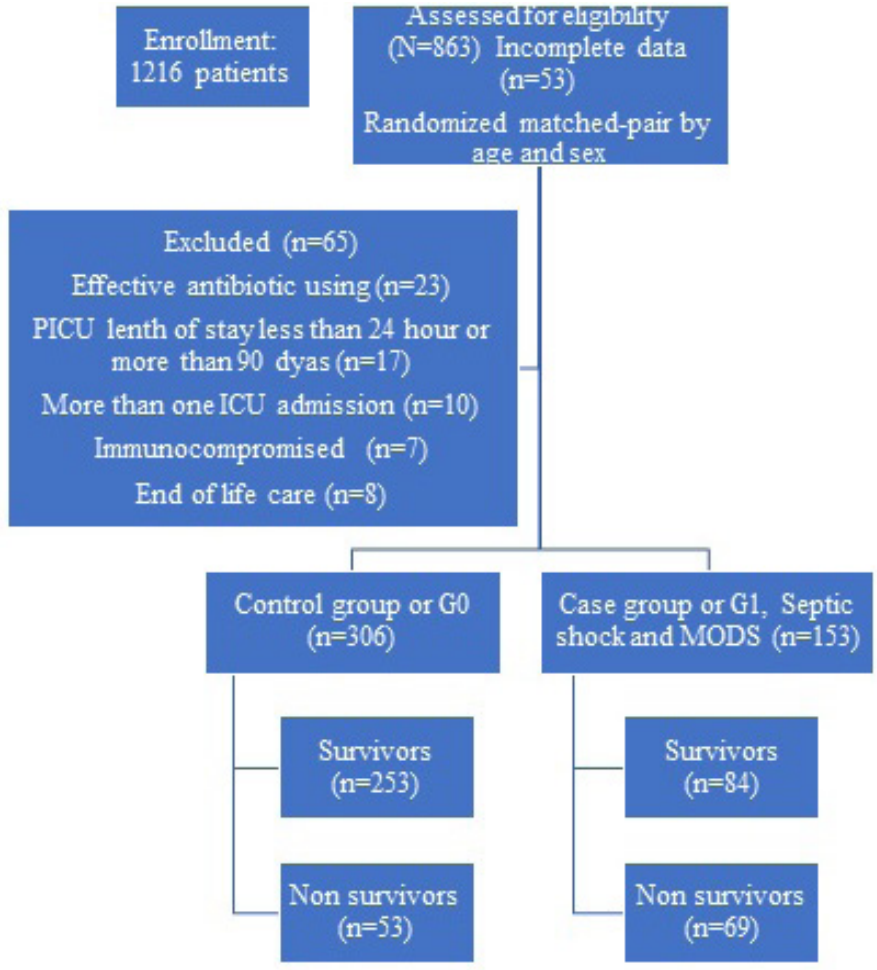

Figure 1: Flowchart describing the study design and selection of participants.

*PICU: pediatric Intensive care unit; ICU: intensive care unit.

Table 1: Baseline features of the enrolled patients.

Variables*	All patients included (n=616)
Age in months, mean (SD+/-)	46.9 (47.8)[a]
Male gender, n (%)	362 (58.8)[b]
BMI (kg/m²), mean (SD+/-)	14.1 (5.3)[a]
Type of admission: Medical/Surgical, n (%)	440 (71.4)/ 176 (28.6)[b]
PICU admission: Infection with or without sepsis, n (%)	344 (55.8)[b]
Comorbidities[α], n (%)	418 (67.9)[b]
Vasoactive Support, n (%)	412 (66.9)[b]
Invasive mechanical ventilation, n (%)	412 (66.9)[b]
ARDS, n (%)	214 (34.7)[b]
Type of infection[β]: Nosocomial infection/ Community infection, n (%)	144 (41.9)/ 200 (58.1)[b]
Infection site: Lung/ Abdominal, n (%)	200 (32.5)/ 58 (9.4)[b]
Gram negative infections, n (%)	64 (56.7)[b]
Confirmed sepsis, n (%)	74 (23.9)[b]
Most common microbiological pathogens[γ], n (%)	
Klebsiella pneumoniae	22 (29.7)[b]
Pseudomonas aeruginosa	17 (13.5)[b]
Staphylococcus aureus	14 (18.9)[b]
Sepsis continuum[b]	
Sepsis and severe sepsis, n (%)	84 (27.1)[b]
Septic shock, n (%)	73 (23.6)[b]
Septic shock and MODS, n (%)	153 (49.3)[b]
PIM 3 (%), median (interquartile range)	4 (1.2-10.7)[c]
PRISM IV (%), median (interquartile range)	6 (2.2-13)[c]
PELOD 2, median (interquartile range)	6,2(1.9-15.7)[c]
Outcomes	
Length of PICU stay (days), median (interquartile range)	7 (3-15)[c]
Invasive ventilation time (days), median (interquartile range)	6 (3-11.25)[c]
Ventilator-free days, median (Interquartile range)	1 (0-5)[c]
Overall mortality on 28th day, n (%)	152 (24.7)[b]
Sepsis and severe sepsis mortality, n (%)	2 (2.4)[b]
Septic shock mortality, n (%)	28 (38.4)[b]
Septic shock and MODS mortality, n (%)	69 (45.1)[b]

*BMI, body index mass; PICU, pediatric intensive care unit; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome. [a] Mean (+/- SD), [b] n (%), [c] Median (interquartile range[IQR]). [α] Neurologic diseases (100[24%]), respiratory diseases and prematurity (58 [13.9%]), gastrointestinal diseases (50 [12%]), and kidney and urological disease (49 [11.7%]). [β] There were 375 cases of infection, with isolated agents in 113 cases, sepsis continuum in 74, and 39 in the control group. [γ] In the sepsis diagnoses, other pathogens included *Stenotrophomonas maltophilia* [5(6.7%)], *Acinetobacter baumannii* [4(5.4%)], *Serratia marcescens* [3 (4%)], *Streptococcus pneumoniae* [3(4%)], *Candida tropicalis* [3(4%)], *and Enterococcus faecalis* [3 (4%)].

respectively). External origin was more frequent in G1 (59.5% vs. 32%, p <0.0001). Clinical illnesses were the main reason for hospitalization in both groups (G0, 64.7% vs. 78.4%, p = 0.0038). Upon nutritional assessment, there was a greater number of underweight patients in G1 (57.5% vs. 41.8%, p <0.0001), as shown in Table 2.

G1 patients had more comorbidities (76.5% vs. 58.2%, p <0.0001), infections with gram-negative bacteria (64.9% vs. 30.8%, p <0.0001), and usage of vasoactive drugs and invasive ventilatory support (95.4% vs. 9.2%, and 94.8% vs. 55.6%, respectively, with p <0.0001 in both). ARDS and severe ARDS were also more frequent in G1 (51.6% vs. 28.8%, and 8.5% versus 3.9%, respectively, both p <0.0001) (Table 2).

Regarding the gasometric values, only the pH (25,2% vs 49%, p = 0.043), sodium bicarbonate (18,6% vs. 51%, p = 0.013), and base excess (20% vs. 52,9%, p = 0.014) were associated with the presence of relevant septic shock and MODS. Among laboratory tests, there was a tendency toward hypernatremia (15% versus 48,4%, p <0.001), hypocalcemia (55,5% vs. 65,3%, p = 0.007), and hyperchloremia (23,2% vs. 76,5%, p = <0.0001) in G1 (Table 2).

The prognostic scores varied in both groups, with higher values in G1 (PRISM IV 22,9% vs. 65,4%, PELOD 2 10,8% vs. 70%, respectively, both with p <0.001). Among the calculated indices, only the CRP/albumin ratio was associated with the presence of shock and MODS (63,4% vs. 27,8%, p <0.001). Furthermore, the G1 group had a longer length of stay (9 vs. 6 days, p <0.0001) and a higher rate of invasive mechanical ventilation (6 vs. 5, p = 0.5837), though the ventilation-free days were reduced (1 vs. 2 days, p = 0.0271), as shown in Table 2.

Table 2: Comparison Between The Characteristics of Pediatric Intensive Care Unit Patients with And without Septic Shock with Multiple Organ Dysfunction Syndrome.

Variable	Control group (n=306)	Case group (n=153)	*p* values
Epidemiologic and clinic features			
Age groups, infants n (%)	138 (45.1)	87 (56.9)	0.059[a]
Male gender, n (%)	194 (63.4)	91 (59.5)	0.475[a]
Origin of patient, another hospitals n (%)	98 (32.0)	91 (59.5)	0.01[b]
Type of admission: Medical, n (%)	198 (64.7)	120 (78.4)	0.0038[a]
Comorbidities , n (%)	236 (77.1)	89 (58.2)	0.01[a]
Nutritional status, underweight (BMI Z-score < −2, n (%)	128 (41.8)	88 (57.5)	0.1[a]
Gram-negative infection, n (%)	12 (30.8)	48 (64.9)	0.001[a]
Vasoactive Support, n (%)	28 (9.2)	146 (95.4)	<0.0001[a]
Invasive mechanical ventilation, n (%)	170 (55.6)	145 (94.8)	<0.0001[a]
ARDS, n (%)	88 (28.8)	79 (51.6)	0.01[a]
ARDS form: severe[α], n (%)	12 (3.9)	13 (8.5)	0.01[a]
Gasometry features, n (%)			
pH <7.3	77 (25.2)	75 (49)	0.043[c]
BIC (mEq/ L) < 15	57 (18.6)	78 (51)	0.013[c]
BE (mEq/ L) < -5	61 (20)	81 (52.9)	0.014[c]
Laboratorial features, n (%)			
Segmented/mm^3 × 10^9 > 9000	90 (29.4)	114 (74.5)	0.01[c]
Lymphocytes/mm^3 × 10^9< 2000	136 (44.4)	69 (45.1)	0.9851[c]
Platelets/mm^3 × 10^9< 80.000	65 (21.2)	62 (40.5)	0.02[c]
Sodium (mmol/L) > 155	46 (15)	74 (48.4)	0.001[c]
Potassium (mmol/L)< 3.5	130 (42.5)	39 (25.5)	0.0502[c]
Total calcium (mg/dL) < 8,5	170 (55.5)	100 (65.3)	0.007[c]
Chlorides (mmol/L) >110	71 (23.2)	117 (76.5)	<0.0001[c]
Calculator index, n (%)			
PRISM IV >10	70 (22.9)	100 (65.4)	0.001[c]
PELOD 2 >10	33 (10.8)	107 (70)	<0.0001[c]
CRP/Albumin ratio > 5	85 (27.8)	97 (63.4)	0.001[c]
Outcomes, n (%)			
LOS (days) >7	121 (39.6)	98 (64)	0.001[c]
IVT (days) >3	70 (22.9)	125 (81.7)	0.005[c]
VFD<2	180 (58.9)	128 (84)	0.0271[c]
Overall mortality on 28th day, n (%)	53 (17.3)	69 (45.1)	<0.0001[a]

*IQR: interquartile range; pH: potential for hydrogen; BIC: sodium bicarbonate; BE: base excess; CRP: C-reactive protein; LOS: length of stay in the PICU; IVT: invasive ventilation time; VFD: ventilator-free days. [a]Chi-square test. [b]Fisher's exact test. [c] Mann-Whitney test. [α]The classification of Acute respiratory distress symptoms (ARDS) were classified according to the current pediatric criteria set by the Pediatric Acute Lung Injury Consensus Conference (PALICC), 2015 [20].

Mortality and survival time

In a comparative analysis between the groups and the 28th -day mortality outcome, we observed a higher percentage of male children (65.2% vs. 43.4%, p = 0.042), infants (58% vs. 45.3%, p = 0.391), patients originally from other hospitals (66.7% vs. 26.4%, p <0.0001), reason for hospitalization of clinical origin (82.6% vs. 75.5%, p = 0.235), presence of comorbidities (69.6% vs. 62.3%, p = 0.795), and younger age (in months) in G1 (58% vs. 45,3%, p = 0.391) (Table 3). Among the non-survivors, gasometric results suggestive of deficiente tissue perfusion were more critical in G1 than in G0, particularly the pH (<7,3) [77,8% vs. 18,9%, p <0.0001], sodium bicarbonate (<15 mEq/L) [70,6% vs. 21,2%, p = 0.0002], and base excess (< -5 mEq/L) [90,1% vs. 27,7%, p <0.0001] (Table 3).

Compared to G1, the laboratory abnormalities in G0, such as lower serum potassium (< 3,5 mEq/L) [63,4% (G1) vs. 12,4% (G0), p <0.0001], hypocalcemia (<8.5 mg/dL) [75,8% vs. 24,5%, p = 0.0042], reduced serum magnesium levels (< 1.5 mg/dL) [66,7% vs. 21,9%, p = 0.0028], hyperchloremia (>110 mmol/L) [77,8% vs. 28,8%, p = 0.008], widening of INR (>1,5) [65,3% vs. 23,2%, p = 0.022], and lower levels of plasma phosphorus (<2 mg/dL) [24,8% vs. 9,1%, p = 0.0237] were associated with mortality. Lymphopenia was observed in both groups, but there was no statistically significant difference in mortality.

The factors with the greatest impact on mortality in G1 included being underweight (p <0.0001), proven infection with gram-negative bactéria (p = 0.002), need for vasoactive support (p <0.0001) and invasive mechanical ventilation (p <0.0001), and evolution to ARDS (p = 0.002). In addition, there was a higher percentage of severe ARDS in this group compared to G0 (13% vs. 1,9%, p = 0.042), as shown in Table 3.

Table 3: Comparison Between the Characteristics of Non-Survivor Pediatric Intensive Care Unit Patients with and without Septic Shock With Multiple Organ Dysfunction Syndrome.

Variable	Control group (n=306)	Case group (n=153)	*p* values
	Nonsurvivors (n=53)	Nonsurvivors (n=69)	
Epidemiologic features			
Age in months, median (IQR)	49 (6-102)	17 (6-72)	0.213[c]
Age groups, infants n (%)	24 (45.3)	40 (58.0)	0.391[a]
Male gender, n (%)	23 (43.4)	45 (65.2)	0.042[a]
Origin of patient, another hospitals n (%)	14 (26.4)	46 (66.7)	<0.0001[a]
Type of admission: Medical, n (%)	40 (75.5)	57 (82.6)	0.235[a]
Comorbidities , n (%)	37 (69.8)	43 (62.3)	0.795[a]
Nutritional status, underweight (BMI Z-score < −2, n (%)	13 (24.5)	60 (87)	<0.0001[b]
Gram-negative infection, n (%)	6 (11.3)	25 (36.2)	0.002[b]
Lymphopenia[α], n (%)	32 (60.4)	40 (60.0)	0.280[a]
Vasoactive Support, n (%)	5 (9.4)	67 (97.1)	<0.0001[b]
Invasive mechanical ventilation, n (%)	36 (67.9)	67 (97.1)	<0.0001[a]
ARDS, n (%)	16 (30.2)	42 (60.9)	0.002[a]
ARDS form: severe, n (%)	1 (1.9)	9 (13.0)	0.042[b]
Ph <7.3	58 (18.9) – 7.43)	119 (77.8)	<0.0001[c]
BIC (mEq/L) < 15	65 (21.2)	108 (70.6)	0.0002[c]
BE (mEq/L) <-5	85 (27.7)	138 (90.1)	<0.0001[c]
Laboratorial features, n(%)			
Potassium (mmol/L) < 3,5	38 (12.4)	97 (63.4)	<0.0001[c]
Total calcium (mg/dL) <8.5	75 (24.5)	116 (75.8)	0.0042[c]
Magnesium (mg/dL) < 1.5	67 (21.9)	102 (66.7)	0.0028[c]
Chlorides (mmol/L) >110	88 (28.8)1	119 (77.8)	0.008[c]
Phosphorus (mg/dL) <2	28 (9.1)	38 (24.8)	0.0237[c]
INR>1.5	71 (23.2)	100 (65.3)	0.022[c]
Calculator index			
PRISMIV (%) >15	72 (23.5)	115 (71.9)	0.01[c]
PELOD2 >10	70 (22.9)	145 (94.8)	<0.0001[c]
CRP/Albumin ratio >5	54 (17.6)	120 (78.4)	0.0007[c]
PLR >25	67 (21.9)	130 (84.9)	0.2337[c]
Sodium-chloride difference >30	140 (45.7)	131 (85.6)	0.0052[c]
NLR > 5	77 (25.2)	124 (81)	0.0002[c]
Outcomes, n, (%)			
LOS (days) >7	153 (50)	68 (44.4)	0.138[c]
IVT (days) >7	153 (50)	66 (43.1)	0.845[c]
VFD<1	288 (94.1)	67 (43.8)	0.0195[c]

*IQR: interquartile range; pH: potential for hydrogen; BIC: sodium bicarbonate; BE: base excess; CRP: C-reactive protein; LOS: length of stay in the PICU; IVT: invasive ventilation time; VFD: ventilator-free days; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio. [a]Chi-square test. [b] Fisher's exact test. [c] Mann-Whitney test. [α]The classification of Acute respiratory distress symptoms (ARDS) were classified according to the current pediatric criteria, according to the Pediatric Acute Lung Injury Consensus Conference (PALICC), 2015 [20].

Table 4: Multiple Logistic Regression Analyses*: Outcomes Odds Ratios with 95% CI.

Outcomes	Model 1			Model 2		
Septic shock with MODS	***OR***	**95% CI**	***p* value**	***OR***	**95% CI**	***p* value**
Origin of patient, another hospitals	2.46	1.57-3.86	<0.0001	2.19	1.20-3.97	*0.010*
ARDS presence	2.94	1.91-4.52	<0.0001	4.15	2.26-7.60	*<0.0001*
28th-day mortality	***OR***	**95% CI**	***p* value**	***OR***	**95% CI**	***p* value**
NLR	1.09	1.05-1.14	<0.0001	1.11	1.06-1.17	<0.0001

[*]OR: Odds Ratio; CI: Confidence Interval; NLR: Neutrophil-to-Lymphocyte Ratio. Model 2, the risk-adjusted odds ratio (OR) for covariate PELOD2, was more than 10 with its respective 95% CI.

Among the calculated indices, the PRISM IV ($p < 0.0001$) and PELOD 2 ($p < 0.0001$) scores and the inflammation and prognosis biomarkers, such as the CRP-albumin ratio ($p = 0.0007$), chlorine-sodium difference ($p = 0.0052$), chlorine/sodium ratio ($p = 0.0176$), and neutrophil-lymphocyte ratio ($p = 0.0002$), were associated with mortality in G1. There was no significant difference between the length of stay in the PICU and the time of invasive mechanical ventilation. However, the time of reduced mechanical ventilation was associated with a greater chance of mortality at 28 days in G1 (VFD<1) [43,8% vs. 94,1%, $p = 0.0195$], as shown in Table 3.

Other variables, such as median age in months, ventilatory parameters, relationship between arterial oxygen pressure and fraction of inspired oxygen, oxygenation index, plateletto-lymphocyte ratio, sodium-chloride difference, chloride-sodium ratio, and neutrophillymphocyte ratio, were assessed. However, there was no evidence of an association between the presence of septic shock and MODS. The external origin and evidence of ARDS were independently associated with the development of septic shock and MODS, both in the crude model (OR: 2.46, 95% CI: 1.57-3.86, $p < 0.0001$ and OR: 2.94, 95% CI: 1.91-4.52, $p < 0.0001$, respectively) and the model adjusted with PELOD 2 (OR: 2.19, 95% CI: 1.20-3.97, $p = 0.010$ and OR: 4.15, CI95%: 2.26-7.60, $p < 0.0001$, respectively), as shown in Table 4.

Discussion

Our findings expand on previous work in this area and highlight many important issues that need to be addressed by health service researchers. The present study reports a high incidence of septic shock with MODS, especially in younger patients (under 2 years of age) [1-5], and in children hospitalized due to comorbidities, like most studies [16,17].

In this study, the presence of infections by gram-negative organisms, changes in coagulation markers, inadequate nutritional status, pulmonary impairment requiring invasive mechanical support, and the presence of ARDS were associated with an increased risk of septic shock with MODS and mortality. These findings reinforce the known evidence that multiple organ failure, marked undernutrition, coagulopathy, and nosocomial infection are independente factors for increased mortality, with the probability of mortality being directly proportional to the number of dysfunctional organs [18-21].

In patients with septic shock with or without BMD, hypocalcemia, hyperchloremia, hypomagnesemia, hypokalemia, and hypophosphatemia were associated with mortality. These are common in septic patients who die, especially those with severe cases, possibly due to therapeutic management. The “gold standard” is volume resuscitation in patients with cardiocirculatory changes with unbalanced crystalloids, associated with metabolic disorders, with hyperchloremic metabolic acidosis being the leading cause. These directly impact mortality and the need for dialysis [22-25].

The association of an increased anion gap, and hyperlactatemia in patients with septic shock and non-surviving MODS confirmed the previous findings and strongly suggested that lactic metabolic acidosis due to poor tissue oxygenation was associated with unfavorable outcomes [26,27]. The results of this study reinforced the complexity and severity of septic syndrome in the pediatric population. It is possible that the high average stay, multiple comorbidities, and the severity of the disease were due to a more complex profile and greater chronicity of patients.

The mortality observed (47.2%), due to septic shock, was associated with the origin of the external services, like other epidemiological studies on sepsis in children from lowresource areas [16-19]. These findings may be explained by the fact that the available services vary per state. As such, our quaternary hospital receives the most complex cases with multiple comorbidities and longer periods of disease progression, causing a worse prognosis and prolonged admission to the PICU. This statement confirmed the high levels of PIM 3, PELOD 2, and PRISM IV found in the group without sepsis from the current study.

The neutrophil-lymphocyte ratio (RNL), obtained from the blood count, has been gaining increasing attention in studies [28-30] due to its potential as a prognostic factor in cardiovascular and oncological diseases, community pneumonia, and even as an auxiliary tool in the early diagnosis of COVID-19. Because of its convenience and low cost, it has been implicated as a biomarker for the early diagnosis of sepsis and as a predictor of mortality in studies of intensive care units for adult patients. However, the lack of a reference value for these analyses is an important limitation, though some studies have adopted an RNL greater than 5 as the cut-off value [28-30].

In the current study’s pediatric population, it was noted that RNL was the main factor related to mortality, like the findings from other related studies. It is important to note that the cut-off point adopted was greater than 5 and that values lower than this have also been associated with mortality and early diagnosis of sepsis in children. Nevertheless, the lack of standardization still generates significant fluctuations in its sensitivity and specificity. Dursun and co-workers (2018) [29] found that an RNL above 1.97 had a sensitivity of 75.6% and a specificity of 38.4% in diagnosing pediatric sepsis early.

The main limitations of the study are related to the fact that it was single-centered, data collection was done only on admission, and analysis was performed retrospectively analyzed, which is associated with selection bias and limited further research on the disease. The serum calcium value used in this study was corrected for albumin. This study was a pioneer in determining the clinical, epidemiological, and laboratory profiles of sepsis in critically ill children in the Amazon region, a peculiar population from geographical, climatic, cultural, and socio-economic perspectives. We hope that this will encourage further studies, in addition to actions and strategies to combat sepsis. The institution of the sepsis protocol in this service has been the first direct outcome of the present study, and its impact is being evaluated in na ongoing study.

Our findings expanded on previous work in this area and highlighted many importante issues that needed to be addressed by health service researchers. The current study reported a high incidence of septic shock with MODS, especially in younger patients (less than 2 years) [1-5] and in children who had been hospitalized due to clinical illnesses associated with comorbidities, in line with the results of previous studies [16,17].

Conclusion

In our study, septic shock with MODS and mortality was associated more with male infants with previous comorbidities, hospitalized for clinical reasons, and coming from Other services. High mortality and high PIM 3, PRISM IV, and PELOD 2 values suggested a greater severity of cases. Furthermore, the main factors associated with a higher risk of septic shock with MODS included the origin of external services, while the neutrophil-lymphocyte ratio was independently associated with the 28th-day mortality.

Despite the progress in the treatment of severe sepsis and septic shock in recente decades, these remain important causes of morbidity and mortality in critically ill children worldwide. In regions with limited resources, especially in the Amazon region, there is still a lack of studies on sepsis and its risk factors among the pediatric population and a lack of preparation in regions that are more distant from external services, delaying the early diagnosis and treatment of pediatric sepsis. The identification of potential risk factors for sepsis with organ dysfunction and its association with mortality helps in the development of preventive and treatment strategies to improve care.

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