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Septic shock in children: are the SEPSIS-3 criteria applicable in the Pediatric Emergency Department? A multicenter study in Latin America

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Abstract

In adults, SEPSIS-3 proposed a new definition to identify sepsis in emergency departments. However, data are lacking regarding its application in children.

Objective: To determine the proportion of children presenting with septic shock (SSh) that met the SEPSIS-3 SSh criteria upon admission to the emergency department, and to compare the clinical course and mortality rates between the two groups.

Methods: We conducted a secondary analysis of data from a prospective multicenter study conducted between October 2019 and June 2021. We included children aged 30 days to 18 years from 10 Latin American centers. Demographic and clinical variables were collected. SSh was defined according to the SEPSIS-3 criteria as sepsis plus the use of vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level > 2 mmol/L. To assess the mortality risk, a multivariate logistic regression model was used. The findings are reported as odds ratios (OR) with the corresponding 95% confidence intervals (CIs).

Results: Out of 219 children, 150 were included, 43 (29%) of whom met the SEPSIS-3 SSh criteria. The median age was 3.8 years (IQR, 1.2-11). No significant demographic differences were observed between the groups. However, we did identify significant differences in clinical markers of severity, including serum lactate levels and C-reactive protein (CRP). In the SEPSIS-3 SSh group, more patients required intubation in the emergency department (44% vs. 13%, p< 0.01), mechanical ventilation support in the pediatric intensive care unit (PICU) (61% vs. 22%, p< 0.01), and admission to the PICU (93% vs. 45%, p< 0.01). In addition, in the SEPSIS-3 SSh group we observed higher Sequential Organ Failure Assessment (SOFA) scores (median 8 [IQR 4-11] vs. 3 [IQR 1-5], p< 0.01), as well as increased mortality (36% vs. 4%, p< 0.01), with an OR for death of 17 (95% CI 5-63).

Conclusion: Children admitted to the emergency department with SSh who met the SEPSIS-3 criteria had higher rates of morbidity and mortality. The low proportion of patients with a positive quick SOFA score indicates its limited validity for early detection of sepsis.

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SHOCK SÉPTICO EN NIÑOS: ¿SON APLICABLES LOS CRITERIOS DE SEPSIS-3 EN URGENCIAS? UN ESTUDIO MULTICÉNTRICO EN LATINOAMÉRICA

Resumen

SEPSIS-3 propuso una nueva definición para identificar adultos con sepsis en Urgencias. En niños, los datos son escasos.

Objetivo: *Describir cuántos niños con shock séptico (ShS) cumplieron el criterio de ShS de SEPSIS-3 al ingreso a Urgencias y comparar evolución clínica y mortalidad.*

Métodos: *Análisis secundario de estudio multicéntrico prospectivo (10/2019-06/2021). Incluimos niños de 30 días a 18 años. Participaron 10 centros latinoamericanos. Recolectamos variables epidemiológicas y clínicas. Definimos ShS según SEPSIS-3 como sepsis más uso de vasopresores para mantener la presión arterial media ≥ 65 mmHg y lactato > 2 mmol/L. Para evaluar riesgo de muerte, realizamos un modelo de regresión logística multivariado. Informamos OR e IC95, consideramos significativa p< 0,05.*

Resultados: *De 219 niños, incluimos 150. Cumplieron el criterio de ShS de SEPSIS-3 43 (29%). Mediana de edad 3,8 años (RIC 1,2-11). No encontramos diferencias epidemiológicas entre grupos. Observamos diferencias en los marcadores clínicos de gravedad, niveles de lactato y PCR. El grupo ShS SEPSIS-3 demandó mayor necesidad de intubación en Urgencias (44% vs. 13%, p< 0,01), requerimiento de asistencia ventilatoria mecánica en Cuidados Intensivos (UTIP) (61% vs. 22%, p< 0,01) e ingreso a UTIP (93% vs. 45%, p< 0,01). También observamos scores de Evaluación Secuencial del Daño Multiorgánico pediátrico (mediana de 8 [RIC 4-11] vs. 3 [RIC 1-5], p< 0,01) y mortalidad (36% vs. 4%, p< 0,01) mayores en ShS SEPSIS-3, con OR de morir de 17 (IC95 5-63).*

Conclusión: *Los niños ingresados en Urgencias con ShS que cumplieron con los criterios de ShS SEPSIS-3 presentaron mayor morbimortalidad. La baja proporción de pacientes que tuvieron un qSOFA positivo muestra su escasa utilidad para la detección temprana de la sepsis.*

INTRODUCTION

Sepsis and septic shock (SSh) remain significant health concerns, with greater impact in low-income settings[1-6]. Prognosis of SSH is "time-dependent" and it is therefore an emergency. It has been shown that with every hour of delay in diagnosis and treatment, mortality rates double[7]. One of the main challenges in the management of sepsis is the delay in its recognition, and pediatric emergency departments (PEDs) play an essential role in addressing this barrier[8,9]. In recent years, sufficiently sensitive, although not very specific, tools have emerged for the early detection of sepsis, facilitating immediate treatment initiation. However, these tools may also result in administering therapies to children without sepsis in some cases. Many PEDs are equipped with such resources, utilized within their triage areas[10-12]. Other tools provide prognostic information on hospital morbidity and mortality, such as the Sequential Organ Failure Assessment (SOFA) score, recently validated in the pediatric population (pediatric SOFA score [pSOFA] [Annex 1])[13-16]. Its usefulness for diagnostic purposes in the context of PEDs is currently debated[17,18].

Another challenge for the adequate management of sepsis is the ongoing lack of consensus on its definition. Recently, emphasis has been placed on using a "theoretical" concept and an "operational" definition aimed at simplifying the diagnosis of sepsis using clinical criteria[19]. In 2005, the Pediatric Sepsis Consensus Conference (PSCC) developed diagnostic criteria for the different stages of sepsis: systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, sepsis with cardiovascular dysfunction, and septic shock[20]. On the other hand, the Surviving Sepsis Campaign (SSC) and the American College of Critical Care Medicine (ACCM) define pediatric SSh clinically or operationally as a condition characterized by infection with either hypothermia or hyperthermia, tachycardia (which may be absent in hypothermia), and altered mental status in the presence of some sign of decreased tissue perfusion or hypotension (late sign)[21,22]. The latter definition is often more practical in PEDs because it allows for quick action and is not conditioned by the availability of resources.

In 2016, the Third International Consensus for Definitions of Sepsis and Septic Shock proposed a new definition for adult patients, known as SEPSIS-3. The authors defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. There was agreement to simplify concepts: the terms SIRS, severe sepsis, and sepsis with multiorgan involvement were eliminated. In addition, three operational definitions were proposed. The first is a simplification of the SOFA score into a quick SOFA (qSOFA), only considering three clinical aspects: altered mental status, increased respiratory rate (> 22 breaths per minute), and/or decreased systolic blood pressure (SBP ≤100 mmHg). The qSOFA is considered positive when at least two of the three above-mentioned criteria are met. A positive qSOFA is interpreted as "suspected sepsis"; "sepsis" was also defined as a

TABLE 1. Operational definitions of sepsis and septic shock (PSCC and SEPSIS-3).

2005 - International pediatric sepsis consensus conference (PSCC)[20]		
SIRS	*The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:* • Core temperature of 38.5°C or 36°C • Tachycardia (> 2 SD above normal for age in the absence of external stimulus, pain, chronic drugs, or an otherwise unexplained persistent elevation over 30 minutes to 4 hours) • In < 1 year old, bradycardia (heart rate < 10th percentile for age) in the absence of a vagal stimulus or congenital heart disease OR otherwise unexplained • Persistent bradycardia over at least 30 minutes • Respiratory rate 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia • Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) OR 10% immature neutrophils	
Infection	A suspected or proven (by positive culture or PCR) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests	
Sepsis	SIRS in the presence of or as a result of suspected or proven infection	
Severe sepsis	Sepsis plus one of the following: • Cardiovascular organ dysfunction • Respiratory distress • ≥ 2 organ dysfunctions	
Septic shock	Sepsis + cardiovascular organ dysfunction	
2016 - SEPSIS-3 (adults)[23]		
Suspected sepsis	Positive quick SOFA	The presence of at least 2 of the following: • Altered mental status • SBP ≤ 100 mmHg • RR ≥ 22 breaths x min + • Suspected infection
Sepsis	SOFA score ≥ 2	
Septic shock	• Vasoactive drugs to maintain MAP ≥ 65 mmHg + • Serum lactate level >2 mmol/L	

SD: standard deviation; HR: heart rate; RR: respiratory rate; PCR: polymerase chain reaction; SBP: systolic blood pressure; MAP: mean arterial pressure.

possible infection associated with a SOFA score ≥ 2 and "septic shock" as sepsis with the requirement for vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg and a serum lactate level > 2 mmol/L (Table 1)[23].

These criteria have been used in adults for the purpose of rapid diagnosis and initiation of treatment in the emergency setting. However, translating these definitions to pediatric patients is challenging due to significant physiological differences between the two age groups. In children, hypotension is considered a late sign, and its presence is associated with increased mortality[24]. Studies in pediatric intensive care units (PICUs) demonstrated that the modified SEPSIS-3 operational criteria for children could identify children with more severe SSh[14,25]; however, limited data are available regarding its applicability in lower resource settings and in PEDs.

Our aim was to analyze, in a population of children diagnosed with SSh, how many met each of the SEPSIS-3 operational criteria upon admission to the PED, and to compare the clinical course and mortality between those who met the SEPSIS-3 operational definition of SSH and those who did not.

MATERIAL AND METHODS

A secondary analysis of a prospective multicenter study conducted between October 2019 and June 2021 was performed. We included a consecutive sample of children older than 30 days and younger than 18 years admitted to the PED with a diagnosis of SSh. SSh was defined when the care coordinator, following an objective clinical evaluation and based on SSC[22] and ACCM[21] criteria, identified the condition as such and initiated specific treatment. The coordinator was a specialist in pediatric emergency and/or pediatric intensive care. Children were excluded if they had received treatment at another institution at the time of admission to the PED, patients under adjustment of therapeutic effort, and those diagnosed with an alternative condition within the first 48 hours, as well as those whose records lacked more than one item of information to calculate the pSOFA[13] score (see p< SOFA in Appendix 1) and in whom serum lactate level measurement had not been performed. Ten tertiary care centers from six Latin American countries (Argentina, Bolivia, Brazil, Colombia, Costa Rica, and Paraguay) participated in the study. Third level of care was defined as

university children's hospitals or other referral centers with 24-hour admission, laboratory and imaging services, PICU, and pediatric subspecialties accessible 24 hours a day. All participating institutions have a structured triage system and a local protocol for the management of SSh. The study was approved by the corresponding Ethics and Research Committees.

Data were collected on demographic variables, comorbidities, and risk factors, and episode data were recorded, including the presence of an evident infectious focus and clinical manifestations. "Adequate treatment during the first hour" was defined if the the following criteria were met: 1) placement of a vascular access in the first 5 minutes, 2) fluid administration in the first 30 minutes, and 3) administration of antibiotics and vasoactive drugs within 60 minutes. In addition, the pSOFA[13] score was obtained at admission. Information on clinical evolution and mortality was retrospectively collected during the first 21 days of admission. As obtaining arterial acid-base status (ABS) is not routine practice in the PED, respiratory variables (pressure and arterial oxygen saturation) from the pSOFA were not recorded and were assumed to be normal. Additionally, when information on a second item was unavailable, it was considered normal. The primary objective was to evaluate compliance with the operational criteria for SSh according to SEPSIS-3 adapted for children (SEPSIS-3 SSh+), defined as positive when patients required vasoactive drugs and had a serum lactate measurement > 2 mmol/L.

Based on the studies by Jabornisky et al.[26] and Fustiñana et al.[27] a sample size of 48 patients per group was calculated to have a power of 80% and an alpha error of 0.05 to evaluate the differences in mortality between the SEPSIS-3 SSh (+) and SEPSIS-3 SSh (-) groups.

As a secondary objective, we assessed compliance with the operational criteria of: a) sepsis according to the PSCC, defined by suspected infection and at least two of the following four criteria: temperature > 38.5 C, tachycardia, tachypnea, and/or altered leukocyte count; b) suspected sepsis according to SEPSIS-3 adapted to children, when the quick pSOFA is positive (at least two of three present: altered mental status, tachypnea, and/or arterial hypotension - the latter two were age-adjusted according to Goldstein et al.[20]; and, c) SEPSIS-3 sepsis adapted to children: pSOFA score ≥ 2[13].

Data were recorded in an ad hoc spreadsheet using RedCap software version 13.4.11. Categorical variables were summarized using frequency and percentage. Continuous variables were described using median and interquartile range (IQR) as measures of central tendency and dispersion. Univariate comparative analysis was conducted using two-tailed tests. The nonparametric Mann-Whitney U test was used for non-normally distributed variables and comparison of medians. Categorical variables were compared using the chi-squared or Fisher's exact test, as appropriate. To assess whether children meeting SEPSIS-3 SSh criteria had an increased risk of mortality, a multivariate logistic regression model was used, and odds ratios (ORs) with their 95% confidence intervals (CIs) are reported. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24.

RESULTS

A total of 219 children with SSh were identified, of whom 22 were excluded because they presented an alternative diagnosis during the first 48 hours after admission. Of the remaining 197, serum lactate levels were not recorded in 40 and in seven more than one variable was missing to calculate the pSOFA. Finally, 150 patients were included, of whom 43 (29%) met the operational criteria for SSh established by SEPSIS-3 (SEPSIS-3 SSh +) (Figure 1). Fifty-five percent were male, with a median age of 3.8 years (IQR 1.2-11). Table 2 shows the patients who met the diagnostic criteria proposed by the PSCC and SEPSIS-3.

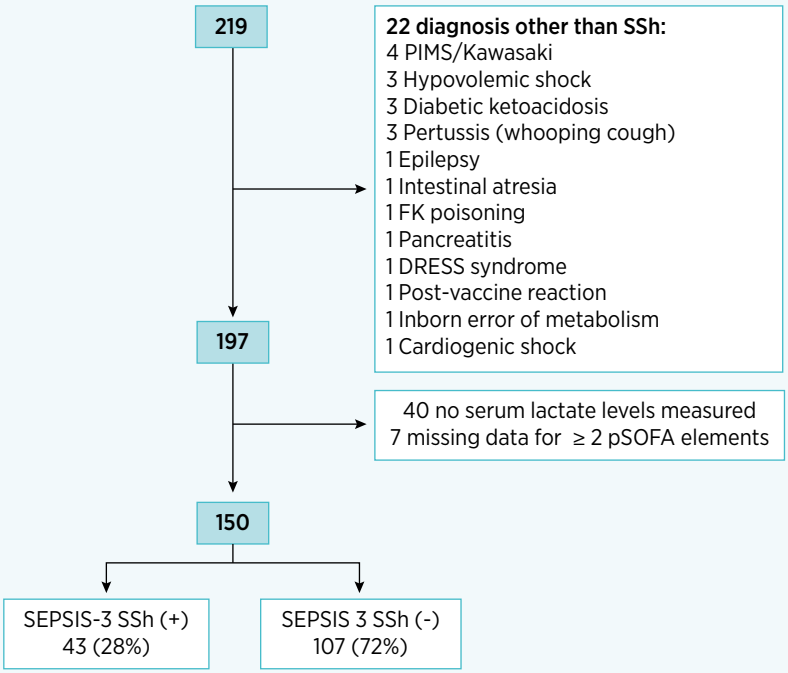
As shown in Table 3, no differences in demographic data were found between the SEPSIS-3 SSh (+) and SEPSIS-3 SSh (-) groups. However, differences were observed in clinical markers of severity, including altered mental status, a greater tendency towards tachypnea, and lower blood pressure values, as well as higher levels of lactate and CRP in the SEPSIS-3 SSh (+) group.

Table 4 shows the clinical course of the children with SSh included in the study. Treatment with vasoactive drugs was required in 93 children (62% with refractory shock to fluid infusion) within the first hour of therapy. Those who did not require vasoactive drugs at admission, did not require them in the 48 hours following admission. Among those who met the SSh SEPSIS-3 (+) criteria, there was a three-fold increase in the need for intubation in the PED (44% *vs.* 13%, p< 0.01) and mechanical ventilation (MV) support in the PICU (61% *vs.* 22%, p< 0.01) and a two-fold increase in the need for PICU admission (93% *vs.* 45%, p< 0.01). Higher pSOFA scores (median 8 [IQR 4-11] *vs.* 3 [IQR 1-5], p< 0.01) and mortality (36% *vs.* 4%, p< 0.01) were also observed in the SEPSIS-3 SSh (+) group.

A multivariate logistic regression analysis was conducted to adjust for potential confounders and evaluate the association between SEPSIS-3 SSh (+) and mortality. The odds ratio (OR) for mortality in the SEPSIS-3 SSh (+) group was 17 (95% CI: 5-63), independent of age less than 6 months, sex, presence of comorbidities (as listed in Appendix 2), and "adequate treatment during the first hour."

DISCUSSION

This study is a secondary analysis of data obtained from a multicenter study focusing on adherence to treatment recommendations for pediatric sepsis in Latin American PEDs[27]. The initial study provided valuable information on the outcome and prognosis of children with SSh who are seen in a context where scientific evidence is limited. In this new analysis, we observed that when applying the operational criteria for SSh adapted to SEPSIS-3 children (children with vasoactive drug requirement and serum lactate > 2 mmol/L), we identified a subgroup that showed a higher organ failure score (pSOFA), increased need for intubation and MV, and higher PICU admission and mortality rates (Table 4). Our findings agree with those of the authors of the adult definitions, who suggest that the SSh definition identifies patients with a 40% mortality risk[23]. Similarly, our results are consistent with pediatric studies indicating that the SEPSIS-3 operational



PIMS: pediatric inflammatory multisystem syndrome; FK: tacrolimus (also FK-506 or fujimycin), immunosuppressive drug; DRESS: drug reaction with eosinophilia and systemic symptoms.

FIGURA 1. Patients included in the study.

TABLE 2. Distribution of PSCC and SEPSIS-3 operational criteria in patients with septic shock.

Operational criteria	n= 150
PSCC sepsis (%)	131 (87)
SEPSIS-3 suspicion of sepsis (%)[1]	88 (59)
SEPSIS-3 sepsis (%)[2]	106 (71)
SEPSIS-3 septic shock (%)[3]	43 (29)

[1]Positive qSOFA; [2]pSOFA score ≥ 2; 3sepsis + vasoactive drugs + serum lactate level > 2 mmol/L. PSCC: International Pediatric Sepsis Consensus Conference (2005).

criteria are specific for identifying patients at higher risk of mortality due to sepsis[13,16,28-30]. These results are anticipated, because when a child with SSh presents with arterial hypotension (decompensated shock), the disease is at a more advanced stage where all the compensatory mechanisms of the child's physiological response have failed. These findings reaffirm, once again, that hypotension should not be considered for early identification of pediatric sepsis and that its presence is associated with higher mortality[24]. Although in our population the SEPSIS-3 SSh operational criterion has not been sensitive in identifying children with a diagnosis of SSh, its application could be useful in predicting the need for more complex resources, including admission to a PICU. These observations are not insignificant, considering that the availability of these resources in Latin America is scarce[9,31].

Timely detection of sepsis has been identified as one of the main barriers for the management of the condition[9]. Late diagnosis delays treatment and increases morbidity and mortality[7]. The SEPSIS-3 expert panel pointed out the possibility to identify adult patients with sepsis using the qSOFA, proposed as a tool for timely screening of patients at risk of unfavorable outcomes, especially valuable in the ED to prompt physicians to increase their vigilance[23]. However, our findings in a cohort of children with SSh demonstrate that this tool failed to identify a significant number of children with SSh, with the pediatric qSOFA yielding negative results in 41% of the cases. These findings are consistent with those reported by various authors regarding the limitations of SEPSIS-3 as an operational criterion for diagnosing and treating the condition in children due to its low sensitivity[16,25,29,30,32-34].

Our study has both strengths and limitations. As a secondary analysis of a prospective multicenter study, its main strength lies in the diverse settings it covers: Latin American PEDs. Applying the SEPSIS-3 SSh operational criteria to children with SSH admitted to the PED could facilitate the transfer of patients to sites that can respond to the more complex demands for the management of sepsis. This finding is particularly important for a condition where prognosis depends on timely intervention. We emphasize the urgent need for early recognition, not only for the diagnosis of sepsis, but also to promptly determine the optimal treatment location for patients already diagnosed. In this regard, the results of our research are important. Another significant aspect of our study was the coordination of the care of each patient by a specialist in pediatric emergency and/or intensive care, which facilitated standardized management of the children included.

Among the limitations, we may mention that, as this was a secondary objective of a non-intervention study, a proportion of patients did not undergo serum lactate measurements, and some other values necessary to calculate the pSOFA score were not available; however, importantly, these patients

TABLE 3. Comparison of characteristics of children who were admitted to PEDs with septic shock and met the SEPSIS-3 operational criteria for septic shock (SEPSIS-3 SSh +) *vs.* those who did not (SEPSIS-3 SSh -).

Population characteristics	SEPSIS-3 SSh (+) n 43	SEPSIS-3 SSh (-) n 107	p (*,**)
Male sex (%)	27 (63)	56 (52)	0.2*
Age (years)	3.8 (1.5-11.5)	4 (1-11)	0.9**
Focus (%)	39 (91)	87 (81)	0.16*
Comorbidities (%)	16 (37)	46 (43)	0.5*
Cold shock (%)	36 (84)	75 (70)	0.08*
Warm shock (%)	7 (16)	12 (11)	0.4*
Hypotension (%)	17 (40)	17 (16)	< 0.01*
Altered mental status (%)	35 (81)	56 (52)	< 0.01*
Delayed capillary refill (%)	34 (79)	73 (68)	0.18*
Flash capillary refill (%)	6 (14)	8 (8)	0.2*
Positive culture (%)	20 (47)	59 (55)	0.3*
HR	150 (140-170)	150 (130-170)	0.3**
RR	40 (28-50)	32 (25-43)	< 0.05**
SBP	90 (74-105)	105 (92-114)	< 0.01**
DBP	53 (40-65)	63 (50-69)	< 0.01**
Serum lactate	3.8 (3-5.9)	2 (1.3-2.9)	< 0.01**
Treatment aims the first hour of sepsis (%)	8 (19)	21 (20)	0.9*
CRP (mg/dl)	77 (25-163)	32 (11-96)	< 0.05**

**Chi-squared test. **Mann-Whitney U test. HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein.*

TABLE 4. Outcome differences between the SEPSIS-3 SSh (+) and SEPSIS-3 SSh (-) groups.

Outcome	SEPSIS-3 SSh (+) n 43	SEPSIS-3 SSh (-) n 107	p (*,**)
Intubation in the PED (%)	19 (44)	14 (13)	< 0.01*
PICU (%)	40 (93)	48 (45)	< 0.01*
PICU days	3,5 (1-7)	4 (2,3-7)	0.3**
MV support (%)	26 (61)	23 (22)	< 0.01*
MV support days	3 (1-6.5)	4 (2-7)	0.6**
Inotropic drugs (%)	43 (100)	49 (46)	< 0.01*
Inotropic drugs days	2 (1-5)	2 (1-4)	0.7**
Days of hospital stay	9 (1-16)	8 (4-14)	0.5**
SOFA score	8 (4-11)	3 (1-5)	< 0.01**
Death (%)	15 (36)	4 (4)	< 0.001*

**Chi-squared test. **Mann–Whitney U test. PED: Pediatric Emergency Department; PICU: Pediatric Intensive Care Unit; MV: mechanical ventilation.*

who were excluded did not have higher mortality rates than those included. In addition, in some cases, in which only one item of the pSOFA score was missing, we assumed this value to be normal, although this assumption may not have been true. On the other hand, all the hospitals that participated were tertiary care centers, and our findings might not have been the same if sites lacking adequate resources – which is common in Latin America - had been included. Furthermore, 41% (62) of the included children had comorbidities, and these rates may not accurately reflect the true population of children with sepsis in our region, potentially affecting the external validity of our findings. In future research, it would be appropriate to include primary and secondary care centers with fewer resources to mitigate this bias. It is also important to note that during the study, the SARS-CoV-2 (COVID-19) pandemic broke out, leading to a significant decrease in the number of visits to the PED.

Finally, the data from our investigation support the specificity of the SEPSIS-3 SSh operational criteria in children admitted to the ED with a diagnosis of SSh, useful to determine

the need for their transfer to institutions with a PICU capable of offering more advanced sepsis management. Similarly, it cautions against relying on the qSOFA as a detection tool, which, because of its moderate sensitivity, may leave patients with a potential risk of death undiagnosed.

In conclusion, our study found that patients admitted to the PED with SSh who met the operational criteria of SEPSIS-3 presented with an increased risk of morbidity and mortality, a greater need for intubation and MV support, and admission to the PICU. Additionally, this group had higher pSOFA scores and mortality rates. These findings could be helpful in the early identification of at-risk patients and support timely decision-making. Furthermore, a significant proportion of patients had negative qSOFA results, indicating limited usefulness of this tool for early sepsis detection in PEDs.

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ANNEX 1. Pediatric Sequential Organ Failure Assessment (pSOFA) Score.

	Score[a]				
Variables	0	1	2	3	4
Respiratory					
PaO_2: FiO_2[b]	≥ 400	300-399	200-299	100-199 with respiratory support	< 100 with respiratory support
or					
SpO_2: FiO_2[c]	≥ 292	264-291	221-264	148-220 with respiratory support	< 148 with respiratory support
Coagulation					
Platelet count × 10^3/ml	≥ 150	100-149	50-99	20-49	< 20
Hepatic					
Bilirrubin, mg/dl	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular					
MAP by age group or vasoactivo infusion, mmHg o µg/kg/min[d]					
< 1 month	≥ 46	< 46	Dopamine hydrochloride ≤ 5 or dobutamine hydrochloride (any)	Dopamine hydrochloride ≥ 5 or epinephrine ≤ 0.1 or norepinephrine bitartrate ≤ 0.1	Dopamine hydrochloride > 15 or epinephrine > 0.1 or norepinephrine bitartrate > 0.1
1-11 months	≥ 55	< 55			
12-23 months	≥ 60	< 60			
24-59 months	≥ 62	< 62			
60-143 months	≥ 65	< 65			
144-216 months	≥ 67	< 67			
> 216 months[e]	≥ 70	< 70			
Neurologic					
Glasgow Coma Scale[f]	15	13-14	10-12	6-9	< 6
Renal					
Creatinine by age group, mg/dl					
< 1 month	< 0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥ 1.6
1-11 months	< 0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥ 1.2
12-23 months	< 0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥ 1.5
24-59 months	< 0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥ 2.3
60-143 months	< 0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥ 2.6
144-216 months	< 1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥ 4.2
> 216 months	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥ 5.0

FiO_2: fraction of inspired oxygen; SpO_2: peripheral oxygen saturation; MAP: Mean arterial pressure.
SI conversion factors:
- *To convert bilirubin to micromoles per liter, multiply by 17.104.*
- *To convert creatinine to micromoles per liter, multiply by 88.4.*
- *To convert platelet count to 10^9/L, multiply by 1.*

[a]The pSOFA score was calculated for every 24-hour period. The worst value for every variable in each 24-hour period was used to calculate the subscore for each of the six organ systems. If a variable was not recorded in a given 24-hour period, it was assumed to be normal and a score of 0 was used. Daily pSOFA score was the sum of the 6 subscores (range, 0-24 points; higher scores indicate a worse outcome). [b]PaO_2 was measured in millimeters of mercury. [c]Only SpO_2 measurements of 97% or lower were used in the calculation. [d]MAP (measured in millimeters of mercury) was used for scores 0 and 1; vasoactive infusion (measured in micrograms per kiligram per minute), for scores 2 to 4. Maximum continuous vasoactive infusion was administered for at least 1 hour. [e]Cutoffs for patients older than 18 years (216 months) were identical to the original SOFA score. [f]Glasgow Coma Scale was calculated using the pediatric scale.
From: Matics T, Sanchez-Pintos N. Adaptation and Validation of pediatric sequential organ failure assessment score and evaluation of sepsis-3 definitions in critically ill children. JAMA Pediatr. 2017; 171: e172352.

ANNEX 2. Distribution of comorbidities in the SEPSIS 3 SSh (+) and SEPSIS 3 SSh (-) groups.

Comorbidity	SEPSIS-3 SSh (+) n 43 (%)	SEPSIS-3 SSh (-) n 107 (%)	Total
Endocrine	0 (0)	1 (1)	1
Gastrointestinal (non hepatic)	2 (5)	3 (3)	5
Genetic	1 (2)	0 (0)	1
Hepatic	0 (0)	1 (1)	1
Hematological	1 (2)	8 (7)	9
Immunodeficiency (primary or secondary)	1 (2)	2 (2)	3
Metabolic	0 (0)	1 (1)	1
Neurosurgical	1 (2)	1 (1)	2
Neurologic	3 (7)	7 (7)	10
Oncological	3 (7)	8 (7)	11
Respiratory	1 (2)	1 (1)	2
Transplant	1 (2)	3 (3)	4
Urological/renal	0 (0)	2 (2)	2
Others	2 (5)	8 (7)	10
Total	**16 (37)**	**46 (43)**	**62**