

Criteria for Pediatric Sepsis—A Systematic Review and Meta-Analysis by the Pediatric Sepsis Definition Taskforce

OBJECTIVE: To determine the associations of demographic, clinical, laboratory, organ dysfunction, and illness severity variable values with: 1) sepsis, severe sepsis, or septic shock in children with infection and 2) multiple organ dysfunction or death in children with sepsis, severe sepsis, or septic shock.

DATA SOURCES: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from January 1, 2004, and November 16, 2020.

STUDY SELECTION: Case-control studies, cohort studies, and randomized controlled trials in children greater than or equal to 37-week-old postconception to 18 years with suspected or confirmed infection, which included the terms “sepsis,” “septicemia,” or “septic shock” in the title or abstract.

DATA EXTRACTION: Study characteristics, patient demographics, clinical signs or interventions, laboratory values, organ dysfunction measures, and illness severity scores were extracted from eligible articles. Random-effects meta-analysis was performed.

DATA SYNTHESIS: One hundred and six studies met eligibility criteria of which 81 were included in the meta-analysis. Sixteen studies (9,629 patients) provided data for the sepsis, severe sepsis, or septic shock outcome and 71 studies (154,674 patients) for the mortality outcome. In children with infection, decreased level of consciousness and higher Pediatric Risk of Mortality scores were associated with sepsis/severe sepsis. In children with sepsis/severe sepsis/septic shock, chronic conditions, oncologic diagnosis, use of vasoactive/inotropic agents, mechanical ventilation, serum lactate, platelet count, fibrinogen, procalcitonin, multi-organ dysfunction syndrome, Pediatric Logistic Organ Dysfunction score, Pediatric Index of Mortality-3, and Pediatric Risk of Mortality score each demonstrated significant and consistent associations with mortality. Pooled mortality rates varied among high-, upper middle-, and lower middle-income countries for patients with sepsis, severe sepsis, and septic shock ($p < 0.0001$).

CONCLUSIONS: Strong associations of several markers of organ dysfunction with the outcomes of interest among infected and septic children support their inclusion in the data validation phase of the Pediatric Sepsis Definition Taskforce.

KEY WORDS: children; mortality; organ dysfunction; sepsis; septic shock; severe sepsis

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Infections account for 26.5% of the global burden of disease (1) and 25% of deaths in children worldwide (2). However, the clinical manifestations of these infections vary from minimal symptoms to multiple organ failure and death. The currently accepted definitions of sepsis, severe sepsis, and septic shock were developed and refined using different criteria to help identify, treat, and study patients with infections who are at higher risk of significant morbidity and mortality (3, 4). However, specific variables identifying children with sepsis and their resulting outcomes have never been rigorously evaluated in a systematic review.

The 2016 sepsis definition update in adult patients (Sepsis-3) included a systematic review of reported criteria used to identify adults with septic shock (5). This review focused on hemodynamic criteria, was primarily limited to studies from upper middle-income countries (UMICs) and high-income countries (HICs), and specifically excluded pediatric studies. Furthermore, results of adult trials cannot be extrapolated to children because of differences in epidemiology (6), mortality rates (7), underlying diseases (8), disease-specific outcomes (9, 10), and differing responses to therapy (11, 12).

Therefore, the Society of Critical Care Medicine (SCCM) convened the Pediatric Sepsis Definition Taskforce to evaluate, develop, and validate criteria for the identification of sepsis in children. As part of this process, the Taskforce conducted a systematic review with the explicit goal of determining the ability of demographic, clinical, laboratory, organ dysfunction, and illness severity variables to capture children with more severe infections. For this purpose, we assessed association of these variables with: 1) sepsis, severe sepsis, or septic shock in children with suspected or confirmed infection and 2) with new or progressive multiple organ dysfunction (NPMODS) or mortality in children with sepsis, severe sepsis, or septic shock.

MATERIALS AND METHODS

The protocol including search strategy has been previously published (13) and is summarized below.

Eligibility Criteria

Inclusion criteria for studies were: 1) the words “sepsis,” “septic shock,” or “septicemia” present in the title or abstract; 2) publication between January 1, 2004, and November 16, 2020; 3) sepsis, septic shock, septicemia, NPMODS, or mortality reported as an outcome; 4) case-control study, cohort study, or randomized trial; and 5) study population of children greater than or equal to 37-week-old postconception to less than 18 years. Studies meeting the following criteria were excluded: 1) no reported data on children with sepsis, severe sepsis, or septic shock; 2) less than 50 children with sepsis, septicemia, severe sepsis, or septic shock; 3) abstracts, case studies, narrative reviews, or surveys; 4) variable values within 24 hours of admission not provided; 5) no comparator group for variable in question; 6) sepsis criteria not specified; 7) article not available; or 8)

focused on criteria only available for research (e.g., gene-expression data). Only 27 non-English language articles (0.4%, 27/7502) were identified by the search (17 at abstract screening and 10 following full-text review). Therefore, non-English language studies were excluded.

Data Sources

We identified eligible studies by searching MEDLINE (including Epub Ahead of Print), Embase, and the Cochrane Central Register of Controlled Trials databases.

Study Selection

The titles, abstracts, and full texts were screened using a previously validated platform Insight Scope (14). Each title and full-text article were screened by two reviewers, and at each screening level and for data extraction, conflicts were resolved by a third reviewer.

Data Extraction and Management

Data were extracted from full-text articles using a Research Electronic Data Capture (REDCap) platform (15) hosted at the Children’s Hospital of Eastern Ontario Clinical Research Unit. Corresponding authors were contacted twice for missing data. The quality of selected articles was determined using the first four domains of the Quality in Prognostics Studies tool for assessment of risk of bias in observational studies (16). The last two domains pertain to confounding and statistical analysis that were not applicable to the unadjusted data used in our meta-analysis. The overall risk of bias was determined as the highest risk of bias attributed to any criterion. Unadjusted data were extracted since many studies did not report adjusted data and others did not specify the variables they adjusted for or adjusted for different variables (17). Studies were categorized as being conducted in low-income countries (LICs), low-middle-income countries (LMICs), UMICs, and HICs according to the World Bank classification of 2019–2020 (18).

Outcomes

The primary outcome for the meta-analysis of articles describing children with infection was the presence of sepsis, severe sepsis, or septic shock as defined in each individual study. The primary outcome for the meta-analysis of articles describing children with sepsis,

severe sepsis, or septic shock was the development of NPMODS and/or death. Mortality was defined as at or prior to hospital discharge.

Data Synthesis and Analysis

Frequencies and descriptive statistics are reported for study demographics and patient characteristics from included studies. We pooled outcomes reported by two or more studies. We calculated unadjusted prognostic odds ratios (ORs) and 95% CIs for dichotomous variables and calculated the mean difference with 95% CIs for continuous variables. We imputed the mean and sd when median, interquartile range, or range and sample size were reported (19, 20). Statistical heterogeneity was assessed using I^2 statistic and visual inspection of the forest plots, and DerSimonian-Laird random-effects model was employed for all comparisons. All analyses were conducted using Stata (StataCorp, Release 16.1. College Station, TX) (21). Baseline sepsis, severe sepsis, and septic shock rates among HIC, UMIC, and LMIC were compared using Kruskal-Wallis tests weighted for study sample sizes.

RESULTS

Overview of Included Studies

The search yielded 12,343 citations of which 969 underwent full-text review for eligibility. Of these, 863 were excluded (**Fig. 1**); 106 citations, representing 35 countries, were retained for the systematic review and 81 articles (154,674 patients) provided sufficient data for the meta-analysis. The remaining 25 articles met the inclusion criteria but studied individual variables that were unable to be combined in the meta-analysis and were, therefore, described in the narrative review. Characteristics of all included studies are summarized in **Table 1**. Studies represented all regions from the World Bank economies (18) with 46.2% (47/106) being conducted in HICs, 30.2% (35/106) in UMICs, 22.6% (23/106) in LMICs, and one in a LIC. All multicenter studies except one (10) included sites from the same income level. The remaining study (10) was conducted in 23/26 HIC and 3/26 UMIC settings and was, therefore, classified as an HIC study. The patient characteristics for included studies are shown in **Table 2**. More than half the patients were male (pooled estimate 55.7%; 95% CI, 54.8–56.6). The majority of studies were of PICU

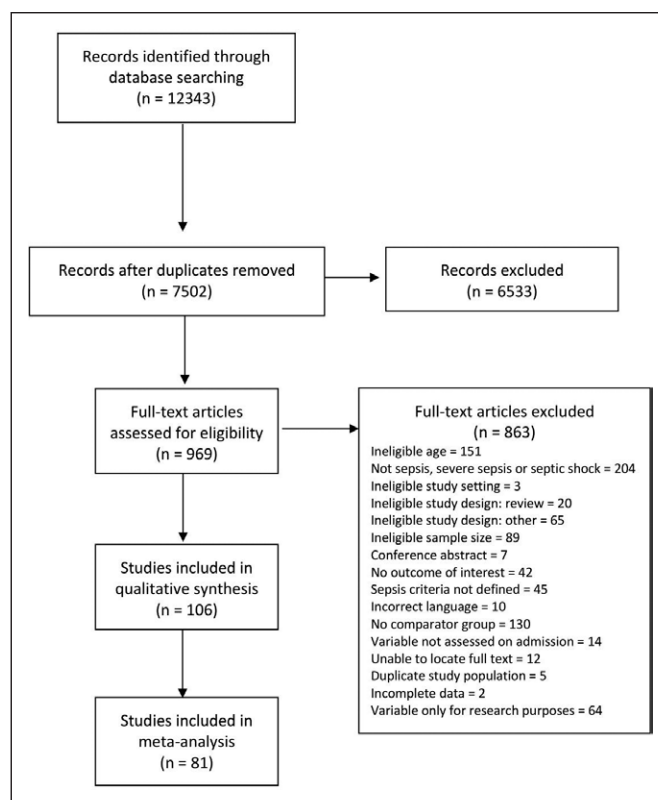


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for included studies.

patients (70.8%, 75/106) followed by those from the emergency department (ED) (10.4%, 11/106). The most commonly used definition of sepsis was the 2005 International Pediatric Sepsis Consensus Conference (2005 IPSCC) criteria (69.8%, 74/106; **Supplementary Table 1**, <http://links.lww.com/CCM/G817>) (3).

Included studies along with the variables assessed in the meta-analysis and narrative review are detailed in **Supplementary Table 2** (<http://links.lww.com/CCM/G818>) and **Supplementary Table 3** (<http://links.lww.com/CCM/G819>), respectively. Forest plots for variables with significant findings are shown in **Supplementary Figure 1** (<http://links.lww.com/CCM/G820>), **Supplementary Figure 2** (<http://links.lww.com/CCM/G821>), **Supplementary Figure 3** (<http://links.lww.com/CCM/G822>), **Supplementary Figure 4** (<http://links.lww.com/CCM/G823>), **Supplementary Figure 5** (<http://links.lww.com/CCM/G824>), **Supplementary Figure 6** (<http://links.lww.com/CCM/G825>), **Supplementary Figure 7** (<http://links.lww.com/CCM/G826>), and **Supplementary Figure 8** (<http://links.lww.com/CCM/G827>), and associations of these variables with the outcomes of sepsis and mortality are summarized in **Table 3**.

TABLE 1.
Characteristics of All Included Studies

Characteristic	Studies in Meta-Analysis (n = 81), n (%)	Patients From Meta-Analysis (n = 154,674), n (%)	Narrative Studies (n = 25), n (%)	Patients From Narrative Studies (n = 5,812)
Publication year				
2004–2008	8 (9.9)	7,861 (5.1)	6 (24.0)	374 (6.4)
2009–2012	5 (6.2)	1,499 (0.1)	0 (0)	0 (0)
2013–2016	13 (16.0)	53,340 (34.4)	7 (28.0)	1,046 (18.0)
2017–2020	55 (67.9)	91,974 (59.4)	12 (48.0)	4,392 (75.6)
Participating sites				
1	58 (71.6)	17,937 (11.6)	22 (88.0)	4,185 (72.0)
2–5	3 (3.7)	1,281 (0.8)	0 (0)	0 (0)
6–10	6 (7.4)	2,035 (1.3)	0 (0)	0 (0)
> 10	14 (17.3)	133,421 (86.3)	3 (12.0)	1,627 (28.8)
Region of primary site ^a				
North America	15 (18.5)	136,120 (88.0)	8 (32.0)	2,312 (39.8)
Latin America and Caribbean	13 (16.0)	3,387 (2.2)	2 (8.0)	57 (1.0)
Europe and Central Asia	13 (16.0)	3,807 (2.5)	7 (28.0)	694 (11.9)
East Asia and Pacific	19 (23.5)	8,053 (5.2)	1 (4.0)	1,510 (26.0)
South Asia	14 (17.3)	1,585 (1.0)	3 (12.0)	249 (4.3)
Middle East and North Africa	5 (6.2)	541 (0.3)	3 (12.0)	585 (10.1)
Sub-Saharan Africa	2 (2.5)	1,181 (0.8)	1 (4.0)	405 (7.0)
World Bank Income classification				
High income country	33 (40.7)	142,364 (92.0)	14 (56.0)	4,351 (7.5)
Upper middle-income country	30 (37.0)	9,377 (6.1)	5 (20.0)	528 (9.1)
Lower middle-income country	17 (21.0)	1,812 (1.2)	6 (24.0)	923 (15.9)
Lower income country	1 (1.2)	1,121 (0.7)	0 (0)	0 (0)
Study design				
Randomized controlled trial ^b	1 (1.2) ^a	50 (0.03)	0 (0)	0 (0)
Prospective cohort	38 (46.9)	9,634 (6.2)	14 (56.0)	1,160 (20.0)
Retrospective cohort	37 (45.7)	145,291 (94.1)	10 (40.0)	4,130 (71.1)
Case-control	5 (6.2)	499 (0.3)	1 (4.0)	72 (1.2)
Primary study setting ^c				
PICU	68 (84.0)	136,599 (88.3)	21 (84.0)	5,072 (87.3)
Emergency department	8 (9.9)	2,078 (1.3)	4 (16.0)	932 (16.0)
Ward	7 (8.6)	12,423 (8.0)	0 (0)	0 (0)
Other	3 (3.7)	3,574 (2.3)	0 (0)	0 (0)

^aSite of the corresponding author and or location of research ethics approval using the World Bank Classification of 2019–2020.

^bSecondary analysis of a randomized controlled trial.

^cTwo settings were unspecified and one included all hospital locations. In addition, some studies included more than one specified study location resulting in a total of more than 81 study locations.

TABLE 2.
Patient Characteristics for All Included Studies

Characteristic	Studies in Meta-Analysis (n = 81), n (%)	Patients in Meta-Analysis (n = 154,674), n (%)	Narrative Studies (n = 25), n (%)	Patients in Narrative Studies (n = 5,812), n (%)
Age groups included ^a				
Neonates (0–30 d)	41 (50.6)	127,574 (82.5)	11 (44.0)	3,657 (62.9)
Babies (31–90 d)	70 (86.4)	151,730 (98.1)	22 (88.0)	1,510 (26.0)
Infants (91 d to 1 yr)	80 (98.8)	154,452 (99.9)	24 (96.0)	5,719 (98.4)
Toddlers (2–5 yr)	79 (97.5)	154,380 (99.8)	24 (96.0)	5,812 (100)
School age (6–12 yr)	73 (90.1)	152,810 (98.8)	22 (88.0)	5,652 (97.2)
Adolescents (13–16 yr)	62 (76.5)	151,283 (97.8)	19 (76.0)	5,248 (90.3)
Young adults (17–18 yr)	44 (54.3)	144,616 (93.5)	13 (52.0)	3,757 (64.6)
Population studied				
Bronchiolitis	1 (1.2)	72 (0.0)	0 (0)	
Meningococcal infections	2 (2.5)	1,151 (0.7)	1 (4.0)	151 (2.6)
Pneumonia	1 (1.2)	222 (0.1)	1 (4.0)	160 (2.8)
Diarrheal illness	2 (2.5)	270 (0.2)	0 (0)	0 (0)
Severe acute malnutrition	1 (1.2)	50 (0.0)	0 (0)	0 (0)
Bone marrow transplant	0 (0)	0 (0)	1 (4.0)	567 (9.8)
Oncology—general	4 (4.9)	768 (0.5)	1 (4.0)	99 (1.7)
Oncology—febrile neutropenia	1 (1.2)	151 (0.1)	0 (0)	0 (0)
Emergency department patients	5 (6.2)	1,664 (1.1)	4 (16.0)	740 (12.7)
Hospital ward patients	6 (7.4)	24,778 (16.0)	0 (0)	0 (0)
Any PICU admission	58 (71.6)	125,539 (81.2)	17 (68.0)	4,095 (70.5)
Sepsis definition used ^b				
2001 SCCM/ACCP criteria	7 (8.6)	2,317 (1.5)	2 (8.0)	93 (1.6)
2005 International Pediatric Sepsis Consensus Conference	57 (70.4)	56,377 (36.4)	17 (68.0)	5,274 (90.7)
ACCM 2002	2 (2.5)	126 (0.1)	1 (4.0)	57 (0.1)
ACCM 2007	1 (1.2)	1,299 (0.8)	1 (4.0)	71 (1.2)
<i>International Classification of Diseases, 9th Edition codes</i>	6 (7.4)	86,594 (56.0)	0 (0)	0 (0)
Bone criteria	2 (2.5)	431 (0.3)	2 (8.0)	166 (2.9)
Sepsis-3	2 (2.5)	7,091 (4.6)	0 (0)	0 (0)
Other	4 (4.9) ^c	439 (0.3)	2 (8.0) ^d	151 (2.6)

ACCM = American College of Critical Care Medicine, ACCP = American College of Chest Physicians, SCCM = Society of Critical Care Medicine.

^aValues for age groups from eligible articles were included in category that provided the closest approximation to the classification used in the article. Articles could have patients from more than one age group resulting in totals being > 100%.

^b1. Bone RC, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655. 2. Levy et al (22). 3. Carcillo JA, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; 30:1365–1378. 4. Goldstein et al (3). 5. Brierley J, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666–688. 6. Singer M, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–810.

^cThree papers referred to hospital guidelines and one defined sepsis as tachycardia plus hypothermia (35.0°C) or hyperthermia (38.5°C), or abnormal WBC count plus poor peripheral perfusion (mean arterial pressure 50 mm Hg and/or absent peripheral pulses or capillary refilling time 3 s) in the absence of clinical dehydration.

^dOne paper used Carrol ED, et al: The role of RANTES in meningococcal disease. *J Infect Dis* 2000; 182:363–366 and one referenced Abraham E, et al: Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: Time for a re-evaluation. *Crit Care Med* 2000; 28:232–235.

TABLE 3.
Summary of Variables With Significant Associations With Outcomes of Interest

Variable	No. of Studies	No. of Participants With Outcome ^a	No. of Participants Without Outcome ^a	Pooled Estimate ^b (95% CI)	Mean Value in Two Groups ^c	p for Heterogeneity	I ² Value (%)
Variables significantly associated with outcome of sepsis, severe sepsis, or septic shock							
Decreased LOC	4	172/369	354/2,565	9.8 (5.8–16.7)		0.080	55.7
PRISM score	2	1,695	3,612	6.0 (4.0–8.0)	9.5 vs 3.5	< 0.0001	93.3
Variables significantly associated with outcome of mortality							
Demographic variables							
Severe acute malnutrition	3	30/135	57/450	4.7 (1.4–16.3)		0.094	57.8
Chronic conditions	11	859/1,464	13,013/25,664	2.4 (1.4–4.1)		< 0.0001	85.7
Oncologic conditions	8 ^d	104/402	616/2,422	2.3 (1.7–3.1)		0.63	0.0
Clinical variables							
Hypotension	4	1,013/1,910	10,828/41,283	2.3 (1.8–2.9)		0.052	61.1
Vasoactive agents	20	623/739	1,831/3,475	6.5 (4.2–10.0)		< 0.0001	59.7
Vasoactive-inotropic score	6	175	468	23.5 (3.4–43.6)	49.3 vs 20.4	< 0.0001	87.5
Stroke index	3	165	295	0.2 (0.1–0.4)	1.8 vs 1.7	0.42	0.0
Mechanical ventilation	30	2,778/3,350	22,874/51,151	11.0 (7.4–16.3)		< 0.0001	84.2
Decreased LOC	3	1,147/1,813	10,975/38,744	4.1 (2.9–5.9)		0.22	33.6
Glasgow Coma Scale	3	134	176	-4.0 (-6.2 to -1.8)	6.6 vs 11.0	0.10	56.5
Laboratory variables							
pH	4	203	334	-0.10 (-0.14 to -0.05)	7.21 vs 7.31	0.077	56.1
Lactate (mmol/L)	17	900	3,867	1.9 (1.2–2.6)	4.6 vs 2.7	< 0.0001	94.4
Base deficit	6	570	2,377	-3.2 (-5.8 to -0.6)	-9.1 vs -5.9	< 0.0001	98.1
Urea (mg/dL)	4	326	1,750	1.5 (0.7–2.3)	9.4 vs 6.2	0.075	56.6
Creatinine (μmol/L)	8	471	2,148	13.0 (4.6–21.5)	62.4 vs 42.8	< 0.0001	89.0
Potassium (meq/L)	3	268	1,447	0.2 (0.02–0.44)	4.5 vs 4.3	0.92	0.0
Platelet count (10 ⁹ /L)	14	585	3,196	-87 (-107 to -67)	90 vs 178	< 0.0001	90.9
Fibrinogen (g/L)	5	324	2,503	-1.5 (-2.5 to -0.6)	2.0 vs 3.6	< 0.0001	97.9
Albumin (g/L)	3	237	563	-4.3 (-8.4 to -0.2)	31.0 vs 35.4	< 0.0001	92.5
Procalcitonin (ng/ml)	9	463	1,266	4.0 (2.0–6.0)	7.8 vs 4.8	< 0.0001	92.2

(Continued)

TABLE 3. (Continued).
Summary of Variables With Significant Associations With Outcomes of Interest

Variable	No. of Studies	No. of Participants With Outcome ^a	No. of Participants Without Outcome ^a	Pooled Estimate ^b (95% CI)	Mean Value in Two Groups ^c	p for Heterogeneity	I ² Value (%)
Alanine aminotransferase (units/L)	3	298	1,262	10.1 (4.0–16.2)	97.3 vs 65.8	0.46	0.0
Organ dysfunction and illness severity variables							
No. of organ dysfunctions	4	1,065	4,683	0.9 (0.3–1.5)	3.4 vs 2.5	< 0.0001	92.6
Renal dysfunction	4	77/160	84/323	4.0 (1.0–18.4)		< 0.0001	86.2
Multiple organ dysfunction syndrome	9 ^c	388/467	816/1,986	7.8 (3.9–15.6)		< 0.0001	75.2
PELOD	12 ^c	442	1,748	6.1 (2.5–9.8)	16.7 vs 8.7	< 0.0001	97.7
PELOD-2	3	110	1,320	8.7 (5.7–11.6)	10.4 vs 1.2	< 0.0001	91.2
Sequential Organ Failure Assessment	2	95	647	3.8 (2.7–4.9)	9.9 vs 5.9	0.16	50.4
Pediatric Sequential (Sepsis-related) Organ Failure Assessment	4	595	756	4.8 (3.7–5.8)	10.0 vs 4.2	0.52	0.0
PRISM	19	821	3,871	11.0 (5.6–16.5)	22.5 vs 11.5	< 0.0001	99.6
PIM-2	2	63	397	12.1 (9.3–14.9)	35.6 vs 18.0	0.33	0.0
PIM-3	5 ^c	245	1,455	7.8 (2.5–13.1)		< 0.0001	89.1

LOC = level of consciousness, PELOD = pediatric logistic organ dysfunction, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality.

^aNumbers reported are totals for those with and without the listed outcome for each parameter for continuous variables. For categorical variables, the numbers shown are the number with the parameter over the total with or without the outcome of interest.

^bPooled estimate is for the odds ratio for categorical variables and the mean difference for continuous variables.

^cThe mean values of nonsurvivors versus survivors are provided for all continuous variables.

^dThe study by Thakkar et al (23) reported on two nonoverlapping cohorts of medical and surgical patients that were, therefore, analyzed separately and counted as two studies.

Variables Associated With Sepsis, Severe Sepsis, Septic Shock in Children With Suspected Infection

Sixteen studies on 9,629 patients provided data for the meta-analysis assessing the association of 16 variables among children with suspected infection with the outcome of sepsis, severe sepsis, or septic shock (for study and patient characteristics, see **Supplementary Table 4**, <http://links.lww.com/CCM/G828>;

and Supplementary Table 1, <http://links.lww.com/CCM/G817>). Sepsis and severe sepsis among infected children were associated with decreased level of consciousness (24–27) and higher Pediatric Risk of Mortality (PRISM) scores (28, 29), respectively (Supplementary Fig. 2, <http://links.lww.com/CCM/G821>; and Supplementary Fig. 8, <http://links.lww.com/CCM/G827>). Our meta-analysis did not demonstrate an association among age, age groups, gender or malnutrition (30–34), and sepsis,

severe sepsis, or septic shock (**Supplementary Table 5**, <http://links.lww.com/CCM/G829>). Sepsis among infected children was not associated with pooled estimates of hemoglobin (35–37), C-reactive protein (CRP) (25, 27), or procalcitonin (38, 39).

Variables Associated With NPMODS and Mortality in Children With Sepsis, Severe Sepsis, or Septic Shock

Mortality rates for sepsis, severe sepsis, and/or septic shock were provided in 86 of 106 included studies. The pooled mortality rate using a random-effects model for patients with sepsis was 10.9% ($n = 47$ studies; 95% CI, 8.9–13.2), for severe sepsis was 23.0% ($n = 26$ studies; 95% CI, 19.6–26.9), and for septic shock was 36.8% ($n = 28$ studies; 95% CI, 29.4–44.9). The pooled mortality rates varied among HIC, UMIC, and LMIC locations for each of sepsis, severe sepsis,

and septic shock patient groups ($p < 0.0001$) (**Fig. 2**). The mortality analysis did not include LICs as there was only one study with eligible data.

Sixty-nine studies on 145,461 patients provided data for the meta-analysis of the association of 54 variables with the primary outcome of mortality (for patient and study characteristics, see Supplementary Table 1, <http://links.lww.com/CCM/G817>; and Supplementary Table 4, <http://links.lww.com/CCM/G828>, respectively). One study reported separately on two populations that were, therefore, reported as two studies in the meta-analysis (23). Only one study reported NPMODS as an outcome, and two reported a composite outcome of NPMODS and death. Meta-analysis with NPMODS as the outcome was not possible as none of these studies assessed the same variables.

Pooled estimates supported an increased odds of mortality in patients with severe acute malnutrition (31, 40, 41), chronic conditions (31, 33, 42–50), and oncologic conditions (23, 31, 47, 51–54) (Supplementary Fig. 1, <http://links.lww.com/CCM/G820>). The evidence did not support an association between age, age groups, or gender with mortality. In addition, no association was noted between, obesity (55–57) or malnutrition (30–34) and mortality, but only a small number of studies assessed these variables.

Clinical Variables

Among children with sepsis, severe sepsis, and septic shock, pooled estimates provide strong support for increased mortality with hypotension (46, 47, 58, 59), use of vasoactive agents/inotropes (26, 31–33, 40, 41, 44, 49, 50, 58, 60–69), increased vasoactive-inotropic score (VIS) (51, 53, 68, 70–72),

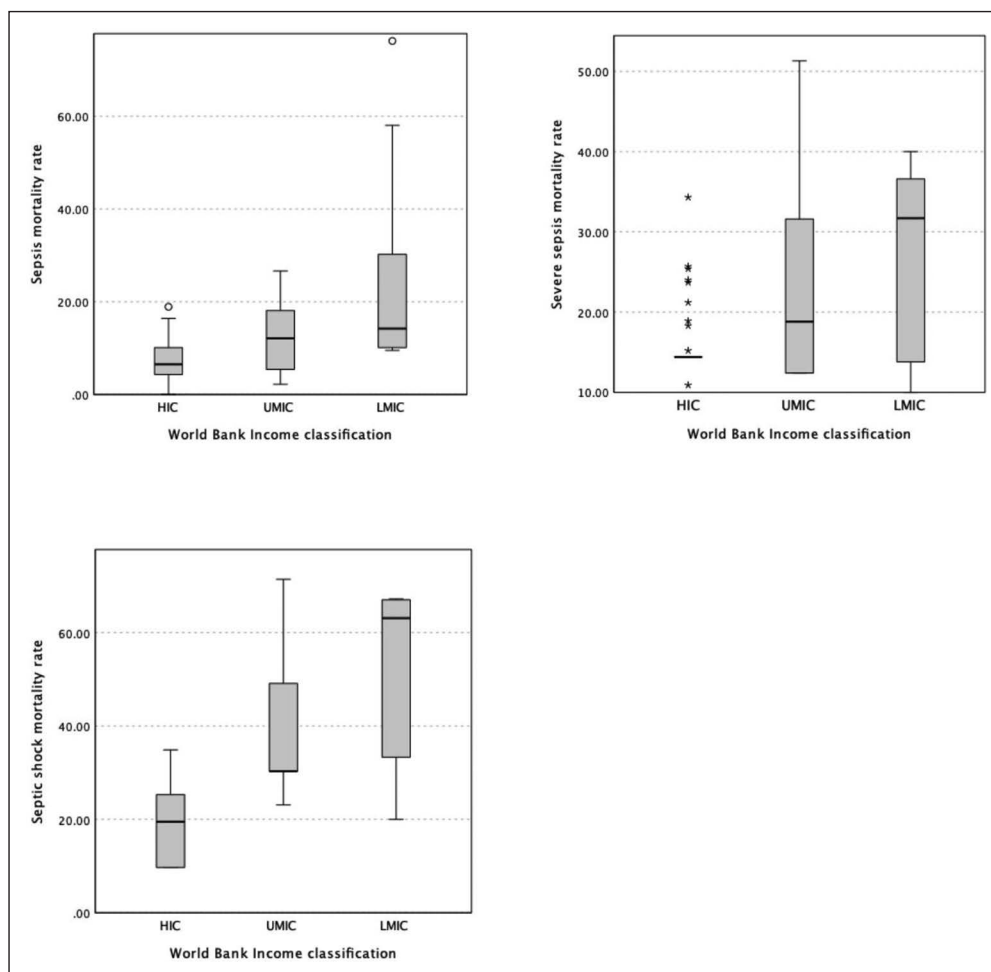


Figure 2. Pooled mortality rates for sepsis, severe sepsis, and septic shock in included studies across World Bank Income classifications. HIC = high-income country, LMIC = low-middle-income country, UMIC = upper-middle-income country.

increased shock index (58, 73, 74), decreased level of consciousness (58, 59, 67), decreased Glasgow Coma Scale (GCS) (53, 70, 75), and mechanical ventilation (26, 28, 31, 32, 40–44, 46, 49–51, 53, 58–62, 65–69, 71, 72, 75–80) (Supplementary Fig. 2, <http://links.lww.com/CCM/G821>). There were no mortality differences significantly associated with heart rate (47, 53, 58, 71, 74, 76), mean blood pressure (53, 71), systolic blood pressure (47, 58, 67, 74, 76), central venous pressures (51, 53, 71), and arterial oxygen saturations (47, 58).

Laboratory Variables

Pooled estimates provide strong support for a difference in the following laboratory measures between nonsurvivors and survivors: lower serum pH (53, 58, 72, 75), higher lactate (43, 50, 51, 53, 60–62, 65, 68, 71, 72, 74–76, 81–83), higher serum base deficit (62, 71, 75, 76, 84, 85), higher urea (58, 76, 81, 86), higher creatinine (53, 58, 71, 76, 81, 83, 85, 86), lower platelet count (41, 43, 50, 53, 58, 62, 71, 77, 81, 83–85, 87, 88), lower fibrinogen (62, 81, 84, 85, 87), higher potassium (62, 71, 76), lower albumin (53, 76, 83), higher procalcitonin (26, 35, 43, 76, 83, 85, 89–91), and higher alanine aminotransferase (ALT) (58, 76, 81) (Supplementary Fig. 3, <http://links.lww.com/CCM/G822>; Supplementary Fig. 4, <http://links.lww.com/CCM/G823>; Supplementary Fig. 5, <http://links.lww.com/CCM/G824>; and Supplementary Fig. 6, <http://links.lww.com/CCM/G825>). Pooled estimates did not support a difference between nonsurvivors and survivors in mean glucose (50, 68, 71, 72, 76), total bilirubin (53, 58, 76, 81, 85, 86), WBC (26, 43, 50, 53, 58, 62, 71, 75–77, 81, 83, 85, 87, 89), hemoglobin (26, 43, 50, 71, 83, 85), international normalized ratio (62, 81), prothrombin time (53, 71, 76, 81, 92), activated partial thromboplastin time (62, 71, 81, 92), and brain natriuretic peptide (51, 66, 76).

Organ Dysfunction Measures and Illness Severity Scores

Our meta-analysis provides strong support for greater organ dysfunction in nonsurvivors compared with survivors as shown by the pooled estimates for renal dysfunction (50, 64, 67, 70), multi-organ dysfunction (MODS) (23, 33, 41, 50, 69, 70, 93, 94), number of organ dysfunctions (28, 40, 64, 83), PEdiatric Logistic Organ Dysfunction (PELOD) score (23, 28, 40, 44, 50, 53, 55,

60, 65, 72, 85), and PELOD-2 (85, 86, 95). Our meta-analysis also provides strong support for greater illness severity in nonsurvivors compared with survivors as shown by the pooled estimates pediatric Sequential (Sepsis-related) Organ Failure Assessment (pSOFA) (50, 58, 70, 95) and Sequential (Sepsis-related) Organ Failure Assessment (SOFA) (85, 86, 95), PRISM (32, 43, 51, 53, 55, 60–62, 64, 68, 70–72, 75, 77, 81, 84, 85, 88), Pediatric Index of Mortality (PIM)-2 (79, 85), and PIM-3 (23, 61, 65, 85) (Supplementary Fig. 7, <http://links.lww.com/CCM/G826>; and Supplementary Fig. 8, <http://links.lww.com/CCM/G827>).

Narrative Review of $n = 25$ Studies

Three studies reported risk factors for developing sepsis or septic shock among children with infection. Two studies reported differing thresholds of CRP (81.9 and 154.3 nmol/dL) and procalcitonin levels (43 and 19.1 ng/mL) for association with septic shock in patients with meningococemia (96) and sepsis (97), respectively. One study of children presenting to the ED with suspected infection found that a lactate level of greater than 3 mmol/L was associated with higher risk of sepsis (98).

In one study of patients with septic shock, those with hematopoietic cell transplants had increased odds of mortality (OR 4.74; 95% CI, 2.56–8.77) (99), and those with progressively higher Logistic Organ Dysfunction Score and alert, verbal, pain, unresponsive score demonstrated increasing positive predictive values for early mortality from 40% to 60% and 39.3% to 50%, respectively (100). Several studies assessed cardiovascular variables. In one study, the Tp-e interval/QT on an electrocardiogram was an independent predictor of mortality in patients with septic shock (101). A VIS of greater than 20 was associated with increased mortality (102). Another study suggested time-dependent cutoffs for shock index values from 0- to 6-hour postadmission (103), and two studies each found an association of a decreased left ventricular ejection fraction (45% and 55%) with mortality (104, 105).

Laboratory values that showed an association with mortality in single studies included red cell distribution width elevation (106); antithrombin III levels below 41.5% (< 1 yr old) and 67.5% (\geq 1 yr old) (92); 25-hydroxy vitamin D less than 50 nmol/L (107); baseline cortisol cutoff of 20 μ g/dL and

postadrenocorticotrophic hormone stimulation level of less than or equal to 9 µg/dL (108); lower serum zinc levels (109); lower high-density lipoprotein, low-density lipoprotein, and cholesterol levels (110); and lower total T3 and T4, and free T3 and T4 hormone levels (111). Two studies assessed serum troponin in sepsis with one reporting an association of serum troponin greater than 1 ng/dL with mortality (112), whereas the other found higher levels of troponin in nonsurvivors compared with survivors (71). Serum lactate levels were studied using three criteria. Serum-lactate-to-albumin ratio greater than 1.17 was associated with increased mortality (113), and lack of lactate clearance (decrease of $\leq 10\%$) or normalization (< 2 mmol/L) was associated with persistent MODS (114).

DISCUSSION

Our systematic review evaluated over 50 variables and derived scores in studies on over 150,000 patients from diverse global settings. To our knowledge, this is the largest systematic review assessing a broad range of variables associated with severity of infection in children (115). The majority of included studies in this review described features among septic children associated with higher mortality. We found evidence of increased odds of mortality for septic patients with severe acute malnutrition, chronic conditions, oncologic disorders, hypotension, use of inotropes, mechanical ventilation, decreased level of consciousness, and lower GCS. In addition, we found significant differences in VIS, base deficit, pH, lactate, platelets, fibrinogen, urea, creatinine, albumin, potassium, ALT, and procalcitonin between nonsurvivors and survivors. These findings provide support for using the above measures of organ dysfunction as hallmarks of sepsis and serve to inform data-driven development of revised pediatric sepsis criteria.

Our study evaluated data from 35 countries in diverse geographic regions and income levels of the World Bank Income classification (18). This is important given that up to 85% of all sepsis cases and related deaths occur in lower income and middle-income countries (2). However, although 18 included studies were conducted in LIC and LMIC countries, these represented only 1.8% (2,784/154,674) of the patients analyzed. The lower representation of LIC/LMIC patients may have resulted in our findings being

more applicable to HIC/UMIC settings as a result of distinct causes of sepsis (116), limited access to and availability of treatments (117), and higher mortality rates (2) in patients with sepsis from LMIC/LIC settings. Large studies in LMIC/LIC settings remain challenging to perform due to the lack of comprehensive registries, electronic health records, and limited laboratory resources, which has important implications for the derivation, dissemination, and uptake of a revised definition of pediatric sepsis.

Only a small proportion of eligible studies (8/81, 9.9%), contributing 1.3% of included patients (2078/154,674), was from pre-ICU settings. This may have resulted in underrepresentation of early clinical variables used to differentiate self-limited febrile illness from critical illness and that may be important in sepsis definitions designed for the pre-ICU phase of illness (118). Considering that most children with sepsis initially present to non-ICU settings, it is imperative that the future work of the Pediatric Sepsis Definition Taskforce also develops and validates tools for the recognition of sepsis outside of the ICU.

Previous sepsis definitions, such as the 2001 Consensus Conference (22) and 2005 IPSCC (3) definitions, included markers of organ dysfunction such as lactate, but their inclusion was the result of a consensus process and was never formally validated. The present systematic review allows prioritization of markers showing robust association with mortality for future revisions of sepsis criteria. Interestingly, bilirubin, used as the sole marker of liver dysfunction in the adult-adapted pSOFA score, was not associated with mortality, whereas another marker of liver dysfunction, ALT, performed well. In addition, measures of metabolic failure (increased serum lactate, acidosis, and base deficit) were confirmed as relevant markers despite not being part of the SOFA score. This review assessed individual variables as well as illness severity and organ dysfunction scores that incorporate combinations of the studied variables. This is an important contribution as many of the studied scores were derived and validated in critically ill children but not specifically studied in those with sepsis.

This review has several limitations. The first is that several variables included in the meta-analysis demonstrated significant heterogeneity. However, since the purpose of this review was to identify potential variables for use in an updated definition of pediatric sepsis

rather than draw conclusions regarding a treatment effect, the actual effect size and its associated I^2 value may be less relevant. Second, our pragmatic approach resulted in the inclusion of studies with different definitions of sepsis. Although this may have limited our ability to find associations of some variables with our outcomes of interest, it may also have contributed to the robustness of the associations for other variables. Finally, for continuous variables, we were not able to determine thresholds for the development of sepsis or for mortality due to lack of data. However, we determined overall mean values for survivors and nonsurvivors for variables with a significant mean difference that could provide initial thresholds in the data validation phase of the Pediatric Sepsis Definition Taskforce project.

CONCLUSIONS

This systematic review rigorously assessed the association of individual variables with development of sepsis in children with infections and the odds of mortality in children with sepsis, severe sepsis, and septic shock. The included studies were from economically diverse regions of the world, populations with diverse underlying conditions, and varying definitions of sepsis. Despite the clinical heterogeneity and limited number of studies for some variables, strong associations with the outcomes of interest were seen for many of the variables assessed, predominantly reflecting measures of organ dysfunction and supporting the inclusion of these variables in the data validation phase of the Pediatric Sepsis Definition Taskforce.

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