LATE BREAKER ARTICLE

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Phoenix Sepsis Criteria in Critically Ill Children: Retrospective Validation Using a United States Nine-Center Dataset, 2012–2018

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OBJECTIVES: To perform: 1) external validation of the Phoenix Sepsis Score and Phoenix sepsis criteria in a multicenter cohort of critically ill children with infection and a comparison with the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria; 2) a study of Phoenix sepsis criteria performance in patient subgroups based on age and comorbidities; 3) an assessment of microbiological profile of children with Phoenix sepsis; and 4) a study of the performance of the Phoenix-8 score.

DESIGN: Secondary, retrospective analysis of a multicenter cohort study from 2012 to 2018.

SETTING: Nine PICUs in the United States.

PATIENTS: PICU admissions with suspected infection.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among 25,680 encounters of children with suspected or confirmed infection on PICU admission (4.6% in-hospital mortality), 11,168 (43%) met Phoenix criteria for sepsis or septic shock (9% in-hospital mortality). The Phoenix criteria generally outperformed the IPSCC criteria at discriminating mortality in all critically ill children with infections and across all subgroup analyses, including age group, malignancy, or technology dependence. Of 11,168 patients who met Phoenix criteria, 28% were negative for IPSCC criteria for sepsis and these had higher in-hospital mortality than those who met IPSCC sepsis criteria but not Phoenix criteria (4.7% vs.1.7%; $p < 0.001$), which was similar to the mortality of patients without sepsis (1.3%). Sepsis was associated with respiratory or bloodstream infection, most commonly *Pseudomonas aeruginosa* or *Staphylococcus aureus*. The Phoenix-8 score had good discrimination of mortality in children with infections, comparable to or better than validated and widely used severity of illness and organ dysfunction scores.

CONCLUSIONS: In 2012–2018, among U.S. patients with suspected or confirmed infection admitted to nine PICUs, those with the highest risk of mortality can be identified using the Phoenix sepsis criteria, including in children of different age groups and those with major comorbidities.

KEYWORDS: critical care; organ dysfunction; pediatrics; sepsis

Sepsis is one of the leading causes of morbidity and mortality in children around the world (1). Having diagnostic criteria that are reliable, reproducible, and have face validity among clinicians is imperative for their use in clinical care, benchmarking, epidemiologic surveillance, and research (2). Recently, the Society of Critical Care Medicine (SCCM) Pediatric Sepsis Definition Taskforce redefined pediatric sepsis as "an infection with life-threatening organ dysfunction in children" (2, 3). Similar to the adult Sepsis-3 criteria for sepsis, it retired the systemic inflammatory response

This article has an accompanying editorial.

DOI: 10.1097/PCC.0000000000003675

RESEARCH IN CONTEXT

- We sought to externally validate the new Phoenix criteria for sepsis and septic shock in critically ill U.S. children with suspected or confirmed infection managed in 2012–2018.
- We aimed to compare the performance of the Phoenix criteria with the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria.
- We also sought to compare the Phoenix-8 score with other validated pediatric scores and criteria for severity of illness.

syndrome (SIRS) and made the concept of "severe sepsis" obsolete, both of which were part of the prior 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria (4, 5). In its place, the Taskforce developed the new Phoenix Sepsis Score (PSS) and the Phoenix criteria for sepsis and septic shock in children using a data-driven approach combined with a modified Delphi process consensus by a diverse group of international experts (2). To do this, a machine learning-based approach was used to derive the new organ dysfunction-based PSS specific for children with infection using the best performing components of validated organ dysfunction scores (3). The new score includes variables for four organ systems (respiratory, cardiovascular, coagulation, and neurologic). In children with suspected infection, the taskforce defined sepsis with a cutoff PSS score of greater than or equal to 2 points and defined septic shock as sepsis with greater than or equal to 1 cardiovascular points. The taskforce also developed and published a more extensive score with eight organ systems, called the Phoenix-8 score, to be used for risk stratification and assessment of organ dysfunction burden as an alternative to other existing scores (6–8).

In this current report, we aimed to perform a multicenter external validation of the PSS and the Phoenix criteria in United States admitted to the PICU and to compare it with the IPSCC criteria. In addition, we aimed to compare the discriminatory performance of the PSS and the Phoenix-8 score against other validated scores of severity of illness.

METHODS

This was secondary analysis of a historically curated dataset of children 0–18 years old admitted to nine U.S. PICUs between January 1, 2012, and January 1, 2018 (9). The original study included data from four additional PICUs, but those sites were part of the original Phoenix study published in 2024 (3), and thus were excluded from this external validation. The institutional review board (IRB) at Lurie Children's Hospital of Chicago served as the central IRB for the original study (IRB No. 2019–2481, approved on February 13, 2019, with a waiver of consent). In this current work, no additional IRB approval was needed, and all research procedures were performed in accordance with the institutional and federal ethical standards of human experimentation and the Helsinki Declaration of 1975.

In the 2012–2018 dataset, we identified patients who had confirmed or suspected infection as those who had received antimicrobials and microbiological testing in the ± 24-hour time window surrounding PICU admission. Data extracted from the electronic health records (EHRs), at each study site, was consistent with prior studies of sepsis in children (10, 11). The final results of the microbiological testing performed in the enrollment time window were extracted from eight of the nine sites (the remaining site did not provide final results). The primary outcome was in-hospital mortality and the secondary outcome was the composite of early death (within 72 hr of PICU admission) or need for extracorporeal membrane oxygenation (ECMO), as used in the 2024 Phoenix criteria derivation study (3).

In this article, we refer to the PSS as the four-organ system score with a possible range of 0–13 points, the Phoenix sepsis criteria as the binary criteria for sepsis based on the cutoff of greater than or equal to 2 PSS points in children with infection, the Phoenix septic shock criteria as the binary criteria based on having Phoenix sepsis plus greater than or equal to 1 cardiovascular points in the PSS, and the Phoenix-8 score as eight-organ system score with a possible range of 0–17 points.

Validation and Comparison of Organ Dysfunction Scores and Criteria

We compared the performance of the PSS and the Phoenix-8 score to the Pediatric Logistic Organ

Dysfunction-2 (PELOD-2) score (6), the pediatric Sequential Organ Failure Assessment (pSOFA) score (7), and the count of organ dysfunctions based on the IPSCC criteria (4), and the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) criteria (8). We used the area under the precision-recall curve (AUPRC) and the area under the receiver operating characteristic (AUROC) curve as the main metrics of performance for the primary and secondary outcomes. We present the mean AUPRC and the mean AUROC derived using five-fold cross-validation. In addition, we evaluated Phoenix-8 score as a measure for severity of illness at admission by comparing it with the Pediatric Risk of Mortality (PRISM)-III score (12), the pSOFA score, and the PELOD-2 score in the first 24 hours (7, 13). We used the DeLong method (14) to compare AUROCs. The IPSCC and the PODIUM criteria were calculated using EHR data based on an approach previously described (15). For the IPSCC cardiovascular criteria, the requirement for greater than 40 mL/kg of fluid bolus was not considered given the limited availability of data about pre-PICU resuscitation fluids and the changes in practice regarding fluid resuscitation.

Validation and Comparison of Criteria for Pediatric Sepsis and Septic Shock

We compared the Phoenix criteria for sepsis and septic shock with the IPSCC criteria for sepsis, severe sepsis, and septic shock using data from the first 24 hours of admission. Because these criteria are binary, we used the positive predictive value (PPV) and sensitivity to assess their diagnostic performance for the primary and secondary outcomes. PPV and sensitivity are the two axes of the precision-recall curve and two of the most important diagnostic metrics in the acute care setting (16). Finally, we also assessed the PPV and sensitivity of "sepsis with remote organ dysfunction," a subset of sepsis patients proposed by the SCCM Taskforce as those that have organ dysfunction in at least one system remote to the site of infection. For this subgroup analysis, we only included patients with positive cultures and a known site of infection.

Reporting and Other Statistical Analyses

Data are presented as numbers, proportions, and percentages. Data summaries are presented as median (interquartile range [IQR]) or as mean (95% CI). Continuous data were compared using the Mann-Whitney *U* test and categorical data were compared using the chi-square test. The major comorbidities of malignancy, transplantation, and technology dependence were determined using the complex chronic condition criteria (17). All statistical analyses were conducted using R, Version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The reporting of this validation study was performed using the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guidelines (18).

RESULTS

There were 25,680 encounters of children with suspected or confirmed infection within 24 hours of admission and 1,194 died (4.6%) during their hospitalization. Among these patients admitted with suspected or confirmed infection to the PICU, 11,168 (43%) met Phoenix criteria for sepsis. Identification of Phoenix criteria for sepsis was associated with older age, presence of a major comorbidity, and higher organ dysfunction (all $p < 0.001$) (**Table 1**). Meeting Phoenix criteria for sepsis was also associated with mortality rate than patients with infection but no sepsis (9% vs. 1.3%; $p < 0.001$). The median time to death for patients with sepsis was 4.6 days (IQR, 1.8–14.3 d), with 41% of deaths occurring within 72 hours of admission (**Fig. S1**, http://links.lww.com/PCC/C579). Among patients who died, early death within 72 hours was associated with higher organ dysfunction burden. Furthermore, on comparing late with early deaths, there was an association with major comorbidities (**Table S1**, http://links.lww.com/PCC/C579). On comparing survivors (n = 14,322) with nonsurvivors (n = 190), in patients with suspected or confirmed infection who did not meet Phoenix criteria for sepsis mortality was associated with low organ dysfunction by any score studied. Also, death was associated with higher proportion of any major comorbidity (73.7%), including malignancy (42.1%), and admission to PICU from an inpatient wards (41.6%) (**Table S2**, http://links.lww.com/PCC/C579).

Among patients meeting Phoenix criteria for sepsis, the most common PSS-based organ dysfunction was respiratory (77.2%), followed by neurologic (61%),

TABLE 1.
Clinical Characteristics of Critically Ill Children With Confirmed or Suspected Infection and With or Without Sepsis Based on the Phoenix Criteria

Clinical Characteristics	Phoenix Criteria for Sepsis		p
	No (*n* = 14,512)	Yes (*n* = 11,168)	
Age, yr, median (IQR)	3.81 (1.02–10.34)	4.87 (1.20–11.76)	< 0.001
Male, *n* (%)	7,959 (54.8)	6,116 (54.8)	0.91
Race/ethnicity, *n* (%)			< 0.001
Asian	629 (4.3)	477 (4.3)	
Black, non-Hispanic	3,163 (21.8)	2,098 (18.8)	
Hispanic	1,892 (13.0)	1,609 (14.4)	
White, non-Hispanic	7,504 (51.7)	5,716 (51.2)	
Multiple or other	1,324 (9.1)	1,268 (11.4)	
Admission location, *n* (%)			< 0.001
Emergency department	8,290 (57.1)	5,575 (49.9)	
Direct	2,036 (14.0)	2,452 (22.0)	
Inpatient	2,802 (19.3)	2,373 (21.2)	
Operating room	1,384 (9.5)	768 (6.9)	
Season, *n* (%)			0.049
Spring	3,694 (25.5)	2,869 (25.7)	
Summer	3,190 (22.0)	2,357 (21.1)	
Fall	3,462 (23.9)	2,583 (23.1)	
Winter	4,166 (28.7)	3,359 (30.1)	
Major comorbidities, *n* (%)			
Malignancy	1,575 (10.9)	1,556 (13.9)	< 0.001
Transplant	486 (3.3)	590 (5.3)	< 0.001
Technology dependent	4,583 (31.6)	4,569 (40.9)	< 0.001
No major comorbidity	8,828 (60.8)	5,453 (48.8)	< 0.001
Organ dysfunction scores/criteria, median (IQR)			
Phoenix Sepsis Score	1 (0–1)	3 (2–4)	< 0.001
Phoenix-8	1 (0–1)	4 (3–6)	< 0.001
Pediatric Logistic Organ Dysfunction-2	2 (2–4)	6 (4–9)	< 0.001
Pediatric Sequential Organ Failure Assessment	2 (1–4)	7 (5–9)	< 0.001
Pediatric Organ Dysfunction Information Update Mandate	0 (0–1)	2 (1–3)	< 0.001
International Pediatric Sepsis Consensus Conference	1 (0–1)	2 (1–3)	< 0.001
Systemic inflammatory response syndrome	7,286 (50.2)	8,049 (72.1)	< 0.001
Pediatric Risk of Mortality III score	3 (2–6)	10 (6–16)	< 0.001
Outcomes			
PICU LOS, median (IQR)	1.90 (0.99–3.73)	4.18 (1.96–8.90)	< 0.001
Hospital LOS, median (IQR)	4.83 (2.80–9.72)	9.66 (4.83–19.77)	< 0.001
Early death or extracorporeal membrane oxygenation, *n* (%)	21 (0.1)	549 (4.9)	< 0.001
In-hospital mortality, *n* (%)	190 (1.3)	1,004 (9.0)	< 0.001

IQR = interquartile range, LOS = length of stay.

The values for the Pediatric Organ Dysfunction Information Update Mandate and the International Pediatric Sespsis Consensus Conference are based on the number of organ systems affected based on the criteria.

TABLE 2.
Distribution and Associated In-Hospital Mortality Across the Phoenix Sepsis Score Organ Dysfunction Criteria in the first 24 Hours of Admission Among Critically Ill Children Meeting Phoenix Criteria for Sepsis

Phoenix Sepsis Score Organ Systems	Patients Meeting Sepsis Criteria (%)	In-Hospital Mortality
Total, *n*	11,168 (100)	9%
Respiratory		
Any points	8,626 (77.2)	10.1%
1 point	4,580 (41.0)	6.9%
2 points	1,557 (13.9)	9.1%
3 points	2,489 (22.3)	16.6%
Cardiovascular		
Any points	6,711 (60)	11.4%
Low mean arterial pressure	5,244 (47)	10.2%
1 point	4,404 (39.4)	7.7%
2 points	840 (7.5)	23.7%
High lactate	1,205 (10.8)	35.3%
1 point	879 (7.9)	24.6%
2 points	326 (2.9)	64.1%
Vasoactive use	3,467 (31)	17.0%
1 point	2,279 (20.4)	14.6%
2 points	1,188 (10.6)	21.5%
Coagulation		
Any points	4,374 (39.1)	16.6%
Low platelets	2,614 (23.4)	17.3%
High international normalized ratio of the prothrombin time	2,992 (26.8)	18.9%
Low fibrinogen	359 (3.2)	42.9%
High D-dimer	824 (7.4)	22.2%
Neurologic		
Any points	6,764 (61)	10.6%
Low Glasgow Coma Scale	6,072 (54.4)	7.2%
Fixed pupils	692 (6.2)	40.8%

cardiovascular (60%), and coagulation (39.1%) (**Table 2**). The organ dysfunction with the highest associated in-hospital mortality was coagulation (16.6%), followed by cardiovascular (11.4%), neurologic (10.6%), and respiratory (10.1%) (Table 2). There were 6711 encounters (60.1% of those with sepsis) who had septic shock and a 11.4% mortality.

At the eight PICUs with microbiological testing results, meeting Phoenix criteria for sepsis, rather than not, was associated with positive microorganism isolated in the first 24 hours (46% vs. 36%; $p < 0.001$). **Table S3** (http://links.lww.com/PCC/C579) shows the microbiological characteristics of patients with positive microorganism isolates stratified by sepsis status. Meeting Phoenix criteria for sepsis, as opposed to not, was associated with bloodstream or respiratory source, a bacterial infection, and viral-bacterial co-detection (all $p < 0.001$). The two most common microorganisms isolated in patients with sepsis were *Pseudomonas aeruginosa* (15.1%) and methicillin-sensitive *Staphylococcus aureus* (13.2%). Having an infection but not meeting Phoenix criteria for sepsis was associated with a urinary or cerebrospinal fluid source, or viral infection, when compared with patients with sepsis (all $p < 0.001$). The two most common microorganisms isolated in patients with infection without sepsis were rhinovirus/enterovirus (17.4%) and respiratory syncytial virus (12.6%).

There were 1686 patients (6.6%) with confirmed or suspected infection on PICU admission who were admitted to the inpatient ward for more than 72 hours prior to PICU admission and met criteria for hospital-acquired infection. Of these, 875 (52%) met Phoenix criteria for sepsis and had a mortality of 19.9%.

Validation and Comparison of Organ Dysfunction Scores and Criteria

The AUPRCs and AUROCs for the PSS, Phoenix-8, PELOD-2, pSOFA, IPSCC count, and PODIUM count are shown in **Table 3**. The PSS had a mean AUPRC of 0.35 (95% CI, 0.33–0.36) for mortality and 0.41 (95% CI, 0.40–0.41) for early death or ECMO, and a mean AUROC of 0.82 (95% CI, 0.81–0.83) for mortality and 0.93 (95% CI, 0.92–0.94) for early death or ECMO. The performance of the PSS was comparable to the performance of Phoenix-8 and PELOD-2 scores and generally higher than pSOFA, IPSCC count, and PODIUM count (Table 3). **Figure 1** presents the association between in-hospital mortality and the proportion of patients across the range in PSS. **Figure S2** (http://links.lww.com/PCC/C579) presents the same information for the Phoenix-8 score.

TABLE 3.

Performance of the Phoenix Sepsis Score and the Phoenix-8 Score Compared With Other Organ Dysfunction Scores to Discriminate In-Hospital Mortality and Early Death or Extracorporeal Membrane Oxygenation

	Area Under the Precision-Recall Curve, Mean (95% CI)		Area Under the Receiver Operating Characteristic Curve, Mean (95% CI)	
Organ Dysfunction Scores in First 24 hr in Infected Children	**In-Hospital Mortality (4.6%)**	**Early Death or ECMO (2.2%)**	**In-Hospital Mortality (4.6%)**	**Early Death or ECMO (2.2%)**
Phoenix Sepsis Score	0.35 (0.33–0.36)	0.41 (0.40–0.41)	0.82 (0.81–0.83)	0.93 (0.92–0.94)
Phoenix-8	0.37 (0.35–0.39)	0.41 (0.39–0.42)	0.84 (0.82–0.86)	0.94 (0.93–0.95)
Pediatric Logistic Organ Dysfunction-2	0.36 (0.33–0.40)	0.40 (0.38–0.42)	0.81 (0.80–0.82)	0.93 (0.91–0.94)
Pediatric Sequential Organ Failure Assessment	0.28 (0.26–0.29)	0.26 (0.24–0.29)	0.82 (0.81–0.83)	0.91 (0.91–0.92)
International Pediatric Sepsis Consensus Conference	0.26 (0.23–02.8)	0.23 (0.21–0.25)	0.80 (0.79–0.81)	0.89 (0.89–0.91)
Pediatric Organ Dysfunction Information Update Mandate	0.26 (0.24–0.29)	0.24 (0.21–0.26)	0.81 (0.80–0.83)	0.90 (0.89–0.92)

ECMO = extracorporeal membrane oxygenation.

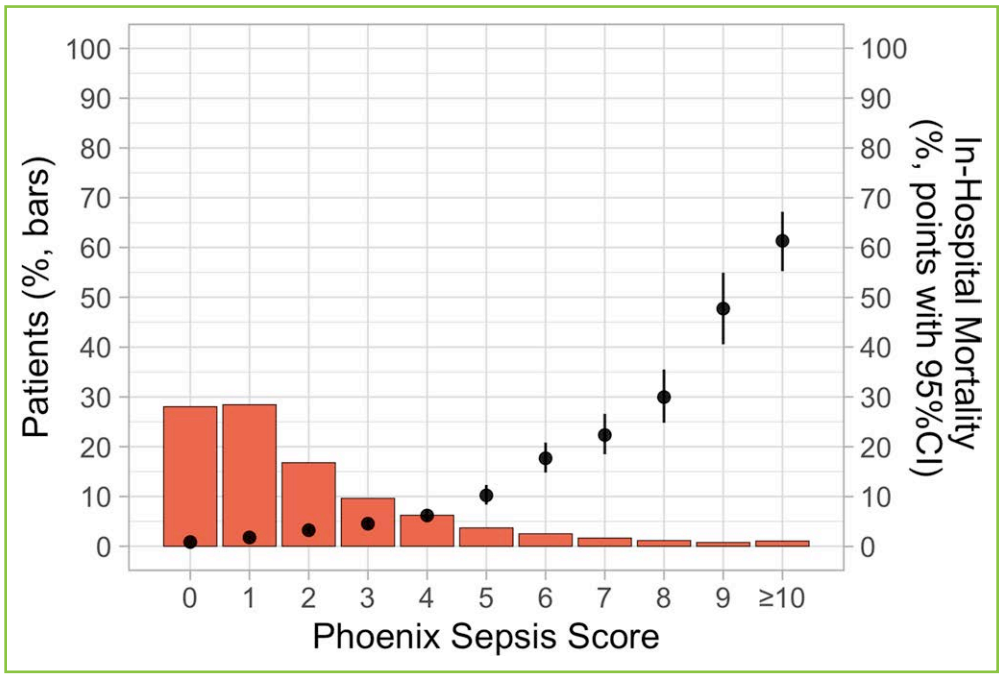

Figure 1. Distribution and associated in-hospital mortality across the Phoenix Sepsis Score in the first 24 hr of admission among critically ill children with confirmed or suspected infection. The *vertical dashed line* separates patients with and without sepsis based on the Phoenix criteria.

Validation and Comparison of Criteria for Pediatric Sepsis and Septic Shock

Figure 2, ***A*** and ***B*** present the PPV and sensitivity for mortality and early death or ECMO using the Phoenix criteria for sepsis compared with the IPSCC criteria for sepsis and severe sepsis. For both the primary (in-hospital mortality) and secondary outcomes (early death or ECMO), the Phoenix criteria had higher performance than either of the IPSCC criteria. **Figure 2**, ***C*** and ***D*** present the PPV and sensitivity of the Phoenix criteria for septic shock compared with the IPSCC septic shock criteria. Again, in both the primary and secondary outcome, the Phoenix criteria had higher performance than the IPSCC criteria. **Figure S3** (http://links.lww.com/PCC/C579) presents the performance stratified by subgroups based on major comorbidities (i.e., no major commodity, technology dependence, and malignancy). Overall, the Phoenix criteria had higher or comparable performance for the

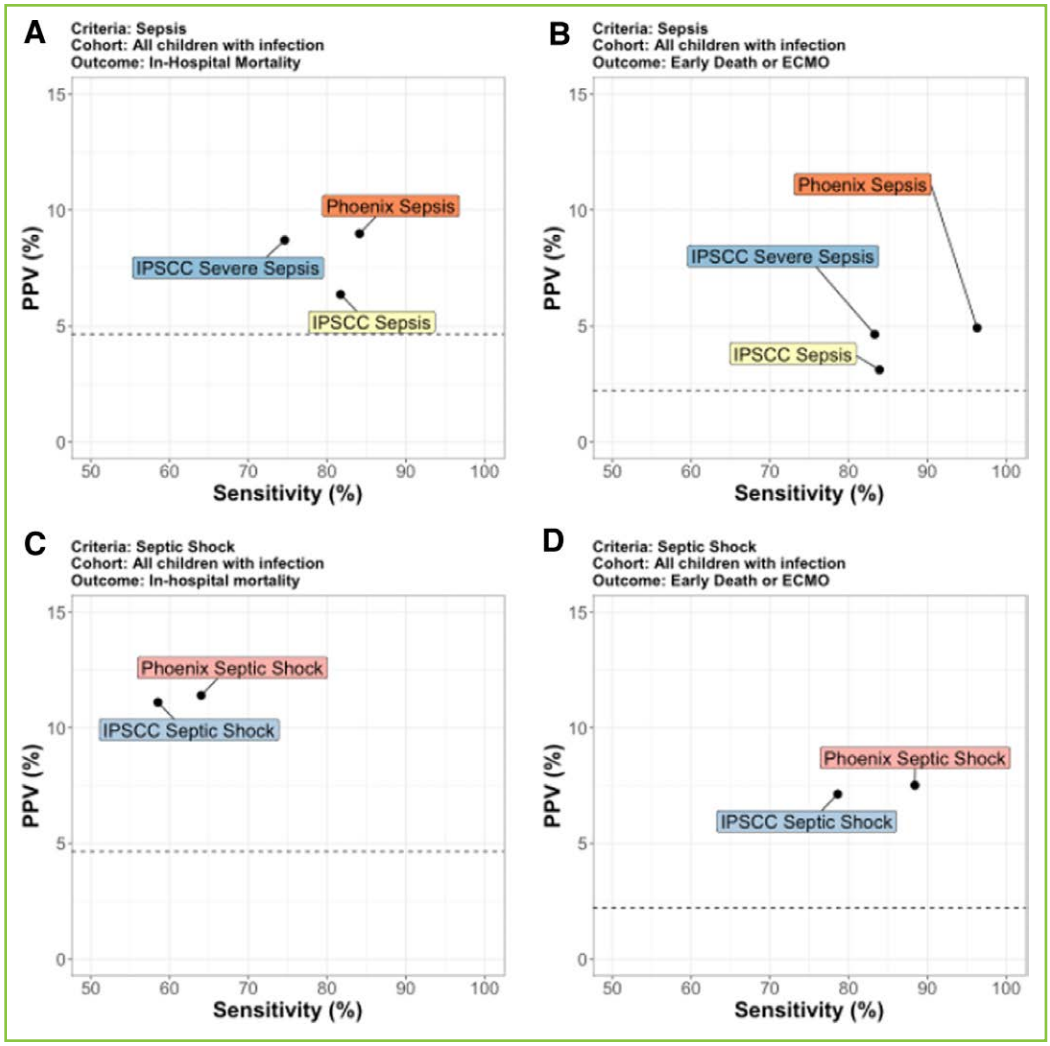

Figure 2. Performance of sepsis criteria. Comparison of the sensitivity and positive predictive value (PPV) of the criteria for sepsis based on the Phoenix criteria vs. the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria to discriminate in-hospital mortality (**A**) and early death or extracorporeal membrane oxygenation (ECMO) (**B**); the comparison of the criteria for septic shock based on Phoenix criteria vs. IPSCC criteria to discriminate in-hospital mortality (**C**) and early death or ECMO (**D**). The baseline rate of the outcome in each group (in-hospital mortality or early death or ECMO) is shown as a *horizontal dashed line*. These figures are similar to the area under the precision-recall curve except at a single threshold for criteria that generate a binary response (e.g., yes/no sepsis criteria met) instead of across the entire range of possible points in the curve. Better performing criteria on these figures will be closer to the *top right corner* of the figure.

primary outcome and higher performance for the secondary outcome in all subgroups.

Figure S4 (http://links.lww.com/PCC/C579) presents the performance stratified by age groups. Overall, the Phoenix criteria had higher performance for the primary outcome of in-hospital mortality across all age groups, although the difference was most notable in younger age groups. **Figure S5** (http://links.lww.com/PCC/C579) presents the performance stratified by culture positive vs. negative status, and again the Phoenix criteria had higher performance than the IPSCC criteria.

Among patients who met Phoenix criteria for sepsis, 3119 (27.9%) did not meet IPSCC criteria for SIRS (i.e., "SIRS-negative sepsis") and these had an in-hospital mortality of 4.7%. On the other hand, among patients who met IPSCC criteria for SIRS, 7167 (46.7%) did not meet Phoenix criteria for sepsis and these had a significantly lower in-hospital mortality rate of 1.7% ($p < 0.001$).

Sepsis With Remote Organ Dysfunction

Among patients with Phoenix criteria for sepsis, who had a positive microorganism isolated, 93% met criteria for sepsis with remote organ dysfunction criteria. Among the 7% of patients meeting Phoenix criteria for sepsis based only on organ dysfunction at the site of infection, the majority were due to moderate-to-severe respiratory dysfunction, and these had an in-hospital mortality of 3.3%.

Performance of Phoenix-8 Score and Severity of Illness at Admission

Phoenix-8 had comparable discrimination to the PRISM III score (AUROC, 0.84 [95% CI, 0.82–0.86] vs. 0.84 [95% CI, 0.83–0.86]; $p = 0.32$) and had better discrimination than PELOD-2 (0.81 [95% CI, 0.80–0.82];

AT THE BEDSIDE

- In U.S. children managed in nine PICUs, 2012–2018, we have found that in those with suspected or confirmed infection, the Phoenix criteria capture a significant proportion of high-risk patients who are missed by the IPSCC criteria.
- In the historical cohort, sepsis was associated with respiratory or bloodstream source of infection, most commonly due to *Pseudomonas aeruginosa* or *Staphylococcus aureus*.
- The Phoenix-8 score can be used as a measure of organ dysfunction burden across eight organ systems and as an alternative to other severity of illness scores at admission to the PICU.

$p < 0.001$) and pSOFA (0.82 [95% CI, 0.81–0.83]; $p < 0.001$). Among critically ill children with suspected or confirmed infections, the most common organ dysfunctions based on the Phoenix-8 score were respiratory (47%), followed by neurologic (33.8%), cardiovascular (30.4%), endocrine (28.3%), renal (21.3%), coagulation (20.4%), immunologic (16.8%), and hepatic (6.8%) (**Table S4**, http://links.lww.com/PCC/C579).

DISCUSSION

In this secondary analysis of a 2012–2018 dataset of admissions to nine PICUs in the United States, we have performed an external validation of the 2024 Phoenix criteria for sepsis and septic shock, the PSS, and the Phoenix-8 score. Our main findings are that: 1) the Phoenix criteria for sepsis and septic shock have higher performance than the IPSCC criteria to ascertain a life-threatening status in patients admitted with infection to the PICU as well as in all subgroup analyses and 2) the PSS had better or comparable performance based on AUPRC and AUROC to discriminate in-hospital mortality and early death or ECMO when compared with Phoenix-8, PELOD-2, pSOFA, IPSCC, and PODIUM criteria despite only requiring information about four organ systems.

Our findings are consistent with the original derivation and validation of the Phoenix criteria for sepsis and septic shock (3). Consistent with that study, we found that the sepsis criteria based on the PSS outperformed the IPSCC criteria, with sensitivity consistently higher than severe sepsis and PPV consistently higher than SIRS-based IPSCC sepsis. Similarly, septic shock criteria based on the Phoenix criteria had higher sensitivity and similar PPV when compared with the IPSCC septic shock criteria (3).

Our study makes several additional key contributions. First, we performed an external validation of the Phoenix criteria specifically in a large, diverse multicenter cohort of critically ill children with suspected or confirmed infection in the United States, albeit from 2012 to 2018. Second, we studied the performance of the Phoenix criteria in several important patient subgroups with major comorbidities commonly encountered in the PICU. We found that the Phoenix criteria generally outperformed the IPSCC criteria in patients with malignancy and those with technology dependence, but this was specifically notable in the secondary outcome of early death or ECMO. This outcome is likely to be more closely related to the sepsis episode than all-cause in-hospital mortality, which can occur later in the course and be secondary to other complications common in patients with major comorbidities. Third, we investigated the outcomes of patients who met Phoenix criteria for sepsis but were negative for SIRS-based IPSCC sepsis criteria. This "SIRS-negative sepsis" subgroup represented over a quarter of patients with Phoenix criteria for sepsis, and they had an in-hospital mortality significantly higher than those who met SIRS-based IPSCC sepsis criteria but were negative for Phoenix criteria (4.7% vs. 1.7%; $p < 0.001$), which was closer to the baseline mortality rate of patients without sepsis (1.3%). This phenomenon of "SIRS-negative sepsis" as a form of high-risk "occult" sepsis has been previously described in the adult sepsis literature (19), and perhaps accounts in part for the high rate of discordance between clinician-based diagnosis of sepsis and the diagnosis based on IPSCC criteria that has been observed in critically ill children around the world (20). Fourth, we found that patients with confirmed or suspected infection who died despite not meeting Phoenix criteria for sepsis in the first 24 hours had low organ dysfunction burden by any of the organ dysfunction scores studied, were disproportionately affected by a major comorbidity (including malignancy in close to half of the cases), and were most

likely to be admitted from the inpatient ward. Taken together, this suggests a more chronic, indolent course and a cause of mortality that in many cases could have been secondary to an underlying condition rather than sepsis. Fifth, we analyzed the microbiological profile of patients with sepsis and compared it with that of patients with infection in the PICU who did not meet Phoenix criteria for sepsis. We found that meeting criteria for sepsis was associated with bacterial infection from a respiratory or bloodstream source, especially due to *P. aeruginosa* and *S. aureus*. This information may be important when considering the type of empiric antimicrobials to use in patients with suspected sepsis, especially when used in combination with local antibiograms and considering patient comorbidities. Finally, we assessed the more comprehensive Phoenix-8 score as a measure of severity of illness at admission to the PICU. We found that the Phoenix-8 score had comparable performance to the PRISM III score, one of the most used severity of illness measures in critically ill children, and better performance than other common organ dysfunction scores. This suggests that the Phoenix-8 score may be useful for adjusting for baseline risk of mortality and to calculate standardized mortality ratios in children with confirmed or suspected infection in the PICU for clinical research and benchmarking purposes. Whether this can be extended to patients without infection remains to be studied.

Our study has several limitations. We used retrospective EHR data from 2012 to 2018 to perform our analyses, which may contain missing or erroneous data. However, we performed extensive data quality and harmonization in this dataset (9). Additionally, it is possible that the score may perform differently in a real-time implementation, where erroneous or delayed data entry may affect the accuracy and timeliness of the score (21). We also assessed the IPSCC septic shock criteria without considering the requirement for 40 mL/kg of fluids administered in 1 hour. However, this likely led to a conservative bias, as including that requirement would probably result in a decrease in the sensitivity of the IPSCC severe sepsis criteria, which was already lower compared with the Phoenix criteria. This is because an additional requirement would result in fewer patients meeting the IPSCC cardiovascular criteria, possibly including some with the outcome of interest. This is particularly relevant because fluid resuscitation practices have evolved over the years (22). Additionally, we did not consider chronic organ dysfunctions in the scoring, such as thrombocytopenia in patients with malignancy, which is a similar approach to the original 2024 Phoenix criteria study as well as the Sepsis-3 criteria in adults (3, 5). This may result in patients with these types of chronic organ dysfunctions having a lower threshold to meet sepsis criteria in the setting of a suspected infection and when meeting criteria for an additional point. However, given the higher baseline probability of sepsis in patients with chronic organ dysfunctions, this may not necessarily be a problem (e.g., a child with leukemia and preexisting thrombocytopenia who now has hypoxemia, hypotension, or requires vasoactives in the setting of a new infection would still be likely to be considered septic by clinicians). However, this needs to be further investigated in these patient populations. In addition, we only assessed hospital-acquired sepsis in patients who were transferred from the inpatient ward to the PICU with a confirmed or suspected infection after 72 hours, but we did not assess PICU-acquired sepsis, since we did not collect information for patients who were admitted without a suspicion of infection and later developed an infection during the PICU course. Finally, this was an external validation performed in U.S. academic medical centers and represents highly resourced settings. Additional validation in low-resource settings as well as other high-resource settings is warranted.

In conclusion, the Phoenix criteria for sepsis and septic shock outperformed the 2005 IPSCC criteria for sepsis, severe sepsis, and septic shock across all outcomes and subgroup analyses, including in children with different age groups and major comorbidities. Furthermore, the Phoenix criteria capture a significant proportion of high-risk patients missed by the IPSCC criteria (i.e., "SIRS-negative sepsis"). The accurate and timely diagnosis of sepsis and septic shock can be used for implementation of clinical best practices based on existing management guidelines (including fluid, ventilator, and nutritional management recommendations) (22), for quality benchmarking, for epidemiological surveillance, and for enrollment in clinical trials and other research studies. However, as discussed in the original articles, the Phoenix criteria are not intended for early recognition of possible or suspected sepsis nor to trigger the initiation of empirical antimicrobials and early organ support, which are especially important in

the outpatient and emergency setting (2, 3). Thus, additional work on developing and validating screening tools adapted to the local context and increasing the vigilance of clinicians and families through education and awareness campaigns is still critical in improving sepsis outcomes around the world. Finally, the more comprehensive Phoenix-8 score had good discrimination of poor outcomes in critically ill children with infections in the first 24 hours, comparable or better than validated and widely used severity scores, suggesting that its use as an organ dysfunction score with both descriptive and predictive value in this population may be of use in both research and clinical care use cases.

ACKNOWLEDGMENTS

We thank the late Dr. Hector Wong from Cincinnati Children's Hospital Medical Center, as well as Dr. Mark Hall from Nationwide Children's Hospital, Dr. Julie Bubeck-Wardenburg from Washington University, and Dr. Grace Chong from the University of Chicago for serving as site investigators and providing data to the original study.

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Drs. Sanchez-Pinto and Bennett were involved in concept and design. Dr. Sanchez-Pinto and Ms. Daniels were involved in analysis. Dr. Sanchez-Pinto was involved in drafting of article. All authors were involved in acquisition and/or interpretation of the data, revising article critically for important intellectual content, and final approval of the version to be published.

This work was supported by grant from the Eunice Kennedy Shriver *National Institute of Child Health and Human Development (R01 HD105939; principal investigators to Drs. Sanchez-Pinto and Bennett).*

Dr. Sanchez-Pinto's institution received funding from the National Institute of Child Health and Human Development (NICHD; R01 HD105939); he disclosed that they own stock in Ilyx, Saccharo, InnoSign, and Celldom. Drs. Sanchez-Pinto, Faustino, Shah, and Bennett received support for article research from the National Institutes of Health (NIH). Dr. Atreya's institution received funding from the National Institute of General Medical Sciences. Drs. Faustino's and Weiss's institutions received funding from the NIH. Dr. Khemani received funding from Orange Med/Nihon Kohden and Bayer Pharmaceuticals. Dr. Weiss' institution received funding from the Centers for Disease Control and Prevention (CDC). Dr. Bennett's institution received funding from the NICHD, the National Heart, Lung, and Blood Institute, the National Center for Advancing Translational Sciences, and the CDC. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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