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PEDIATRIC ORIGINAL

Prediction of pediatric sepsis mortality within 1 h of intensive care admission

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Abstract

Purpose: The definitions of sepsis and septic shock have recently been revised in adults, but contemporary data are needed to inform similar approaches in children.

Methods: Multicenter cohort study including children <16 years admitted with sepsis or septic shock to ICUs in Australia and New Zealand in the period 2012–2015. We assessed septic shock criteria at ICU admission to define sepsis severity, using 30-day mortality as outcome. Through multivariable logistic regression, a pediatric sepsis score was derived using variables available within 60 min of ICU admission.

Results: Of 42,523 pediatric admissions, 4403 children were admitted with invasive infection, including 1697 diagnosed as having sepsis/septic shock on admission. Mortality was 8.5% (144/1697) and 50.7% of deaths occurred within 48 h of admission. The presence of septic shock as defined by the 2005 consensus was sensitive but not specific in predicting mortality (AUC = 0.69; 95% CI 0.65–0.72). Combinations of hypotension, vasopressor therapy, and lactate >2 mmol/l discriminated poorly (AUC <0.60). Multivariate models showed that oxygenation markers, ventilatory support, hypotension, cardiac arrest, serum lactate, pupil responsiveness, and immunosuppression were the best-performing predictors (0.843; 0.811–0.875). We derived a pediatric sepsis score (0.817; 0.779–0.855), and every one-point increase was associated with a 28.5% (23.8–33.2%) increase in the odds of death. Children with a score ≥6 had 19.8% mortality and accounted for 74.3% of deaths. The sepsis score performed comparably when applied to all children admitted with invasive infection (0.810; 0.781–0.840).

Conclusions: We observed mortality patterns specific to pediatric sepsis that support the need for specialized definitions of sepsis severity in children. We demonstrated the importance of lactate, cardiovascular, and respiratory derangements at ICU admission for the identification of children with substantially higher risk of sepsis mortality.

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Take-home message: We observed mortality patterns specific to pediatric sepsis which indicate the need for pediatric-specific sepsis definitions. Applying the 2005 criteria for septic shock was sensitive but not specific in predicting sepsis mortality. We demonstrate the relevance of lactate, cardiovascular, and respiratory derangements at ICU admission to identify children with substantially higher sepsis mortality; a simple derived pediatric sepsis score, based on variables known within 60 min of ICU admission, was able to identify children with sepsis at substantially higher risk of mortality.

The investigators of the ANZICS CORE and PSG groups are fully listed in the ESM 2.

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Keywords: Childhood, Mortality, Infection, Sepsis, Septic shock

Introduction

The concept of sepsis has recently undergone a major revision and is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In the 2015 Sepsis-3 consensus statement, the definition of septic shock encompasses a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [1–3]. The recent recommendations recognize the need for easily accessible clinical parameters providing meaningful information on disease severity to allow rapid patient stratification [4]. These revised septic shock definitions were established on the basis of systematic reviews, a Delphi process, and testing in three independent adult patient cohorts, and focused on hypotension, need for vasopressor therapy, and hyperlactatemia as the key features of septic shock. In contrast, the current pediatric sepsis consensus definition published in 2005 require either hypotension, or vasopressor therapy, or hyperlactatemia in addition to other markers of decreased organ perfusion [5]. These 2005 pediatric septic shock definitions have not been validated and there is a lack of recent data on pediatric sepsis to inform the revision of shock definitions specific to pediatric age groups. Prevalence and mortality of septic shock in children are comparable to adults [6–8], but the evidence for treatment benefit of sepsis management in children is limited [9–11]. Recent studies have challenged the positive predictive value of traditional criteria for sepsis and septic shock, indicating a need for improved sepsis severity definitions in children [12, 13].

We hypothesized that the majority of pediatric sepsis mortality occurs early, and that rapidly available clinical parameters can discriminate children with sepsis at much higher mortality already at ICU admission. The first aim of this study was to characterize patterns of mortality in a contemporary binational cohort of children. The second aim was to test the predictive value of the 2005 septic shock definition in comparison to combinations of hypotension, vasopressor requirement, and hyperlactatemia in identifying pediatric patients at high risk of mortality at ICU admission. The third aim was to develop a simple prediction model for sepsis mortality using variables known within 60 min of ICU admission to provide a tool for rapid patient stratification based on sepsis severity.

Methods

Patients

We performed a multicenter binational cohort study of patients below 16 years admitted to PICU or general ICU in Australia and New Zealand between 1 January 2012 and 31 December 2015 using the Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry [7, 14]. The study was approved by the Human Research and Ethics Committee (Mater Health Services, Brisbane, Australia). Only non-elective admissions were included.

Definitions

Patients were eligible if they had either sepsis and/or septic shock (including toxic shock) as the principal diagnosis or as the underlying diagnosis at ICU admission, or if they had any invasive infection (including meningitis, pneumonia/pneumonitis, peritonitis, necrotizing fasciitis, osteomyelitis, endocarditis, tracheitis, epiglottitis) and also had sepsis and/or septic shock (including toxic shock) in any other diagnostic field. Sepsis and septic shock were prospectively captured in the registry data forms throughout the study period according to the 2005 consensus definition [5]: The coding for septic shock required the presence of systemic inflammatory response syndrome (SIRS) and suspected or proven infection in the presence of cardiovascular organ dysfunction.

In view of previously reported discrepancies between physician-based sepsis diagnosis and consensus definitions [15], findings obtained in this sepsis/septic shock cohort were tested in a larger cohort of 4403 patients admitted to ICU with any invasive infection, independently of whether they were coded as sepsis or septic shock on admission. Invasive infections were defined as meningitis, pneumonia/pneumonitis, peritonitis, necrotizing fasciitis, osteomyelitis, endocarditis, tracheitis, epiglottitis, sepsis, septic shock, or toxic shock as the principal diagnosis or as the underlying diagnosis at ICU admission.

The primary outcome was mortality within 30 days of ICU admission. The 30-day mortality was calculated using length of stay in ICU and length of stay in hospital for patients that died in ICU or in hospital. Data on ICU and hospital length of stay, and mortality in ICU and in hospital were available for 100% of patients. We performed sensitivity analyses using ICU mortality and hospital mortality as outcomes (Supplementary Table 1). Patients discharged home alive from the hospital before 30 days were assumed to have survived.

Population data were accessed through the Australian Bureau of Statistics (http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/3ADCB8E8492A9156CA25808900122529?opendocument)

Table 1 Baseline, severity characteristics, and pathogens in 1697 children admitted to Intensive Care Units with sepsis and septic shock. Characteristics of all 4403 children admitted with invasive infections are shown for comparison

Characteristic	Sepsis or septic shock on admission *N* = 1697	Septic shock as per 2005 consensus definitions[a] *N* = 748	Invasive infection on admission[b] *N* = 4403
Age			
Median (IQR)	1.65 (0.20–7.51)	3.15 (0.55–9.76)	2.1 (0.62–6.68)
Neonates <28 days	12.6% (213)	7.6% (57)	6.7% (295)
Infants (28–364d)	29.9% (507)	24.9% (186)	24.9% (1097)
1–4 years	24.9% (422)	26.2% (196)	36.8% (1618)
5–9 years	13.8% (234)	16.7% (125)	16.0% (706)
10–15 years	18.9% (321)	24.6% (184)	15.6% (687)
Sex			
% Male	55.9% (949)	55.0% (411)	55.5% (2442)
Category			
PICU admission[d]	78.9% (1339)	73.8% (552)	75.5% (3325)
Interhospital transport	35.5% (603)	38.9% (291)	34.5% (1520)
Indigenous status			
Indigenous or Torres Strait Islander	14.4% (243)	16.1% (120)	12.8% (559)
Risk category			
Immuno-deficiency or –suppression[e]	15.2% (258)	15.6% (117)	8.2% (360)
Chronic neurological	7.8% (132)	8.4% (63)	15.0% (660)
Chronic respiratory	2.5% (42)	2.3% (17)	6.0% (264)
Congenital heart disease	5.7% (97)	3.5% (26)	5.1% (225)
Prematurity	10.6% (180)	7.6% (57)	8.8% (387)
Chronic renal failure	1.3% (22)	2.0% (15)	0.7% (27)
Any comorbidity	48.8% (828)	47.1% (352)	44.0% (1937)
Severity			
Mean PICU length of stay (SD)	6.40 (8.59)	6.40 (8.59)	4.72 (7.47)
Mechanical ventilation in the first hour	38.4% (652)	51.1% (382)	37.5% (1649)
Extracorporeal membrane oxygenation	2.4% (40)	4.4% (33)	1.2% (54)
PIM2 (mean probability of death)	6.66% (12.89)	10.5% (17.33)	4.43% (9.13)
30-day mortality	8.5% (144)	15.1% (113)	5.2% (227)
Pathogen group			
Pathogen			
Bacteria			
N. meningitidis	5.2% (89)	8.4% (63)	2.5% (112)
S. pneumoniae	2.4% (40)	2.8% (21)	2.9% (129)
S. aureus	9.5% (162)	11.6% (87)	5.9% (262)
Group A *Streptococcus, viridans streptococcus*	6.2% (105)	7.4% (55)	1.5% (64)
Group B *streptococcus*	2.9% (49)	2.3% (17)	2.6% (113)
E. coli	4.8% (82)	4.1% (31)	2.1% (91)
Pseudomonas aeruginosa	2.1% (36)	3.2% (24)	11.5% (508)
Other bacteria	13.6% (247)	3.6% (27)	2.5% (112)
Sum of patients with bacterial diagnosis	42.7% (724)	49.3% (369)	2.9% (129)
Fungal			
Fungal (*Candida, Aspergillus* spp, other fungal)	2.5% (42)	2.7% (20)	5.9% (262)
Virus			
Sum of patients with viral coinfection	13.0% (221)	12.8% (96)	21.9% (965)

Table 1 continued

Characteristic	Sepsis or septic shock on admission *N* = 1697	Septic shock as per 2005 consensus definitions[a] *N* = 748	Invasive infection on admission[b] *N* = 4403
No identified organism			
No bacterial, fungal, or viral organism identified	48..9% (829)	43.3% (324)	55.0% (2420)

PICU pediatric intensive care unit, *BMT* bone marrow transplant, *PIM2* paediatric index of mortality 2

[a] Arterial hypotension (5th percentile for age), or need for vasoactive drug to maintain BP in normal range, or two of the following: unexplained metabolic acidosis: base deficit < minus 5.0 mEq/L; increased arterial lactate >2 times upper limit of normal; oliguria: urine output <0.5 mL/kg/h; prolonged capillary refill: >5 s; core to peripheral temperature gap >3 °C [17]

[b] Invasive infection: meningitis, pneumonia/pneumonitis, peritonitis, necrotizing fasciitis, osteomyelitis, endocarditis, tracheitis, epiglottitis, sepsis, septic shock, or toxic shock as the principal diagnosis or as the underlying diagnosis at ICU admission

[c] *p* value based on Two-sample Wilcoxon rank-sum (Mann–Whitney) test

[d] Remaining admissions were to mixed ICUs

[e] Defined as either primary immunodeficiency and secondary immunodeficiency, including bone marrow transplants, oncology patients under active treatment, other solid organ transplant patients, systemic immunosuppressions such as for rheumatologic disease

and Statistics New Zealand (http://www.stats.govt.nz/estimates-projections).

Statistics

Data are presented as percentages and numbers or means with standard deviation. *T* tests were used to compare normally distributed data, Wilcoxon rank-sum tests for skewed data, and χ^2 tests for categorical data by subgroups. We examined time to death using Kaplan–Meyer survival curves and made comparisons using the log-rank test.

In the absence of a true gold standard for septic shock, we compared the predictive performance of different criteria for identifying patient groups at higher risk of mortality [2], using four approaches: (1) the 2005 (Sepsis-2) pediatric consensus septic shock definition [5]; (2) six combinations of either hypotension, vasopressor requirement, and serum lactate levels >2 mmol/l) [1, 2]; (3) a multivariable logistic prediction model; (4) a derived pediatric sepsis score model. We compared the performance of different severity definitions for all patients, and for the subgroup of patients with and without comorbidities. Findings from the sepsis/septic shock cohort were then tested in the larger invasive infection cohort. In each group, we assessed the discrimination of the model by measuring the corresponding receiver operating characteristics area under the curves (AUC). The Hosmer–Lemeshow goodness of fit test was used to assess calibration and a non-significant test result was considered to indicate good calibration.

Sepsis mortality prediction models were developed using a stepwise unbiased logistic regression approach. Mortality prediction models were based on patient characteristics, physiological parameters, and treatment interventions available within 60 min of ICU admission. In sepsis episodes where PaO_2/FiO_2 ratio was not available during the first hour of admission, SpO_2/FiO_2 ratio was transformed into PaO_2/FiO_2 as previously described [16]. Ventilation during the first hour of admission was defined as provision of either invasive or non-invasive ventilation. Arterial hypotension was defined as systolic blood pressure <5th percentile for age and sex [17]. The data collection rules for physiologic data were based on the data collection rules for PIM; data represented the first value of each variable measured within the period from the time of first face-to-face contact between the patient and a doctor from the ICU or a doctor from a specialist pediatric transport team to 1 h after arrival in the ICU. We used a backward stepwise elimination procedure to eliminate non-significant predictors based on $p > 0.05$. A sepsis scoring system was derived from multivariate models by allocating scores between 0 and 10 based on the model coefficient to each of the variables in the final multivariate model. To keep the points system simple, continuous variables were cut so that the log odds of each continuous range covered the existing coefficients for categorical variables. Where appropriate, we used cutoffs for continuous variables using thresholds published in validated scoring systems [1, 18, 19]. If a variable was not measured, it was assumed to be normal [18]. All analyses were conducted using Stata (version 14.0, Stata Corp, College Station, Texas, USA). *p* values less than 0.05 were considered significant.

Results

Cohort description and severity on admission as per 2005 and 2015 septic shock definition

During the 4-year study period, 42,523 patients under 16 years were admitted to ICU. Of all non-elective admissions (28,759), 4403 (15.3%) were admitted because of an

invasive infection, including 1697 (5.9%) patients coded as sepsis on admission (Table 1). A total of 748 children with sepsis (44.1%) met septic shock criteria as per the 2005 consensus definition. Of all patients with sepsis, 869 (51.2%) did not have a major underlying comorbidity. Mortality was 5.2% (227/4403) for all invasive infections, 8.5% (144/1697) for sepsis/septic shock, and 15.1% (113/748) for septic shock. Overall, 132/144 (91.7%) sepsis/septic shock deaths occurred in ICU.

Patterns of death and presence of shock criteria

Among all patients admitted with sepsis/septic shock that died, the median time from ICU admission to death was 1.9 days; 36.8% (53/144) died within 24 h and 50.7% (73/144) died within 48 h (Supplementary Fig. 1). In children without comorbidities, the median time to death was 16 h with 54.5% dying within 24 h and 72.7% within 48 h. Although the survival curves were significantly different for children presenting with shock as defined by the 2005 consensus statement at ICU admission ($\chi^2 = 69.62$, $p < 0.001$), prediction of 30-day mortality demonstrated modest discrimination (AUC = 0.69; 95% CI 0.65–0.72). While the sensitivity (78.5%) and negative predictive value (96.7%) were good, the specifity and positive predictive value were low (59.1% and 15.1%, respectively, Supplementary Table 1). When testing the predictive validity of six potential septic shock groups, defined by combinations of hypotension, vasopressor therapy, and hyperlactatemia (>2 mmol/l) at ICU admission, performance was worse than the 2005 definition (AUC <0.60, Supplementary Table 1), with the highest mortality observed in children presenting with hypotension requiring vasopressors and lactate >2 mmol/l (32.0%).

Mortality was independently correlated with lactate on presentation to ICU (Fig. 1, Supplementary Table 2): A lactate of ≥2, ≥ 3, or ≥4 mmol/l on admission was associated with an adjusted respective mortality of 7.4, 8.4, and 9.5% in children presenting with sepsis or septic shock.

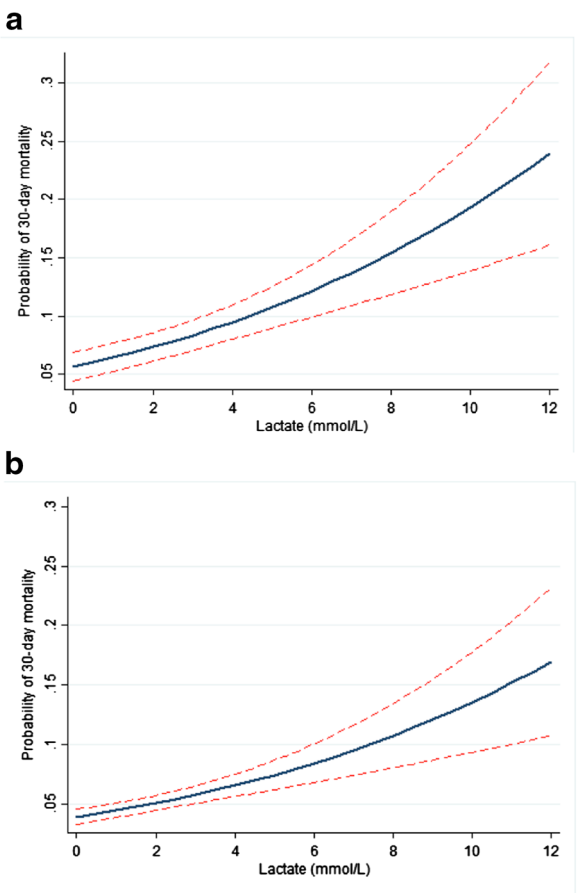

Fig. 1 Adjusted 30-day mortality prediction for serum lactate levels at admission to ICU in children admitted with sepsis/septic shock on admission (**a**, $N = 1697$) and in all children admitted with invasive infections (**b**, $N = 4403$). Adjusted mortality risk is shown for each lactate level with the corresponding 95% confidence intervals. The probability of mortality for each lactate serum level was adjusted on the basis of the simplified model, including PaO_2/FiO_2, ventilation during the first hour, systolic blood pressure <5th percentile for age, cardiac arrest pre admission, pupils, and immunosuppression. Arterial, venous, and capillary lactate measurements were used

Development of logistic mortality prediction model

We developed prediction models for sepsis mortality using variables known within no more than 60 min after ICU admission. Multivariate models showed that oxygenation markers, ventilatory support in the first hour, arterial hypotension (systolic blood pressure <5th percentile [17]), cardiac arrest preceding ICU admission, serum lactate, and bilaterally dilated unresponsive pupils were the best performing organ-specific predictors of mortality (Table 2). The presence of immunosuppression was independently associated with mortality. The final multivariate model predicted sepsis mortality with an AUC of 0.843 (95% CI 0.811–0.875), and observed and predicted mortality were similar across deciles of risk (goodness of fit; $\chi^2 = 6.45$, $p = 0.597$).

Derived pediatric sepsis score

We then derived a pediatric sepsis score from the simplified prediction model using seven parameters known within 60 min of ICU admission. We allocated scores of 0 to 10 for each predictor, based on the coefficient in the multivariable model (Table 3). The performance of this novel score was comparable to the multivariate models (AUC 0.817, 95% CI 0.779–0.855, Fig. 2), with every point increase in the score associated with a 28.5% (95%

Table 2 Uni- and multivariate prediction models for 30-day mortality in children admitted to ICU with sepsis and septic shock

Predictor variable		Univariate model		Multivariate model		Multivariate model	
				Full model		Simplified model	
Group	**Predictor**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Respiratory	FiO_2/PaO_2 ratio[a]	2.763 (2. 076–3.676)	<0.001	1.672 (1.201–2.327)	0.002	1.687 (1.211–2.349)	0.002
	Ventilation during the first hour	3.711 (2.580–5.338)	<0.001	2.090 (1.320–3.311)	0.002	1.909 (1.215–3.001)	0.005
Circulatory	Systolic BP <5th percentile	3.240 (2.234–4.698)	<0.001	1.782 (1.155-2.749)	0.009	1.882 (1.225–2.891)	0.004
	Cardiac arrest pre admission	9.473 (5.142–17.451)	<0.001	2.540 (1.170–5.515)	0.018	2.740 (1.263–5.944)	0.011
	Shock on admission based on 2005 consensus definition	5.270 (3.497–7.941)	<0.001	2.483 (1.558–3.956)	<0.001	2.501 (1.573–3.977)	<0.001
Metabolic	Lactate (mmol/l)	1.287 (1.223–1.349)	<0.001	1.177 (1.117–1.240)	<0.001	1.176 (1.116-1.238)	<0.001
Neurologic	Dilated, unresponsive pupils	143.441 (18.607–1111.783)	<0.001	45.489 (4.882–423.828)	0.001	48.826 (5.202–458.310)	0.001
Patient factor	Immunosuppression[b]	1.834 (1.217–2.763)	0.004	3.271 (2.002–5.344)	<0.001	3.187 (1.964–5.170)	<0.001
	Readmission	1.000 (1.000–1.001)	0.235	1.001 (1.000–1.001)	0.014	NA	NA
	Retrieval	1.208 (0.852–1.714)	0.289	NA			
	Male	0.819 (0.582–1.153)	0.253	NA			
	Admission from operating room	0.205 (0.050–0.838)	0.027	0.157 (0.029–0.847)	0.031	NA	NA
Model performance	Patient group	ROC AUC	*p* value	ROC AUC		ROC AUC	
	All patients ($N = 1697$)	NA	NA	0.843 (0.811–0.875)		0.834 (0.801–0.867)	

Table 2 continued

Predictor variable		Univariate model		Multivariate model			Multivariate model	
				Full model			Simplified model	
Group	Predictor	OR (95% CI)	*P* value	OR (95% CI)	*p* value		OR (95% CI)	*p* value
No comorbidity ($N = 869$)	NA		NA	0.908 (0.872–0.945)			0.898 (0.855–0.942)	
With comorbidity ($N = 828$)	NA		NA	0.781 (0.731–0.831)			0.771 (0.721–0.821)	

OR odds ratio, *CI* confidence interval, *BP* blood pressure, *ROC AUC* area under the curve of receiver operating characteristics test

[a] PaO_2/FiO_2 ratios were calculated if both were measured; derived PaO_2/FiO_2 ratios were calculated if only $SatO_2/FiO_2$ was available. Values were assumed to be normal (score = 0) if no measure was available

[b] Including primary immunodeficiency and secondary immunodeficiency (bone marrow transplant, oncology, transplant, other immunosuppressions)

CI 23.8–33.2%) increase in the relative odds of mortality. The goodness of fit test indicated adequate calibration ($\chi^2 = 3.65$, $p = 0.601$). The score performed better in children without comorbidities (AUC 0.877, 95% CI 0.824–0.931) than children with comorbidities (AUC 0.751, 95% CI 0.695–0.806). The score performed better than PIM2 and PIM3 in all patients (PIM2 AUC 0.763, 95% CI 0.719–0.807; PIM3 0.775, 95% CI 0.730–0.819), in previously healthy patients (PIM2 0.836, 95% CI 0.773–0.898; PIM3 0.843, 95% CI 0.782–0.904), and in children with comorbidities (PIM2 0.700, 95% CI 0.639–0.761; PIM3 0.710, 95% CI 0.647–0.772).

Application to all admissions with invasive infection

To assess if the model discriminated infected patients at risk of death irrespective of whether they were defined as having sepsis on admission, we then applied the sepsis score to all children admitted with any invasive infection to ICU ($N = 4403$, Fig. 2d). The discrimination of the score among all children with invasive infection was highly comparable to those in the sepsis cohort (AUC 0.810, 95% CI 0.781–0.840). Each one-point increase in the score was associated with a 31.3% (95% CI 27.5–35.3%) increase in the relative odds of mortality, with better performance observed in children without comorbidities ($N = 2466$, AUC 0.876, 95% CI 0.828–0.923) compared to children with comorbidities ($N = 1937$, AUC 0.742, 95% CI 0.701–0.782).

Stratification of patients into mortality risk classes

We then used the pediatric sepsis score to establish cutoffs defining five bands of sepsis severity: very low, low, moderate, high, and very high risk of mortality at ICU admission, translating into crude mortalities ranging from 1.3 to 49.5% (Fig. 2 and Supplementary Table 3). Patients with a pediatric sepsis score of 6 and higher represented 31.9% of all sepsis admissions and accounted for 74.3% of all sepsis deaths with a crude mortality of 19.8%. These increased risk groups represented 1.27% (541/42,523) of all ICU admissions and occurred at a population-based average annual incidence of 2.39/100,000 children aged less than 16 years.

Discussion

Meaningful definitions of sepsis severity have to reliably capture a subset of patients where severe physiological derangements lead to substantially greater mortality risk [1–3, 20]. We demonstrate in a contemporary binational prospective cohort that the majority of fatal pediatric septic shock presentations are fulminant, with 3 out of 4 deaths in previously healthy children occurring within 48 h of ICU admission. Therefore, severity definitions need to be applicable very early upon presentation to ICU

Table 3 Statistically derived pediatric sepsis score

	Definition	Points by severity level			
		0	3	5	10
Respiratory	PaO_2/FiO_2 ratio	≥300	100 to <300	<100	
	Ventilation during the first hour	No	Yes		
Circulatory	Systolic BP <5th percentile				
	<12 months		<65		
	>1 to <2 years		<67 (M), <68 (F)		
	>2 to <3 years		<70 (M), <71 (F)		
	>3 to <4 years		<73 (M), <71 (F)		
	>4 to <5 years		<75 (M), <74 (F)		
	>5 to <6 years		<78 (M), <76 (F)		
	>6 to <7 years		<78 (M), <78 (F)		
	>7 to <8 years		<79 (M), <78 (F)		
	>8 to <9 years		<82 (M), <81 (F)		
	>9 to <10 years		<82 (M), <83 (F)		
	>10 to <11 years		<85 (M), <85 (F)		
	>11 to <12 years		<87 (M), <85 (F)		
	>12 to <13 years		<89 (M), <87 (F)		
	>13 to <14 years		<90 (M), <90 (F)		
	>14 to <15 years		<94 (M), <92 (F)		
	>15 to <16 years		<95 (M), <93 (F)		
	Cardiac arrest pre admission	No		Yes	
Metabolic	Lactate (mmol/l)	<3.0	3.0 to <6.0	6.0 to <10.0	≥10.0
Neurologic	Pupils	Both reactive			Both dilated, unresponsive

PaO_2/FiO_2 ratios were calculated if both were measured; derived PaO_2/FiO_2 ratios were calculated if only $SatO_2/FiO_2$ was available. Values were assumed to be normal (score = 0) if no measure was available

BP blood pressure

to prevent morbidity and mortality, as late recognition of septic shock is associated with worse outcomes [21]. Although shown to be sensitive, the 2005 septic shock consensus criteria—which essentially capture presence of hypotension *or* vasopressor therapy *or* hyperlactatemia—were not designed to predict mortality. In the Delphi process used for the development of the adult Sepsis-3 consensus definitions, key features of septic shock agreed upon were the presence of arterial hypotension *and* vasopressor therapy *and* hyperlactatemia. When assessing six combinations of potential septic shock groups on the basis of these three criteria in our cohort, such definitions failed to identify many children who died. We therefore developed a pediatric sepsis score based on a small set of parameters that are easily available to clinicians and researchers within 60 min of ICU admission and which predicted sepsis mortality with greater accuracy than PIM3 [14]. Our findings demonstrate that discrimination of infected patients at risk of death is possible irrespective of whether they were defined as having sepsis or not, which may inform the translation of Sepsis-3 into meaningful pediatric sepsis severity definitions [1].

Using an unbiased approach, we demonstrated the key relevance of respiratory, cardiovascular, metabolic, and neurologic parameters to capture sepsis severity. Pediatric recommendations for sepsis management [22, 23] consider arterial hypotension as a late sign of pediatric septic shock with poor sensitivity. A recent pediatric European study based on a Delphi approach showed good discrimination when refractory septic shock was defined using a combination of worst lactate >8 mmol, worst vasopressor–inotropic score >200, and myocardial dysfunction [24]. Increasing levels of lactate were strongly and independently associated with the risk of mortality in our study [18, 25–28]. We were unable to assess the impact of renal or hepatic failure on lactate. Further independent predictors of sepsis mortality were the need for respiratory support, (derived) PaO_2/FiO_2 ratio, and presence of immunosuppression—the latter representing an increasing cohort of ICU patients [29]. While definitions of cardiorespiratory, metabolic, and neurologic variables of our derived score show similarity with validated scoring systems, including the SOFA score [1] and the pediatric logistic organ dysfunction score-2 (PELOD-2) [18],

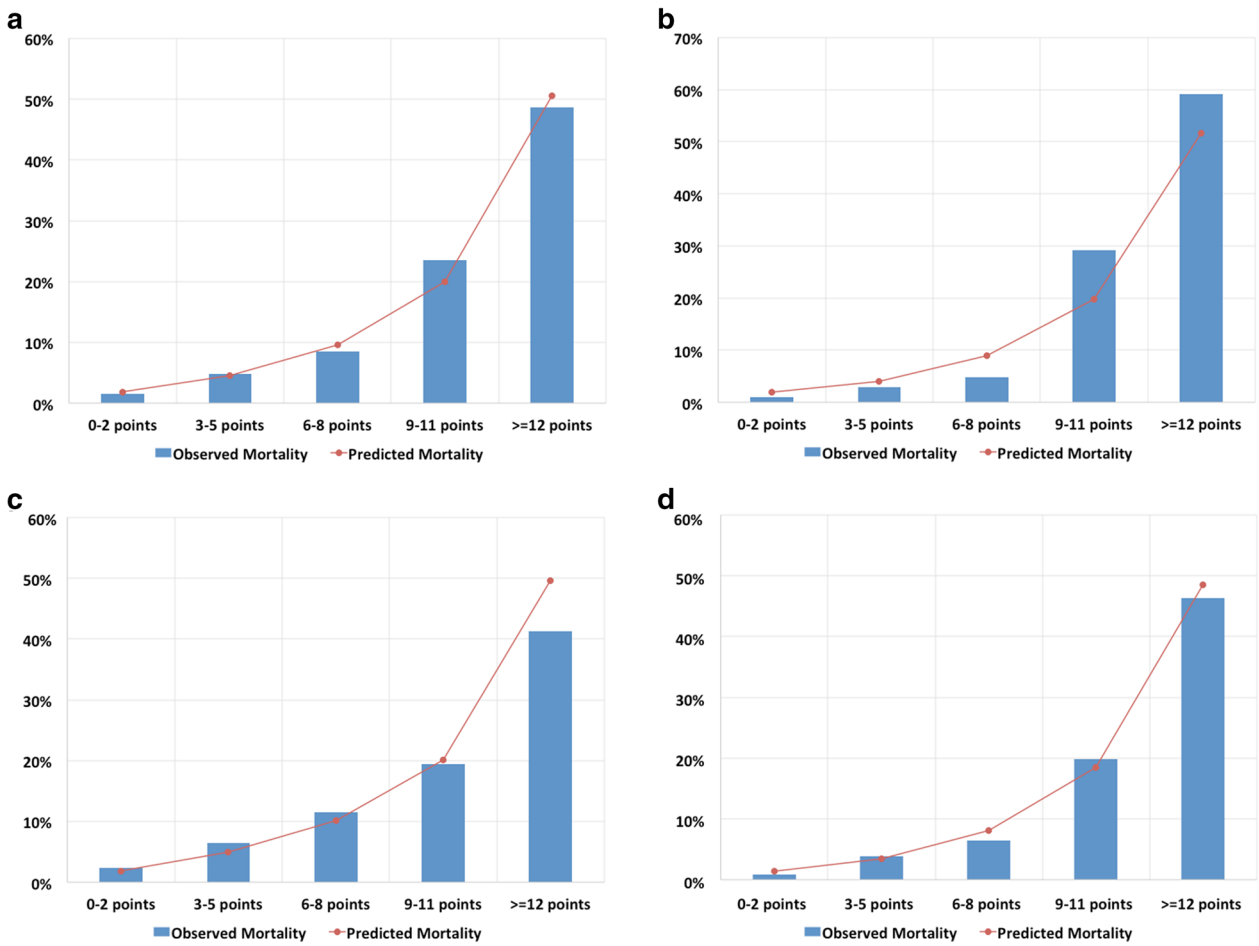

Fig. 2 Observed and predicted 30-day mortality in children admitted to ICU based on pediatric sepsis score are shown. **a** All patients with sepsis/septic shock, **b** sepsis/septic shock patients with no comorbidity, **c** sepsis/septic shock patients with comorbidities, **d** all patients with invasive infection

the study dataset did not include platelet count, serum bilirubin, or creatinine on ICU admission, which is an important limitation. However, the categorizations used in the SOFA score refer to "worst in 24 h" parameters and are specific for adults, and the complexity of SOFA may represent challenges in resource-limited settings [30, 31].

In our study, 51% of pediatric sepsis deaths, including 73% of deaths in previously healthy children, occurred within 48 h of ICU admission. While we did not have access to data on pre-ICU sepsis-related mortality, our results are in agreement with a previous study in the UK, which observed that 55% of fatalities happened within 24 h of ICU referral [32]. This pattern of early mortality implies that trials addressing early sepsis mortality will need to identify eligible patients, consent, randomize, and start interventions within a very short time frame. Currently, extracorporeal life support may represent the only therapy capable of rapid hemodynamic stabilization in refractory septic shock [27, 33]. Pathogen virulence, host susceptibility, such as undiagnosed primary immunodeficiencies [34], and delays in initiation of antimicrobial and shock treatment [21] have been shown to account for fulminant presentations.

Strengths of this study include the population-based design using a contemporary large binational prospective ICU dataset, which includes 94% of all children below 16 years of age requiring intensive care, thereby reducing selection bias. In contrast to previous sepsis outcome studies reporting on the worst abnormal value during a 24-h period [18, 24, 35], we restricted analyses to variables known within a maximum of 60 min after ICU admission, emphasizing the need for early accurate identification of patient groups for targeted interventions. Considering the high proportion of very early sepsis deaths, severely deranged physiological parameters persisting beyond the first hours of admission may represent

a description rather than prediction of death. Given concerns of validity of sepsis coding [15, 36], we tested findings from the sepsis/septic shock cohort in a larger cohort of children admitted with invasive infections. Of note, rapid clinical severity stratifications may be combined with biomarker-based scoring systems for future clinical trials to select subgroups most likely to benefit from targeted interventions [37, 38].

A number of limitations need to be considered, as this study used data prospectively collected for the binational registry rather than data specifically collected for sepsis research. The 2005 consensus definitions are provided in the data collection manual and training material; however, discrepancies in clinical diagnosis of sepsis and the diagnosis based on the consensus guidelines have been described [4, 15]. The registry audits of data quality did not allow us to specifically compare the reliability of sepsis coding across different hospitals and data collectors. The performance of the logistic model and score for sepsis outcome prediction was assessed in the population used to develop them and will require independent validation. Finally, using mortality as outcome does not capture the impact of sepsis on patients surviving with major long-term morbidity.

In conclusion, we observed that 2005 septic shock definitions, while sensitive, discriminated poorly to predict sepsis mortality. We demonstrated that a few variables available within 60 min of ICU admission, in particular lactate, can stratify children into sepsis groups at substantially higher risk of mortality. Further research on the role of lactate monitoring in sepsis management algorithms is warranted [39]. Our findings indicate that meaningful and rapid severity classification can be achieved within an hour of PICU admission using simple cardiorespiratory and metabolic indicators. These should be considered when establishing revised definitions for septic shock in children.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-017-4701-8) contains supplementary material, which is available to authorized users.

Abbreviations
BMT: Bone marrow transplant; ECMO: Extracorporeal membrane oxygenation; OR: Odds ratio; PICU: Pediatric intensive care unit; PIM: Pediatric index of mortality; SSC: Surviving Sepsis Campaign; SOFA: Sequential (Sepsis-related) Organ Failure Assessment.

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Compliance with ethical standards

Conflicts of interest
This work was supported by a Clinical Research Seeding Grant from Mater Research Institute—The University of Queensland. Dr Straney receives salary support from the National Medical Health and Research Council (NHMRC) Australian Resuscitation Outcomes Consortium (Aus-ROC) Centre of Research Excellence #1029983 (https://www.ausroc.org.au).

Ethical approval
The study was based on existing dataset and performed according to the Helsinki declaration.

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