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Validation of a paediatric sepsis screening tool to identify children with sepsis in the emergency department: a statewide prospective cohort study in Queensland, Australia

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ABSTRACT

Objective The Surviving Sepsis Campaign guidelines recommend the implementation of systematic screening for sepsis. We aimed to validate a paediatric sepsis screening tool and derive a simplified screening tool.

Design Prospective multicentre study conducted between August 2018 and December 2019. We assessed the performance of the paediatric sepsis screening tool using stepwise multiple logistic regression analyses with 10-fold cross-validation and evaluated the final model at defined risk thresholds.

Setting Twelve emergency departments (EDs) in Queensland, Australia.

Participants 3473 children screened for sepsis, of which 523 (15.1%) were diagnosed with sepsis.

Interventions A 32-item paediatric sepsis screening tool including rapidly available information from triage, risk factors and targeted physical examination.

Primary outcome measure Senior medical officer-diagnosed sepsis combined with the administration of intravenous antibiotics in the ED.

Results The 32-item paediatric sepsis screening tool had good predictive performance (area under the receiver operating characteristic curve (AUC) 0.80, 95% CI 0.78 to 0.82). A simplified tool containing 16 of 32 criteria had comparable performance and retained an AUC of 0.80 (95% CI 0.78 to 0.82). To reach a sensitivity of 90% (95% CI 87% to 92%), the final model achieved a specificity of 51% (95% CI 49% to 53%). Sensitivity analyses using the outcomes of sepsis-associated organ dysfunction (AUC 0.84, 95% CI 0.81 to 0.87) and septic shock (AUC 0.84, 95% CI 0.81 to 0.88) confirmed the main results.

Conclusions A simplified paediatric sepsis screening tool performed well to identify children with sepsis in the ED. Implementation of sepsis screening tools may improve the timely recognition and treatment of sepsis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study identified the screening criteria which were most predictive of paediatric sepsis and derived a simplified sepsis screening tool.
⇒ This study validated a paediatric sepsis screening tool used in a statewide quality improvement initiative, thereby addressing a key gap highlighted by the 2020 Surviving Sepsis Campaign.
⇒ Although the screening tool performed well, the average acuity of the cohort was low, consistent with contemporary paediatric cohorts in the emergency department.
⇒ Limitations include risk of selection bias, and the study was not designed to demonstrate patient-centred outcome benefits of applying the sepsis tool.
⇒ These finding require external validation, particularly in low-income and middle-income settings.

INTRODUCTION

Survival of patients with sepsis strongly depends on timely recognition and initiation of treatment.[1 2] In neonates and children, sepsis remains accountable for an estimated three million annual deaths, and mortality rates of those requiring admission to intensive care continue to be high.[3 4] The WHO and the Global Sepsis Alliance highlight the importance of improving the early recognition of sepsis.[5] The 2020 paediatric Surviving Sepsis Campaign guidelines specifically recommend that healthcare institutions implement systematic screening of children who present acutely unwell to enhance the time-critical recognition of septic shock and other sepsis-associated organ dysfunction, based on very low quality evidence.[6]

Although observational evidence indicates the benefit of protocolised care for paediatric sepsis,[1 7–14] most quality improvement programmes do not report on the accuracy of screening for sepsis. By consequence,

there is a lack of evidence on features to include in sepsis screening tools. Only a small number of—mostly single-centre studies—have reported specifically on screening for sepsis, including two-tiered approaches with electronic health record-based triggers followed by clinician assessment.[9 15–17] While screening tools favour sensitivity at the expense of specificity, the implementation of poorly performing screening may fail to improve care for children with sepsis. In addition, oversensitive screening may jeopardise resource allocation to broader emergency department (ED) patient groups, and potentially favour unnecessary antibiotic usage.[18 19]

In the state of Queensland, Australia, a statewide Sepsis Collaborative was launched in 2018 to address the priorities stated in the National Action Plan on sepsis.[20] This quality improvement programme incorporated a systematic sepsis screening tool embedded in a sepsis pathway designed specifically for children. We hypothesised that this screening tool would perform well to identify children with clinician-diagnosed sepsis. In addition, we aimed to derive a simplified screening tool for future application.

METHODS

Multicentre, prospective observational cohort study including children aged less than 18 years who were screened for sepsis on the paediatric sepsis pathway in EDs participating in the Queensland Sepsis Collaborative (online supplemental material 1). Details on this sepsis quality improvement programme have been published elsewhere.[21]

Briefly, the Queensland Sepsis Collaborative is an statewide quality improvement programme, with the aim to improve the recognition, treatment and outcomes of patients with sepsis in Queensland.[22] A dedicated paediatric sepsis pathway was designed in iterative multidisciplinary workshops incorporating evidence and information from published or online available paediatric sepsis tools.[1 23 24] The pathway consisted of a screening tool, a management tool and antimicrobial stewardship guidance. Paper printed pathways were distributed to the participating EDs, and clinicians were trained to manually enter data on the pathway sheets, which were collected with the patient charts. Data were then entered by trained ED nurses at the participating sites into the electronic case report form on REDCap hosted by Clinical Excellence Queensland, with regular auditing for data quality assurance. The sepsis pathway including the screening tool was implemented across 16 EDs in the state of Queensland, Australia, of which 12 contributed data for this project.

We included children assessed between 4 August 2018 and 31 December 2019 who were screened for sepsis on the pathway. We excluded children with an interhospital transfer who were directly admitted to intensive care and children where no pathway had been used.

Paediatric sepsis screening tool overview

The screening portion of the paediatric sepsis pathway contained a total of 32 criteria, which were grouped into four sepsis screening blocks: (1) nine Sepsis Indicators (ie, triggers to screen), (2) six Sepsis Risk Factors, (3) eight Severe Illness Features and (4) nine Moderate Illness Features (online supplemental material 2). These 32 criteria were used as predictors for the analyses.

Screening was initiated if the ED clinician (doctor or nurse, at triage or during initial assessment) suspected that the child may have sepsis, and/or the child met one or more of the Sepsis Indicator criteria. During screening, the treating clinician marked on the form if each of the specified criteria were present. Children who met any of the Severe or Moderate Illness Features were escalated to senior medical officer (SMO) review.

Outcome

The primary outcome was sepsis, defined as treatment for sepsis, which was operationalised by two criteria: (1) decision of the SMO that 'sepsis is likely' and (2) treatment with intravenous antibiotics in the ED. These criteria were chosen as they represent a pragmatic intention-to-treat cohort.[25 26] Children who were screened but who did not meet both of these criteria were classified as no sepsis. If a child was missing either of the two criteria for the outcome, namely, SMO review and antibiotics, it was assumed that these procedures were not performed, and these children were coded as no sepsis.

Patient and public involvement

During this project, the Queensland Sepsis Collaborative established a paediatric sepsis family group, which was represented as well at the Steering Group, and which contributed to workshops on the screening tool design and implementation. This led to the development of the Queensland Paediatric Sepsis Programme Family Support Structure.[27]

Statistical analysis methods

Demographics and clinical characteristics were compared between those classified as sepsis and no sepsis. Continuous variables were not normally distributed, confirmed through visual inspection of the Q-Q plot, and as such the Wilcoxon rank-sum test was used. The χ^2 test or Fisher's exact test (for low expected cell counts) were used for categorical variables. A $p<0.05$ was used to denote statistical significance for these comparisons. The number and percentage of children with each criterion were reported to ascertain the prevalence of each criterion and the φ correlation coefficient (for dichotomous data) was calculated between all pairs of predictors to identify any predictors with high correlations that may result in multicollinearity problems. To examine the predictive performance of each of the sepsis screening blocks to identify children with sepsis, a separate multivariable logistic regression analysis for each screening block was initially undertaken and the ORs and 95% CIs were reported

for each criterion within each block. The discriminative ability of each block to predict the outcome was assessed using the area under the receiver operating characteristic curve (AUC).

To create the final prediction model, all 32 predictors were initially included in a logistic regression model and were iteratively removed using backward elimination, based on the largest reduction in the Akaike information criterion (AIC).[28] The final model was obtained when removing predictors no longer resulted in a reduction in the AIC. This final model was then internally validated using 10-fold cross-validation. Calibration of the predicted probabilities obtained through cross-validation was assessed by a calibration plot. The performance of the model was evaluated by the AUC, and the sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of the model were reported at different risk thresholds, corresponding to Youden's index, a sensitivity of 0.9 and a sensitivity of 0.85. Risk thresholds corresponding to high sensitivity rates were selected, as it is recommended that screening tests should prioritise sensitivity to reduce the false negative rate. A sensitivity analysis incorporating demographic and ED admission characteristics of gender, triage category, hospital category and admission time as adjustment variables in the final model was undertaken and evaluated by the AUC.

Given previously reported challenges in defining paediatric sepsis,[29] we performed two sensitivity analyses on the final model where we tested the model's performance when using the outcomes sepsis-associated organ dysfunction (children with sepsis as defined above, who met criteria for organ dysfunction within 24 hours of presentation to ED, as per the 2005 International Pediatric Sepsis Definition Consensus Conference[30] and septic shock (children with sepsis as defined above, who met criteria for septic shock within 24 hours of presentation to ED.[30]

All modelling was performed using R (V.4.1.1)[31] and the code used to create the models are available online (https://github.com/TrishGilholm/Paediatric-Sepsis-Screening). As this is a secondary analysis of data obtained from a quality improvement initiative, an a priori sample size calculation was not undertaken; therefore, all statistical comparisons are to be interpreted with caution. 95% CIs for all ORs were reported alongside the corresponding statistic in place of p values.[32 33]

Reporting follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis standards.[34]

RESULTS

Participants

Five hundred and twenty-three (15.1%) out of 3473 children screened on the pathway during the intervention period met criteria for sepsis (table 1). The children with sepsis were younger, had lower weight, had higher priority triage categories, were more likely to be treated at the quaternary site and had higher likelihood of, meningitis, abdominal, urinary tract infection and sepsis without a source compared with children classified as no sepsis.

Assessment of sepsis screening blocks

Of the 32 criteria assessed on the sepsis screening tool, the Sepsis Indicators had the highest prevalence overall, with the most prevalent criteria being history of fever and parental concern (table 2 and online supplemental efigure 1). Pairwise φ correlation coefficients predominantly ranged between weakly negative (φ=−0.25) to weakly positive (φ=0.25), indicating no strong relationships between the variables (online supplemental efigure 2). Eight out of 496 pairwise correlations had low-level positive correlation (0.25<φ<0.5) but no correlations exceeded 0.5, indicating absence of multicollinearity. When evaluating each of the sepsis screening blocks, the Severe Illness Features were the most predictive of sepsis, followed by the Sepsis Indicators, and Sepsis Risk Factors, while the Moderate Illness Features were the least predictive (table 3, figure 1, online supplemental etable 1). The performance of the 32-item tool to predict sepsis, as measured by the AUC, was 0.80 (95% CI 0.78 to 0.82). The final model also maintained a similar predictive performance when demographic and ED admission variables were included (AUC 0.81; 95% CI 0.79 to 0.83) (online supplemental etable 2) with minimal change to the effect size for each individual criterion.

Derivation of final model

Of the 32 criteria, 15 were removed through backward elimination, and one (parental/healthcare worker concern as a Moderate Illness Feature) was removed prior to analysis because it was already represented by the Sepsis Indicator criteria. The final model consisted of 16 features (table 3): healthcare worker concern, ill appearance ('looks sick'), altered behaviour, age <3 months, reduced immune defence, chronic disease, need for supplementary oxygen to maintain saturations, respiratory distress, tachycardia, hypotension, increased lactate, altered level of consciousness measured by the Alert Voice Pain Unresponsiveness (AVPU) scale, non-blanching rash, hypothermia, prolonged capillary refill ≥3 s and cold extremities. The strongest associations (OR >2) were found for age <3 months, immunocompromised status, hypotension, increased lactate, non-blanching rash, hypothermia and cold extremities (table 3, online supplemental etable 1 and 2). The final model had better discrimination than the four separate blocks (AUC 0.80; 95% CI 0.78 to 0.82) (table 3, figure 1), and retained similar predictive performance as the full 32-item model.

Model performance and sensitivity analyses

The calibration plot displayed good agreement between predicted and observed probabilities (online supplemental efigure 3). To reach a sensitivity of 90% (95% CI 87% to 92%), the final model reached a specificity of 51% (95% CI 49% to 53%) with a PLR of 1.83 (95% CI 1.75 to 1.92) and an NLR of 0.20 (95% CI 0.15 to 0.26) (online

Table 1 Demographics and clinical characteristics of the children classified as 'no sepsis' and 'sepsis"

Characteristic	Overall, N=3473	No sepsis, N=2950	Sepsis, N=523	P value
Demographics				
Age (years)*	2.1 (0.9, 5.6)	2.3 (1.0, 5.7)	1.3 (0.2, 4.6)	<0.001
Male	1903 (55%)	1598 (54%)	305 (58%)	0.224
Weight (kg)*	13 (9, 21)	13 (10, 21)	11 (5, 18)	<0.001
ED admission details				
Triage category				<0.001
1 (highest priority)	74 (2%)	33 (1%)	41 (8%)	
2	1250 (36%)	953 (33%)	297 (57%)	
3	1763 (51%)	1609 (55%)	154 (30%)	
4	350 (10%)	324 (11%)	26 (5.0%)	
5 (lowest priority)	6 (0.2%)	5 (0.2%)	1 (0.2%)	
Unknown	30 (1%)	26 (1%)	4 (1%)	
Admission time				0.599
Midnight to 6:00 hour	342 (10%)	292 (10%)	50 (10%)	
6:00 hour to midday	1064 (31%)	916 (31%)	148 (28%)	
Midday to 18:00 hour	1222 (35%)	1029 (35%)	193 (37%)	
18:00 hour to midnight	845 (24%)	713 (24%)	132 (25%)	
Hospital category†				<0.001
Quaternary	1062 (31%)	843 (29%)	219 (42%)	
Dedicated paediatric	1286 (37%)	1110 (38%)	176 (34%)	
Mixed	1125 (32%)	997 (34%)	128 (24%)	
Focus of infection				
Sepsis and/or meningitis	243 (7%)	72 (2%)	171 (33%)	<0.001
Sepsis (no meningitis)	189 (5%)	88 (3%)	101 (19%)	<0.001
Pneumonia	268 (8%)	184 (6%)	84 (16%)	<0.001
Intra-abdominal	57 (2%)	36 (1%)	21 (4%)	<0.001
Urinary	138 (4%)	90 (3%)	48 (9%)	<0.001
Soft tissue/bone	103 (3%)	86 (3%)	17 (3%)	0.782
CVAD	2 (<0.1%)	1 (<0.1%)	1 (0.2%)	0.279
Febrile neutropenia	25 (1%)	13 (0.4%)	12 (2%)	<0.001
Other	335 (10%)	297 (10%)	38 (7%)	0.055
Organ dysfunction				
Any organ dysfunction	518 (15%)	308 (10%)	210 (40%)	<0.001
Respiratory	48 (1%)	20 (1%)	28 (5%)	<0.001
Cardiovascular	260 (8%)	145 (5%)	115 (22%)	<0.001
Central nervous system	230 (7%)	132 (5%)	98 (19%)	<0.001
Renal	16 (1%)	9 (0.3%)	7 (1%)	0.004
Haematological	26 (1%)	9 (0.3%)	17 (3%)	<0.001
Hepatic	55 (2%)	36 (1%)	19 (4%)	<0.001
Patient outcomes				
ICU admission	36 (1%)	12 (0.4%)	24 (5%)	<0.001

*Statistics presented: median (IQR).
†The collaborative sites providing data for this study included a single quaternary paediatric ED; three specialised paediatric ED sites (accredited by the Australian College of Emergency Medicine for advanced training in Pediatric Emergency Medicine and eight mixed EDs without a dedicated paediatric department.
CVAD, central venous access device; EDs, emergency departments; ICU, intensive care unit.

supplemental etable 3). Sensitivity analyses on children with sepsis-associated organ dysfunction (n=210, 6.0%; AUC 0.84; 95% CI 0.81 to 0.87) and septic shock (n=146, 4.2%; AUC 0.84; 95% CI 0.81 to 0.88) confirmed the main findings (online supplemental etable 4).

DISCUSSION

In this statewide prospective study, a paediatric sepsis screening tool performed well to identify children with sepsis in the ED. We identified the most discriminative criteria available from rapid patient history and vital sign assessments and

Table 2 Criteria assessed on the paediatric sepsis screening tool, and the prevalence of each criteria in children with sepsis and without sepsis

Block	Criteria	No sepsis N=2950	Sepsis N=523
Sepsis Indicators	1. Parental concern	1607 (54%)	315 (60%)
	2. Healthcare worker concern	919 (31%)	279 (53%)
	3. History of fever or hypothermia	1938 (66%)	323 (62%)
	4. Looks sick	1291 (44%)	305 (58%)
	5. Altered behaviour or reduced level of consciousness	363 (12%)	130 (25%)
	6. Total CEWT score of 4 or more	1006 (34%)	237 (45%)
	7. Re-presentation within 48 hours	184 (6%)	34 (7%)
	8. Unexplained pain/restlessness	465 (16%)	92 (18%)
	9. Deterioration during current illness	352 (12%)	90 (17%)
Sepsis risk factors	1. Age less than 3 months	244 (8%)	140 (27%)
	2. Indwelling medical device	44 (2%)	17 (3%)
	3. Aboriginal and Torres Strait Islander/Pacific Islander/Maori	143 (5%)	26 (5%)
	4. Immunocompromised/asplenia/neutropenia/unimmunised	69 (2%)	31 (6%)
	5. Recent trauma or surgery/invasive procedure/wound within the last 6 weeks	63 (2%)	17 (3%)
	6. Chronic disease or congenital disorder	96 (3%)	45 (9%)
Severe Illness features	1. Need oxygen to keep oxygen saturation ≥92%	122 (4%)	73 (14%)
	2. Severe respiratory distress/tachypnoea/apnoea (CEWT respiratory score 3)	255 (9%)	108 (21%)
	3. Severe tachycardia or bradycardia (CEWT heart rate score 3)	358 (12%)	152 (29%)
	4. Hypotension (CEWT blood pressure score>=2)	17 (1%)	13 (3%)
	5. Lactate ≥2 mmol/L	137 (5%)	161 (31%)
	6. Altered AVPU	86 (3%)	66 (13%)
	7. Non-blanching rash	85 (3%)	38 (7%)
	8. Hypothermia (CEWT temperature score 2)	11 (0.4%)	13 (3%)
Moderate illness features	1. Moderate respiratory distress/tachypnoea (CEWT respiratory score 2)	250 (9%)	24 (5%)
	2. Moderate tachycardia (CEWT heart rate score 2)	425 (14%)	48 (9%)
	3. Capillary refill ≥3 s	113 (4%)	24 (5%)
	4. Unexplained pain or restlessness	210 (7%)	20 (4%)
	5. Low blood glucose level (<4 mmol/L)	32 (1%)	4 (1%)
	6. Pale or flushed/mottled	376 (13%)	42 (8%)
	7. Cold extremities	73 (3%)	20 (4%)
	8. Reduced urine output	243 (8%)	25 (5%)
	9. Parental/healthcare worker concern	600 (20%)	85 (16%)

AVPU, Alert, Verbal, Pain, Unresponsive scale; CEWT, Children's Early Warning Tool.

derived a more parsimonious screening tool which yielded comparable predictive performance to the full 32-item screening tool. The tool has been implemented successfully across a range of paediatric and mixed EDs, and in principle can be digitalised for sites with electronic health records. The study thereby addresses a gap highlighted by the 2020 Surviving Sepsis Campaign paediatric guidelines, relating to the lack of evidence on best approaches to screening and challenges surrounding successful implementation.[6] Due to the risk of selection bias, and considering the sample size, independent validation including patient-centred endpoints will be required.

A body of observational evidence demonstrates clear benefits stemming from the implementation of protocolised care bundles for children with sepsis, such as improved process measures, shorter intensive care unit (ICU) length of stay or lower mortality.[1 7–14] Yet, most studies did not attempt to untangle effects related to improved recognition from those related to timely delivery of treatment bundles. Due to the non-specific nature of presenting signs and symptoms of children with sepsis,[35] screening tools must be evaluated carefully, to enable recalibration and to avoid causing trigger or alarm fatigue.

The criteria associated with sepsis included risk factors based on patient history (such as young infants or immunosuppressed patients), healthcare worker concern and features indicating likely organ dysfunction. Lactate as a rapidly available point of care laboratory value emerged as one of the strongest sepsis predictors, concurring with previous studies,[36–38] in addition to respiratory, cardiovascular

Table 3 ORs and 95% CIs are shown for each of the models evaluating the sepsis screening blocks and the final model derived through backward elimination

	Sepsis screening blocks models		Final model	
Predictor variable	**OR**	**95% CI**	**OR**	**95% CI**
Sepsis Indicators				
1. Parental concern	1.08	0.89 to 1.32	–	–
2. Healthcare worker concern	2.15	1.76 to 2.62	1.48	1.18 to 1.84
3. History of fever or hypothermia	0.83	0.68 to 1.01	–	–
4. Looks sick	1.28	1.04 to 1.57	1.50	1.19 to 1.90
5. Altered behaviour or reduced level of consciousness	1.97	1.55 to 2.49	1.38	1.04 to 1.83
6. Total CEWT score of 4 or more	1.45	1.19 to 1.77	–	–
7. Re-presentation within 48 hours	0.95	0.63 to 1.39	–	–
8. Unexplained pain/restlessness	0.97	0.75 to 1,25	–	–
9. Deterioration during current illness	1.09	0.83 to 1.42	–	–
AUC Sepsis Indicators	0.66	0.63 to 0.68		
Sepsis risk factors				
1. Age <3 months	4.33	3.41 to 5.48	4.64	3.50 to 6.14
2. Indwelling medical device	1.16	0.59 to 2.19	–	–
3. Aboriginal and torres strait Islander/Pacific Islander/Maori	1.10	0.70 to 1.68	–	–
4. Immunocompromised/ asplenia/neutropenia/ unimmunised	2.13	1.33 to 3.37	3.19	1.93 to 5.18
5. Recent trauma or surgery/invasive procedure/wound within the last 6 weeks	1.31	0.72 to 2.28	–	–
6.Chronic disease or congenital disorder	3.09	2.04 to 4.60	1.96	1.24 to 3.06
AUC sepsis risk factors	0.62	0.59 to 0.65		
Severe illness features				
1. Need oxygen to keep oxygen saturation ≥92%	1.90	1.30 to 2.76	1.86	1.24 to 2.76
2. Severe respiratory distress/tachypnoea/apnoea (CEWT respiratory score 3)	1.76	1.30 to 2.37	1.69	1.23 to 2.30
3. Severe tachycardia or bradycardia (CEWT heart rate score 3)	1.91	1.48 to 2.46	1.92	1.46 to 2.50
4. Hypotension (CEWT blood pressure score ≥2)	2.26	0.90 to 5.39	2.04	0.79 to 5.11
5. Lactate ≥2 mmol/L	7.19	5.51 to 9.38	5.99	4.51 to 7.95
6. Altered AVPU	2.36	1.58 to 3.50	1.92	1.24 to 2.96
7. Non-blanching rash	2.22	1.40 to 3.46	2.43	1.49 to 3.87
8. Hypothermia (CEWT temperature score 2)	6.03	2.44 to 14.90	6.63	2.63 to 16.60
AUC severe illness features	0.72	0.69 to 0.74		
Moderate illness features				
1. Moderate respiratory distress/tachypnoea (CEWT respiratory score 2)	0.62	0.39 to 0.97	–	–
2. Moderate tachycardia (CEWT heart rate score 2)	0.74	0.52 to 1.03	–	–
3. Capillary refill ≥3 s	1.75	1.05 to 2.84	1.60	0.96 to 2.59
4. Unexplained pain or restlessness	0.60	0.36 to 0.94	–	–
5. Low blood glucose level	0.83	0.24 to 2.17	–	–
6. Pale or flushed/mottled	0.62	0.42 to 0.90	–	–
7. Cold extremities	2.20	1.25 to 3.73	2.73	1.54 to 4.63
8. Reduced urine output	0.62	0.39 to 0.94	–	–
9. Parental/healthcare worker concern	0.89	0.68 to 1.16	–	–
AUC moderate Illness features	0.57	0.55 to 0.60		
AUC full screening tool model*			0.80	0.78 to 0.82
AUC final model†			0.80	0.78 to 0.82

AUC of each model are reported in italics.
*Model including each of the above shown predictors used in the Queensland Paediatric Sepsis Screening Tool.
†Model restricted to the predictors of the final model derived through backward elimination.
AUC, area under the curve; AVPU, Alert, Verbal, Pain, Unresponsive Scale; CEWT, Children's Early Warning Tool.

and neurological criteria. Our findings are supported from a secondary analysis of a large trial in African children with infection, which revealed the importance of respiratory, cardiovascular and neurological signs.[39] In agreement with our findings, Romaine *et al* demonstrated that a modified score based on age-adjusted heart rate, respiratory

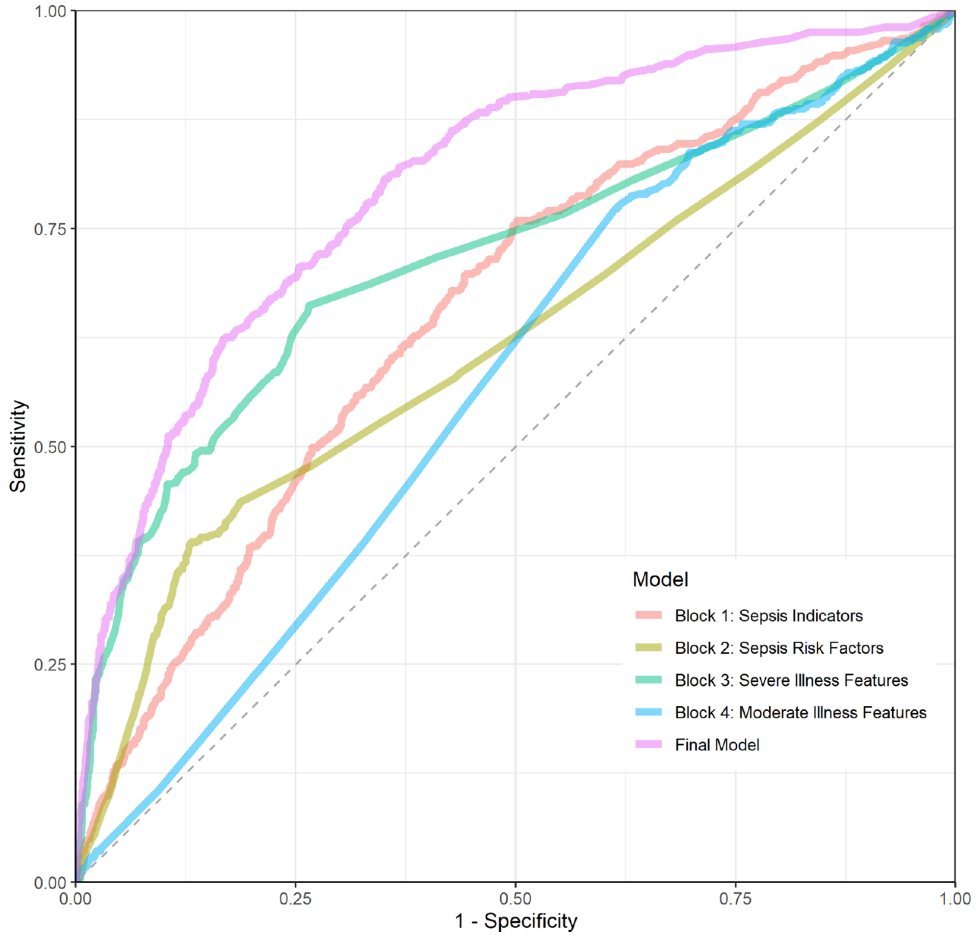

Figure 1 Receiver operating characteristic (ROC) curves are shown for the models for each of four blocks contained in the sepsis screening tool, and for the final model, validated using 10-fold cross-validation.

rate, capillary refill and AVPU predicted ICU admission in febrile children.[40] Of note, most paediatric early warning scores (PEWS) incorporate similar features to our derived model.[41 42] However, the development and validation of PEWS primarily focused on sick children in ED rather than specifically on children with sepsis. Finally, the performance of our model is comparable to a weighted model to predict hypotensive septic shock in children which was derived from 2464 ED encounters, including 11.4% with shock, and which contains several similar features to our model, such as blood pressure, temperature, respiratory rate and cancer as underlying disease.[43]

Several limitations of this study need to be considered which limit the generalisability of the findings. First, data were only available on those patients where the screening tool was applied, and we did not have data on all ED admissions to estimate the degree of selection bias. While the indicator criteria (ie, triggers to screen) were designed to capture most children evaluated for infection, the diagnostic performance related to a clinician deciding to apply the screening tool to a patient was not assessed. Therefore, we cannot rule out that broad application of the screening tool to all comers in ED may yield substantially variable performance. In addition, we did not have data on microbiological results (such as blood cultures) in the ED population to compare against. This challenge is magnified as there is no accepted gold standard of sepsis and there is inherent variability of 'clinician-diagnosed sepsis'.[44] Second, the average acuity in the cohort was low, with only 1% admitted to intensive care and three deaths. As a result, our model may not have been powered to detect certain potentially relevant features that had low prevalence in our sample, and the study was not powered to analyse the impact on patient-centred outcomes. Third, although the primary outcome of clinician-diagnosed sepsis represents an intention-to-treat population,[25 26 45] clinicians were not blinded to the sepsis tool and the use of the tool may have influenced the diagnosis. To account for paediatric sepsis coding practices,[29 46] we performed sensitivity analyses which showed that the model performed well to identify children with sepsis-associated organ dysfunction, and with septic shock, respectively. Fourth, the information captured by the screening tool was static, whereas clinicians may integrate dynamic information such as progression during initial ED observation, or response to treatment in their decision-making.[19] Finally, although the screening tool was tested in over 3000 paediatric patient encounters across 12 institutions, our findings require external validation. In particular, there is urgency to adapt and validate sepsis screening support tools for low-income and middle-income settings in the future.

In conclusion, the findings from this multicentre study demonstrate reasonable diagnostic performance of a systematic screening tool to identify children with sepsis in the ED. While independent validation in other cohorts is required, our findings lend support for the use of systematic screening for sepsis as recommended by the Surviving Sepsis Campaign. Future studies should investigate whether such tools assisting clinicians in ruling in or ruling out children in need of immediate treatment will result in improved patient outcomes.

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