Accuracy of a Modified qSOFA Score for Predicting Critical Care Admission in Febrile Children

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Abbreviations: Alert/Voice/Pain/Unresponsive scale (AVPU), area under the receiver operating characteristic curve (AUC), blood pressure (BP), capillary refill time (CRT), central nervous system (CNS), confidence interval (CI), C-reactive protein (CRP), critical care (CC), electronic patient record (EPR), Emergency Department (ED), Fluid Expansion as Supportive Therapy (FEAST), Glasgow Coma Scale (GCS), heart rate (HR), high-dependency unit (HDU), intensive care unit (ICU), interquartile range (IQR), length of stay (LOS), Liverpool quick Sequential Organ Failure Assessment (LqSOFA), National Early Warning Score (NEWS), National Institute for Health and Care Excellence (NICE), net reclassification improvement (NRI), Pediatric Early Warning Score (PEWS), pediatric intensive care unit

(PICU), positive predictive value (PPV), quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2), quick Sequential Organ Failure Assessment score (qSOFA), respiratory rate (RR), systemic inflammatory response syndrome (SIRS), systolic blood pressure (SBP), United Kingdom (UK).

Table of Contents Summary

The Liverpool qSOFA, a rapid bedside assessment, has greater discrimination than the qSOFA in predicting critical care admission in febrile children in the Emergency Department.

What's known on this subject?

The qSOFA has been shown to more accurately predict mortality or ICU transfer than SIRS or the qPELOD-2 in an Emergency Department population, but with only moderate prognostic accuracy.

What this study adds

In this retrospective study of >12000 febrile children, the Liverpool qSOFA (LqSOFA) outperforms the qSOFA in predicting critical care admission. LqSOFA is a rapid bedside tool which should undergo implementation testing.

Contributors' Statement Page

Prof Carrol conceptualized and designed the study, analysed data, reviewed and revised the manuscript, and oversaw all aspects of the study.
Dr Romaine drafted the initial manuscript, cleaned data, analysed data, and reviewed and revised the manuscript.
Drs Khanijau, Wright, and McGalliard, Mr Leigh and Ms Potter, collected data, cleaned data, conducted initial analyses, and reviewed and revised the manuscript.
Mr Edwardson and Mr Johnston designed the data collection instruments, and conducted data extraction from the electronic patient record, and reviewed and revised the manuscript.
Dr Kerr supervised management and flow of patients in the ED, and reviewed and revised the manuscript.
Ms Sefton iteratively developed the PEWS used in the study, provided advice on earlier drafts of the manuscript, and reviewed and revised the manuscript.
Dr Schlapbach contributed to study design, analysed data, provided advice on earlier drafts of the manuscript, and critically reviewed and revised the manuscript.
Dr Pallmann supervised the data analysis, analysed data, and critically reviewed and revised the manuscript.
All authors approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Abstract

Background and Objectives

The identification of life-threatening infection in febrile children presenting to the Emergency Department (ED) remains difficult. The quick-Sequential Organ Failure Assessment (qSOFA) was only derived for adult populations, implying an urgent need for pediatric scores. We developed and validated a novel, adapted qSOFA score (Liverpool qSOFA (LqSOFA)) and compared its performance with qSOFA, PEWS, and NICE High Risk criteria in predicting critical care (CC) admission in febrile children presenting to the ED.

Methods

The LqSOFA (range, 0-4), incorporates age-adjusted heart rate, respiratory rate, capillary refill, and consciousness level on the Alert/Voice/Pain/Unresponsive scale. The primary outcome was CC admission within 48 hours of ED presentation, the secondary outcome was sepsis-related mortality. LqSOFA, qSOFA, PEWS, and NICE High Risk scores were calculated, and performance characteristics, including area under the receiver operating characteristic curve (AUC), calculated for each score.

Results

In the initial (n=1121) cohort, 47 CC admissions (4.2%) occurred, and in the validation (n=12241) cohort 135 CC admissions (1.1%) occurred, and 5 sepsis-related deaths. In the validation cohort, LqSOFA predicted CC admission with an AUC of 0.81 (95% CI, 0.76-0.86), versus qSOFA (0.66; 95% CI, 0.60-0.71), PEWS (0.93; 95% CI, 0.90-0.95), and NICE High Risk (0.81; 95% CI, 0.78-0.85). For predicting CC admission, the LqSOFA outperformed the qSOFA, with a net reclassification index of 10.4% (95% CI, 1.0%-19.9%).

Conclusions

This large study demonstrates improved performance of the LqSOFA over qSOFA in identifying febrile children at risk of CC admission and sepsis-related mortality. Further validation is required in other settings.

Introduction

Acute febrile illness is one of the most common reasons for presentation to the pediatric emergency department (ED).[1] Within this heterogeneous group of patients, only a small minority will have sepsis. However, for these children mortality rates remain high,[2] and delays in recognition and treatment of sepsis lead to an increased risk of mortality.[3] To date, a sensitive and specific tool to identify patients with sepsis in the ED remains elusive. In adults, the quick Sequential Organ Failure Assessment (qSOFA) score is proposed as a screening tool for clinicians outside the intensive care unit (ICU) to promptly identify patients with infection who are more likely to have poorer outcomes.[4,5] The presence of at least 2 of the 3 qSOFA components, altered mentation, raised respiratory rate (RR), and low systolic blood pressure (SBP), was associated with an increased risk of mortality, but the derivation and validation of Sepsis-3 and the qSOFA did not involve pediatric data.

The use of the qSOFA to identify pediatric sepsis has many limitations. Firstly, several studies in both adult and pediatric populations have reported poor sensitivity, ranging from 37-70% in predicting in-hospital mortality,[6-8] and only 36-54% in predicting ICU admission.[7-10] Secondly, many qSOFA studies have used mortality as their primary outcome,[4,6-8] but mortality in pediatric ED settings is <1%, therefore critical care (CC) admission is a more suitable outcome, as this allows assessment of whether the score can identify those patients requiring additional support, regardless of survival.[10] Thirdly, hypotension is a late sign of pediatric septic shock.[3] Furthermore, blood pressure (BP) is infrequently measured in the pediatric ED.[11]

Schlapbach et al.[6] compared the prognostic performance of an age-adjusted qSOFA with systemic inflammatory response syndrome (SIRS) criteria in pediatric ICU patients with

infection and demonstrated the qSOFA was not substantially superior to SIRS criteria at predicting mortality and prolonged ICU stay. A small pediatric ED study comparing the qSOFA, quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2), and SIRS criteria for their ability to predict mortality or ICU admission found the qSOFA had the greatest predictive validity but achieved only moderate prognostic accuracy.[9]

To address these limitations, we amended the age-adjusted qSOFA to create a novel score known as the Liverpool qSOFA (LqSOFA). While different scoring systems vary in relation to the number of items considered, and the cut-offs applied, past literature indicates that respiratory, cardiovascular, and central nervous system (CNS) alterations are the most consistent features of severe illness in children and adults. Accordingly, the qSOFA in adults is based on RR, SBP, and Glasgow Coma Scale (GCS).[4] In contrast to adults, hypotension represents a late sign of pediatric septic shock.[3] Therefore, a predictive score that incorporates earlier signs of shock, such as tachycardia and prolonged capillary refill time (CRT),[3,12] could improve upon the sensitivity demonstrated by the qSOFA. A study assessing various vital signs for their ability to predict severity of infection in an ED population reported heart rate (HR) to be the most sensitive.[13] Several studies in both adults and children have found a prolonged CRT acts as a marker for sepsis,[12,13] and is associated with a greater degree of organ dysfunction (as measured by SOFA score),[14] and risk of mortality.[15,16] The Alert/Voice/Pain/Unresponsive (AVPU) scale is the standard assessment of neurological state in pediatric EDs in the United Kingdom (UK). It is quick and simple to measure, and has been shown to correlate well with GCS.[17] For these reasons, we a priori selected RR, HR, CRT, and AVPU for the LqSOFA. A recent secondary analysis of the Fluid Expansion as Supportive Therapy (FEAST) study demonstrated the relevance of respiratory, cardiovascular, and CNS dysfunction in identifying patients at a greater risk of mortality,

further supporting this approach.[18] The 2005 Pediatric Sepsis Consensus[19] thresholds for abnormal HR and RR, used in both SIRS and the age-adjusted qSOFA, were based on values which were likely determined through clinical consensus.[20] In contrast, evidence-based sets of reference ranges have since been developed, on ED[21] and hospitalised patients,[22] which may be more discriminative in the febrile ED population. Therefore, we compared these two sets of reference ranges to identify the most suitable for use in the LqSOFA.

The aim of the present study was to develop and validate a novel, rapid, bedside scoring system for use in febrile children attending the ED to predict CC admission within 48 hours. We compared the performance of our score with the age-adjusted qSOFA, the Pediatric Early Warning Score (PEWS) in routine use at our hospital, and NICE High Risk criteria.[23]

Patients and Methods

Study population and definitions

The study was conducted at a single-center: Alder Hey Children's Hospital, Liverpool, UK. This is one of Europe's largest pediatric hospitals, managing around 60 000 ED attendances annually.[24] The initial cohort used to amend the qSOFA into the LqSOFA (referred to as amendment cohort) used a previously published prospective dataset of febrile children (<16 years) attending the ED between November 2010 and April 2012.[24] Children were eligible if the treating clinician decided to perform blood tests. 1872 patients were recruited to this study, 670 were excluded due a lack of capacity for study recruitment in ED, 15 declined consent, and 4 were excluded due to a primary immunodeficiency. The remaining cohort of 1183 cases was used to develop the LqSOFA score using age-adjusted percentile ranges and rapid-assessment adaptations of other components of the qSOFA score (Supplementary Material). For the validation cohort, children were identified retrospectively from the hospital

electronic patient record (EPR) if they presented to the ED between 1 September 2015 and 31 August 2017. Eligible cases were identified by reviewing ED and CC admissions during this period. Fever was defined as a temperature ≥38°C recorded in the ED, or a history of fever reported in the previous 3 days. Exclusion criteria were missing observation data, no history of fever, and transfer from another hospital. Missing observation data was defined as missing 2 or more components required to calculate any of the scoring systems. If only 1 component was missing (i.e. not measured), this was deemed to be normal. Ethical approval was granted for both cohorts (research ethics committee reference: 10/H1014/53 and 16/LO/1684).

Outcome definitions

The primary outcome was CC admission within 48 hours of ED attendance. The secondary outcome was sepsis-related mortality. This was defined as CC admission within 48 hours of ED presentation with suspected sepsis, which led directly or indirectly to in-hospital death within 28 days of admission, as determined by a review of the clinical notes.

Score calculations

The variables for LqSOFA were developed using adapted qSOFA components (Supplementary Material). Two evidence-based sets of reference ranges for abnormal HR and RR (O'Leary et al.[21] and Bonafide et al.[22]) were compared in the amendment cohort, with the highest performing reference range selected for use in the LqSOFA (Supplementary Material). Scores for LqSOFA, qSOFA, PEWS, and NICE High Risk criteria were calculated using the worst observations recorded in the ED. Each scoring system differs in both the included vital signs and the age-thresholds used; these can be seen in full in the Supplementary Material. PEWS was in routine use clinically and was therefore calculated electronically in real-time, whereas scores for the other 3 systems were calculated retrospectively for study purposes only, using individually documented vital sign information

in the EPR. As with the qSOFA, each component in the LqSOFA could be scored as 0 or 1, making a total possible score of 4 (Table 1). If blood tests were performed, the worst lactate and worst C-reactive protein (CRP) recorded in the ED were collected.

Statistical analysis

We assessed the prognostic ability of each scoring system using the area under the receiver operating characteristic curve (AUC). Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, odds ratio, and accuracy were calculated for each score alongside an asymptotic 95% confidence interval (CI). LqSOFA and qSOFA were compared using net reclassification improvement (NRI).[25] Statistical analyses were performed using SPSS version 25 and R version 3.6.1.[26] Graphics were generated using ggplot2[27] and eulerr.[28]

Results

Study population

A total of 62 (5.2%) cases were excluded from the amendment cohort due to missing observation data, leaving 1121 cases for the amendment cohort (Supplementary Material). Of 14 121 cases identified for the validation cohort, 1880 were excluded: 1249 (8.8%) due to missing observation data, 454 (3.2%) due to no history of fever, 96 (0.7%) due to duplicate cases, 77 (0.5%) due to ≥16 years of age, and 4 (0.03%) due to transfer from another hospital (Figure 1). Importantly, 848 (75.6%) and 8354 (68.2%) cases in the amendment and validation cohorts, respectively, did not have any BP measurements recorded whilst in the ED. Demographic characteristics, clinical outcomes, and scores of the amendment and validation cohorts are summarised in Table 2.

Amendment cohort

Using the 99th centile cut-offs from Bonafide et al.,[22] the LqSOFA score achieved an AUC of 0.78 (95% CI, 0.71-0.85) in predicting CC admission within 48 hours, compared to the qSOFA (AUC 0.61; 95% CI, 0.52-0.70), and NICE High Risk (AUC 0.73; 95% CI, 0.65-0.81). The performance of each score and biomarkers at different cut-offs are shown in Figure 2 and Supplementary Table 6.

Validation cohort

LqSOFA was then applied to the independent validation cohort. A total of 135 children (1.1%) were admitted to CC within 48 hours, 115 to the high-dependency unit (HDU), 28 to the ICU, and 8 to both units. Of those 135 admitted to CC, 127 (94.1%) met Sepsis-3 diagnostic criteria on day 1 of admission, whilst 108 (80.0%) met 2005 Pediatric Sepsis Consensus criteria.[19,29] Lactate was measured in 451 (3.7%) cases, of these 186 (41.2%) had a lactate ≥2 and 27 (6.0%) of ≥4. CRP was measured in 1628 (13.3%) cases. 10 children (0.08%) died, 5 of which (0.04%) were directly attributable to sepsis.

Comparison of qSOFA, LqSOFA, PEWS, and NICE High Risk

For predicting CC admission in the validation cohort, PEWS demonstrated the greatest discriminative ability (AUC 0.93; 95% CI, 0.90-0.95), followed by LqSOFA (AUC 0.81; 95% CI, 0.76-0.86) and NICE High Risk (AUC 0.81; 95% CI, 0.78-0.85), with qSOFA (AUC 0.66; 95% CI, 0.61-0.71) the least discriminative (Table 3, Figure 3). For predicting sepsis-related mortality, PEWS showed the greatest discrimination (AUC 0.96; 95% CI, 0.92-1), followed by LqSOFA (AUC 0.87; 95% CI, 0.65-1), qSOFA (AUC 0.81; 95% CI, 0.55-1), and NICE High Risk (0.72; 95% CI, 0.58-0.86) (Table 3, Supplementary Figure 2). Performance of the scores at various cut-offs as binarized scores are shown in Table 3 and Table 4. Comparing LqSOFA with qSOFA using a cut-off of ≥2 for both scores, the NRI for

those admitted to CC within 48 hours was 10.37% (95% CI, 0.90-19.84) and for those not admitted 0.07% (95% CI, -0.15-0.29), yielding an overall NRI of 10.44% (95% CI, 0.96-19.91). Figure 4 demonstrates the percentage of patients admitted to CC within 48 hours, by score, for each of the 4 systems; Supplementary Figure 3 demonstrates this for sepsis-related mortality. Supplementary Figure 4 shows the number of critical care admissions predicted by each scoring system or combination of systems.

Lactate and CRP

For the primary outcome, poor discrimination was seen with both lactate (AUC 0.63; 95% CI, 0.56-0.69) and CRP (AUC 0.55; 95% CI, 0.49-0.61) (Table 3, Figure 3). For the secondary outcome, both lactate (AUC 0.89; 95% CI, 0.71-1) and CRP (AUC 0.83; 95% CI, 0.68-0.98) demonstrated good predictive ability (Table 3, Supplementary Figure 2). Several standard performance metrics of CRP and lactate, as well as each of the 4 scoring systems, are presented in Table 3 and Table 4.

Discussion

Our data show that a simple 4-item score demonstrates improved discriminant ability compared to the age-adjusted qSOFA and NICE High Risk criteria. Our novel, rapid, bedside score for children, the LqSOFA score, has demonstrated good discriminative ability in predicting CC admission in febrile ED patients in a large independent validation cohort. In the ED, it is important to identify the “needle in the haystack”: those children requiring further investigation and urgent treatment. The use of a sepsis-specific score in a pediatric ED may be of limited value due to the low prevalence, whereas predicting which children might require CC admission may be more useful.

LqSOFA

For predicting CC admission, the LqSOFA demonstrated good prognostic value. Using a cut-off of ≥2, the score showed excellent specificity but was limited by a relatively low sensitivity, consistent with sensitivities reported for the qSOFA in both adults and children.[7-10] Given that the these scores are designed as tools to aid clinician decision making, rather than simply predict outcome, it has been argued that this rate of false negatives is unacceptably high.[10] However, a cut-off of ≥1 for the LqSOFA produced a more favourable balance of sensitivity and specificity. Overall, the LqSOFA demonstrates superior discriminative ability than that reported with the qSOFA in the pediatric population, both in the present study and compared to previous research.[6,9,30] In the present study the LqSOFA demonstrated the greatest positive predictive value (PPV) of all 4 scoring systems, although this was only 34%. The low values for PPV seen across all scoring systems likely reflect the low prevalence of sepsis within the ED population, and highlight the difficulty in identifying such cases. There has rightly been a focus in recent years on preventing cases of sepsis being missed, leading to the prioritisation of sensitivity over other performance measures. In the present study, NICE High Risk achieved excellent sensitivity, greater than the LqSOFA and PEWS, but at the cost of limited specificity. The potential disadvantages of relying on such scoring systems, in overdiagnosis and overtreatment of sepsis, are significant.[31] Therefore, scoring systems with high sensitivity but poor specificity should be avoided in favour of more balanced scoring systems, ideally those that are quick and simple to calculate. The use of CRT and HR as a proxy for cardiovascular dysfunction means the LqSOFA can be calculated rapidly using routine clinical observations and without any equipment, such as appropriately-sized BP cuffs, a significant advantage over other scoring systems. In addition, shock in children may be present before hypotension is measured,[3] therefore these parameters may detect impending shock earlier. This facilitates its potential for standardised use across many

other settings including primary care and resource-poor settings. The large number of age categories in the LqSOFA potentially provides greater accuracy, but also increases the complexity of the score in comparison to other systems with fewer age categories (e.g. NICE High Risk). However, when used electronically this greater complexity would not equate to a more time-consuming or complicated tool for the clinician; the number of components in any given scoring system has a far greater impact in this regard. Overall, the primary limitation of the use of the LqSOFA is the lower sensitivity achieved in comparison to PEWS. However, the excellent specificity suggests the LqSOFA may be useful in determining which children are at low risk of CC admission, or in situations where discriminant ability is prioritised over sensitivity.

qSOFA

For predicting both the primary and secondary outcome, the qSOFA performed less well than the LqSOFA and PEWS. Our results are consistent with previous research. Schlapbach et al.[6] reported an AUC of 0.64 for the qSOFA in predicting mortality in a pediatric ICU (PICU) cohort. A limitation of their study is the use of a PICU population, given that "quick" organ dysfunction scores are designed to alert the clinician to those at risk of sepsis and most PICU patients will already have some sort of organ dysfunction and/or organ support. In an ED study, Van Nassau et al.[9] assessed the ability of the qSOFA to predict PICU transfer and/or mortality, reporting an AUC of 0.72 and a sensitivity of 50%, although their study used a relatively small sample (n=864). Our study provides further evidence that the qSOFA lacks the prognostic ability to justify its introduction into routine practice in the pediatric ED.

A further limitation of using the qSOFA in the pediatric population, highlighted by the present study, is the infrequency of BP measurements in the pediatric ED. In the validation cohort, 8354 (68.2%) cases did not have their BP recorded whilst in the ED; this is consistent

with previous research.[32] The lack of BP data may have affected the performance of the qSOFA, however, to exclude these cases from the study would mean excluding the vast majority of eligible cases. The results generated from such an analysis would provide very little information on the potential "real-world" performance of the score. BP is included in many PEWS,[33] however, BP may not be measured at triage; NICE sepsis guidance recommends BP is measured only when tachycardia or prolonged CRT are present.[23] The infrequency of BP measurements may lead to missed opportunities for the early detection of sepsis. In the present study, almost one quarter of those admitted to CC within 48 hours did not have their BP measured whilst in the ED, suggesting the absence of BP measurement is not confined to "well" children. A score which does not require BP measurement, such as LqSOFA, therefore presents a significant advantage.

PEWS

PEWS demonstrated the greatest discriminative ability for both the primary and secondary outcomes, consistent with previous research.[33] Most PEWS are designed to identify deterioration in hospitalised children and have therefore not been validated in an ED setting. A previous ED study demonstrated that PEWS was an independent predictor of ICU admission within 48 hours, or death within 30 days, in unselected pediatric ambulance patients presenting to the ED.[34] The large number of different heterogeneous PEWS in use is a disadvantage, as this leads to inconsistency in detecting and responding to acute illness. qSOFA and especially LqSOFA therefore offer an advantage over PEWS as standardised tools to improve sepsis recognition. Importantly, PEWS was the only scoring system in routine clinical use during the study, and hence PEWS scores were known by treating physicians. This may have influenced decisions regarding transfer to critical care, potentially altering the performance of the score in comparison to the other scoring systems which had not been applied clinically. Furthermore, compared to only 3 and 4 items in the qSOFA and

LqSOFA, respectively, PEWS often include several more variables and are therefore more complicated and time-consuming to calculate (Supplementary Figure 1).[33] Whilst a granular score may perform better than a parsimonious score such as ours, it may be less feasible in practice for rapid assessment in a busy ED.

NICE High Risk criteria

A previous study compared the NICE High Risk criteria in adults, with qSOFA, National Early Warning Score (NEWS), and SIRS for their ability to predict mortality in an ED and ward setting.[35] NICE High Risk criteria achieved a sensitivity of only 58.9% and were not independently associated with an adverse outcome. In the present study, for the primary outcome we found good discriminative ability suggesting NICE High Risk criteria correlate well with risk of CC admission, and the criteria correctly identified all 5 sepsis-related deaths. However, 55% of validation cohort cases were positive for NICE High Risk criteria, suggesting the criteria lack the specificity to be useful alone as a screening tool for possible sepsis in the ED. Given that the guidelines recommend senior review for children with NICE High Risk features,[23] implementation is likely to have huge resource implications in an already stretched health service. Importantly, our analysis did not include many other NICE High Risk features such as cyanosis, non-blanching rash, and "appears ill to healthcare worker", suggesting the NICE High Risk criteria could be simplified.

Lactate and CRP

A strong association between lactate and mortality in pediatric sepsis has previously been reported.[36] In the present study lactate showed good discriminative ability for sepsis-related mortality, providing further support for including lactate measurement in risk stratification in pediatric sepsis.[37] CRP demonstrated poor versus good discrimination for the primary versus

secondary outcomes, respectively, which is consistent with several studies reporting CRP as a poorer predictor of sepsis than other available biomarkers.[38]

Comparison of all scores

All 4 scoring systems in the present study used different age-specific thresholds. Schlapbach et al.[6] noted the lack of age-specific cut-offs for the original qSOFA and therefore applied those used in the corrected 2005 Pediatric Sepsis definitions.[19,39] These age-specific thresholds are notably lower than those described by Bonafide et al.[22] and used in the LqSOFA. NICE High Risk and the PEWS in the present study generally use thresholds in between these two. This lack of consensus in age-specific thresholds may explain a large part of the difference in prognostic ability seen between the scoring systems and highlights the urgent need for standardisation of reference ranges. The Bonafide et al.[22] reference ranges for hospitalised children are closer to the febrile child population than the O'Leary et al.[21] reference ranges for low acuity children presenting to the ED, or the Fleming et al.[20] reference ranges for healthy children used in our PEWS, and are therefore the best ranges to identify children with severe enough illness to require CC admission.

For operationalisation of the score in the ED, a highly sensitive score (NICE High Risk ≥1) could be used as a screening test in triage to identify the group at risk for sepsis, followed by a highly specific score (LqSOFA≥2) to identify those children at highest risk of poor outcome. This can be implemented electronically (such as reported by Balamuth et al.[40]), with an LqSOFA score ≥2 prompting immediate senior review.

Strengths and limitations

To our knowledge, this is the largest study assessing the performance of quick assessment scores, including the qSOFA, in a pediatric ED population. Our population reflects a real-world high income ED setting, with a low prevalence of sepsis. We compared different age-

specific cut-offs and 2 other prediction scores for sepsis: NICE High Risk and qSOFA. The LqSOFA can be calculated rapidly across a variety of different healthcare settings, as no equipment is required. Limitations include use of retrospective data, cases from a single centre, criteria of critical care admission which may depend on local practice, and the low mortality. In addition, hypothermic patients presenting with sepsis may have been missed.

Conclusion

Overall, the findings of the present study demonstrate the superior performance of LqSOFA and question the use of the qSOFA to identify patients at risk of sepsis in the pediatric ED. The LqSOFA requires further evaluation in other settings prior to recommending more widespread use as entry criterion into randomised controlled trials in the pediatric ED.

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Tables

Table 1. Scoring thresholds for each component of LqSOFA		
Criterion	**Points allocated**	
	1 point	**0 points**
Capillary refill time	≥3 seconds	<3 seconds
AVPU	VPU	A
Heart rate	>99th centile Bonafide et al.[22] age-specific thresholds	≤99th centile Bonafide et al.[22] age-specific thresholds
Respiratory rate	>99th centile Bonafide et al.[22] age-specific thresholds	≤99th centile Bonafide et al.[22] age-specific thresholds
Abbreviations: AVPU, Alert/Voice/Pain/Unresponsive scale. LqSOFA, Liverpool quick Sequential Organ Failure Assessment.		

Table 2. Summary of demographic characteristics, clinical outcomes, and scores of the amendment and validation cohorts

Characteristics	Amendment cohort	Validation cohort
Number of cases	1121	12241
Age in years, median (IQR)	2.3 (4.7)	2.5 (3.8)
Male, n (%)	621 (55.4)	6527 (53.3)
Admitted to ward, n (%)	817 (72.9)	1481 (12.1)
CC admission within 48 hours (%)	47 (4.2)	135 (1.1)
Hospital LOS in days, median (IQR)	3 (3)	1.04 (2.73)
CC LOS in days, median (IQR)	2 (5)	2.23 (4.33)
In-hospital mortality, n (%)	1 (0.09)	10 (0.08)
Sepsis-related mortality, n (%)	1 (0.09)	5 (0.04)
LqSOFA ≥2, n (%)	79 (7.0)	155 (1.3)
LqSOFA ≥1, n (%)	369 (32.9)	1919 (15.7)
qSOFA ≥2, n (%)	31 (2.8)	149 (1.2)
qSOFA ≥1, n (%)	1027 (91.6)	11579 (94.6)
PEWS ≥3, n (%)	..[a]	1465 (12.0)
PEWS ≥2, n (%)	..[a]	5211 (42.6)
NICE High Risk ≥2, n (%)	199 (17.8)	1357 (11.1)
NICE High Risk ≥1, n (%)	737 (65.7)	6787 (55.4)

Abbreviations: IQR, interquartile range; CC, critical care; LOS, length of stay; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute for Health and Care Excellence.

[a] PEWS not in-use at the hospital when amendment cohort data collected.

Table 3: AUCs for primary and secondary outcomes for LqSOFA, qSOFA, PEWS, NICE High Risk, lactate, and CRP in the validation cohort

Predictor	Definition	Primary outcome: critical care admission within 48 hours	Secondary outcome: sepsis-related mortality
		AUC (95% CI)	AUC (95% CI)
LqSOFA	LqSOFA score	0.81 (0.76-0.86)	0.87 (0.65-1)
	LqSOFA ≥2	0.69 (0.64-0.75)	0.79 (0.53-1)
	LqSOFA ≥1	0.78 (0.74-0.83)	0.82 (0.62-1)
qSOFA	qSOFA score	0.66 (0.61-0.71)	0.81 (0.55-1)
	qSOFA ≥2	0.64 (0.58-0.70)	0.79 (0.53-1)
	qSOFA ≥1	0.53 (0.48-0.57)	0.53 (0.29-0.77)
PEWS	PEWS	0.93 (0.90-0.95)	0.96 (0.92-1)
	PEWS ≥3	0.88 (0.84-0.91)	0.94 (0.91-0.97)
	PEWS ≥2	0.75 (0.72-0.78)	0.79 (0.68-0.90)
NICE High Risk	NICE High Risk	0.81 (0.78-0.85)	0.72 (0.58-0.86)
	NICE High Risk ≥2	0.75 (0.70-0.80)	0.55 (0.28-0.81)
	NICE High Risk ≥1	0.70 (0.66-0.73)	0.72 (0.58-0.86)
Lactate	Lactate	0.63 (0.56-0.69)	0.89 (0.71-1)
	Lactate ≥4 mmol/l	0.58 (0.51-0.65)	0.85 (0.59-1)
	Lactate ≥2 mmol/l	0.61 (0.55-0.68)	0.66 (0.41-0.92)
CRP	CRP	0.55 (0.49-0.61)	0.83 (0.68-0.98)

Abbreviations: AUC, area under receiver operating characteristic curve; CI, confidence interval; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute for Health and Care Excellence; CRP, C-reactive protein.

Table 4: Comparison of prognostic performance for LqSOFA, qSOFA, PEWS, NICE High Risk, and lactate in the validation cohort								
Primary outcome: critical care admission within 48 hours								
Scoring system	**Odds ratio (95% CI)**	**Sensitivity; % (95% CI)**	**Specificity; % (95% CI)**	**Positive predictive value; % (95% CI)**	**Negative predictive value; % (95% CI)**	**Positive likelihood ratio (95% CI)**	**Negative likelihood ratio (95% CI)**	**Accuracy; % (95% CI)**
LqSOFA ≥2	76.1 (51.2-113.1)	39.2 (31.0-48.0)	99.2 (99.0-99.3)	34.2 (28.1-40.9)	99.3 (99.2-99.4)	46.6 (35.0-62.0)	0.6 (0.5-0.7)	98.5 (98.3-98.7)
LqSOFA ≥1	14.4 (9.9-21.0)	71.9 (63.4-79.3)	85.0 (84.3-85.6)	5.1 (4.5-5.6)	99.6 (99.5-99.7)	4.8 (4.3-5.4)	0.3 (0.3-0.4)	84.8 (84.2-85.4)
qSOFA ≥2	44.3 (29.2-67.2)	28.9 (21.4-37.3)	99.1 (98.9-99.3)	26.2 (20.4-32.9)	99.2 (99.1-99.3)	31.8 (23.0-43.9)	0.7 (0.6-0.8)	98.3 (98.1-98.5)
qSOFA ≥1	15.7 (1.0-252.4)	100 (97.3-100)	5.5 (5.1-5.9)	1.2 (1.2-1.2)	100	1.1 (1.1-1.1)	0	6.5 (6.1-7.0)
PEWS ≥3	51.9 (31.5-85.5)	86.7 (79.8-91.9)	88.9 (88.3-89.4)	8.0 (7.4-8.6)	99.8 (99.7-99.9)	7.8 (7.1-8.5)	0.2 (0.1-0.2)	88.8 (88.3-89.4)
PEWS ≥2	17.3 (9.1-32.9)	92.6 (86.8-96.4)	58.0 (57.1-58.9)	2.4 (2.3-2.5)	99.9 (99.7-99.9)	2.2 (2.1-2.3)	0.1 (0.1-0.2)	58.4 (57.5-59.2)
NICE High Risk ≥2	13.1 (9.3-18.7)	60.7 (52.0-69.0)	89.5 (88.9-90.0)	6.0 (5.3-6.9)	99.5 (99.4-99.6)	5.8 (5.0-6.7)	0.4 (0.4-0.5)	89.2 (88.6-89.7)
NICE High Risk ≥1	13.0 (6.3-26.5)	94.1 (88.7-97.4)	45.0 (44.1-45.9)	1.9 (1.8-2.0)	99.9 (99.7-99.9)	1.7 (1.6-1.8)	0.1 (0.1-0.3)	45.5 (44.6-46.4)
Lactate ≥4 mmol/l	8.2 (3.6-18.9)	17.8 (10.9-26.7)	97.4 (95.2-98.8)	66.7 (48.1-81.2)	80.4 (78.9-81.8)	6.9 (3.2-15.0)	0.8 (0.8-0.9)	79.6 (75.6-83.2)
Lactate ≥2 mmol/l	2.1 (1.3-3.3)	55.5 (45.2-65.3)	62.9 (57.6-67.9)	30.1 (25.7-35.0)	83.0 (79.5-86.0)	1.5 (1.2-1.9)	0.7 (0.6-0.9)	61.2 (56.5-65.7)
Secondary outcome: sepsis-related mortality								
LqSOFA ≥2	119.3 (19.8-718.8)	60.0 (14.7-94.7)	98.8 (98.6-99.0)	1.9 (0.9-4.0)	100	48.3 (23.2-100.1)	0.4 (0.1-1.2)	98.7 (98.5-98.9)
LqSOFA ≥1	21.6 (2.4-193.0)	80.0 (28.4-99.5)	84.4 (83.7-85.0)	0.2 (0.1-0.3)	100	5.1 (3.3-7.9)	0.2 (0.0-1.4)	84.4 (83.7-85.0)

qSOFA ≥2	124.2 (20.6-748.9)	60.0 (14.7-94.7)	98.8 (98.6-99.0)	2.0 (1.0-4.0)	100	50.3 (24.1-104.7)	0.4 (0.1-1.2)	98.8 (98.6-99.0)
qSOFA ≥1	0.6 (0.0-11.4)	100 (47.8-100)	5.4 (5.0-5.8)	0.04 (0.04-0.04)	100	1.1 (1.1-1.1)	0	5.5 (5.1-5.9)
PEWS ≥3	81.2 (4.5-1468.7)	100 (47.8-100)	88.1 (87.5-88.6)	0.3 (0.3-0.4)	100	8.4 (8.0-8.8)	0	88.1 (87.5-88.6)
PEWS ≥2	14.9 (0.8-268.7)	100 (47.8-100)	57.5 (56.6-58.3)	0.1 (0.1-0.1)	100	2.4 (2.3-2.4)	0	57.5 (56.6-58.4)
NICE High Risk ≥2	2.0 (0.2-18.0)	20.0 (0.5-71.6)	88.9 (88.4-89.5)	0.1 (0.0-0.4)	100	1.8 (0.3-10.4)	0.9 (0.6-1.4)	88.9 (88.3-89.4)
NICE High Risk ≥1	8.8 (0.5-160.0)	100 (47.8-100)	44.6 (43.7-45.5)	0.1 (0.1-0.1)	100	1.8 (1.8-1.8)	0	44.6 (43.7-45.5)
Lactate ≥4 mmol/l	52.9 (5.3-527.5)	75.0 (19.4-99.4)	94.6 (92.1-96.5)	11.1 (5.9-19.9)	99.8 (98.7-100)	14.0 (7.0-27.8)	0.3 (0.1-1.4)	94.5 (91.9-96.4)
Lactate ≥2 mmol/l	4.3 (0.4-41.9)	75.0 (19.4-99.4)	59.1 (54.3-63.7)	1.6 (0.9-2.8)	99.6 (98.0-99.9)	1.8 (1.0-3.3)	0.4 (0.1-2.3)	59.2 (54.5-63.8)

Abbreviations: CI, confidence interval; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute for Health and Care Excellence.

Figure Legends

Figure 1. Flow diagram summarising the composition of the validation cohort

Abbreviations: CC, critical care; ED, emergency department; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute for Health and Care Excellence.

Figure 2. Receiver operating characteristic curves for each scoring system or blood biomarker in predicting critical care admission in the amendment cohort

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; NICE, National Institute of Health and Care Excellence; CRP, C-reactive protein.

PEWS data not available because it was not in-use at the hospital when amendment cohort data collected.

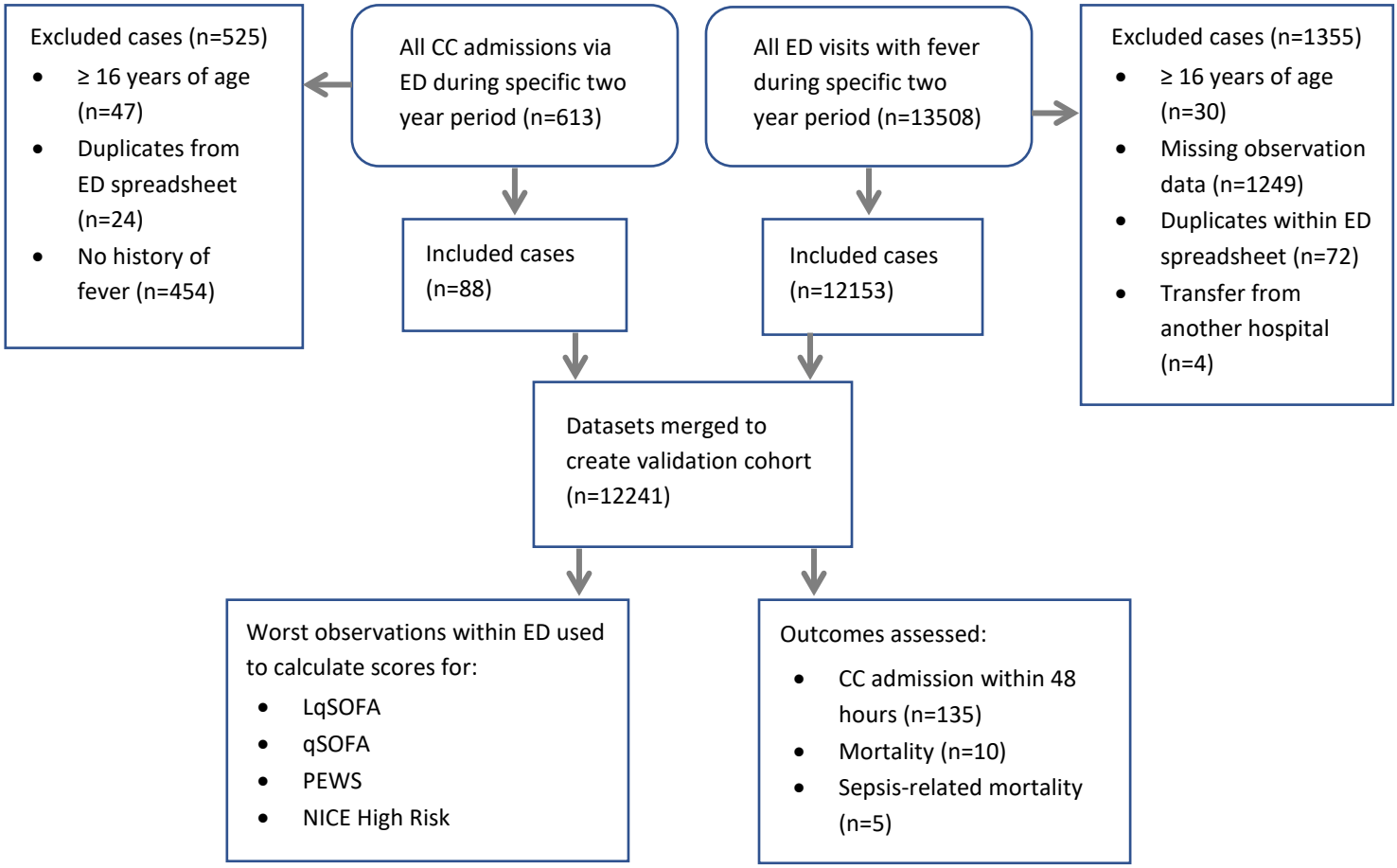
Figure 3. Receiver operating characteristic curves for each scoring system or blood biomarker in predicting critical care admission in the validation cohort

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute of Health and Care Excellence; CRP, C-reactive protein.

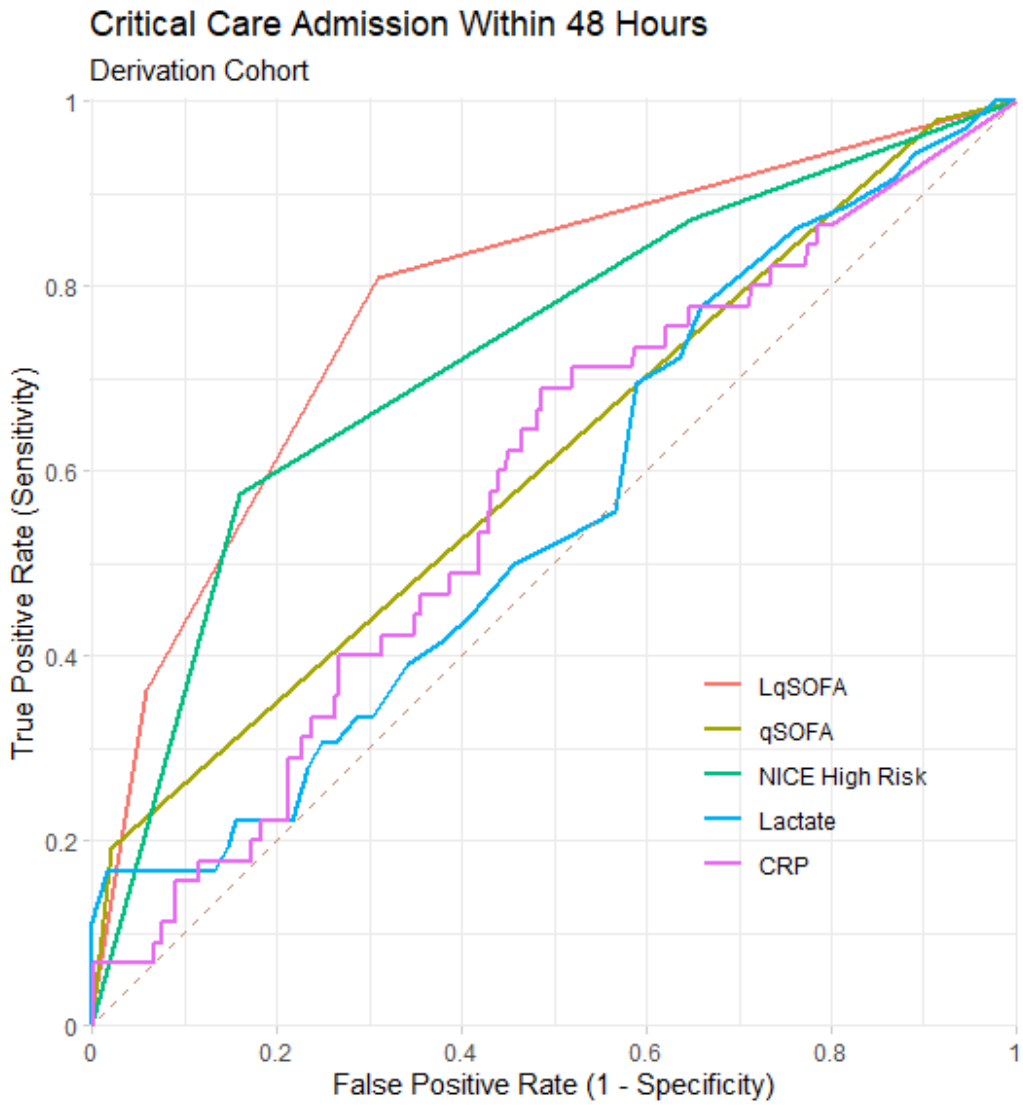
Figure 4: Percentage of validation cohort patients admitted to critical care by LqSOFA score, qSOFA score, NICE High Risk, and PEWS, annotated with raw figures above each bar

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Pediatric Early Warning Score; NICE, National Institute of Health and Care Excellence; CRP, C-reactive protein.

Figure 1. Flow diagram summarising the composition of the validation cohort



Abbreviations: CC, critical care; ED, emergency department; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Paediatric Early Warning Score; NICE, National Institute for Health and Care Excellence.



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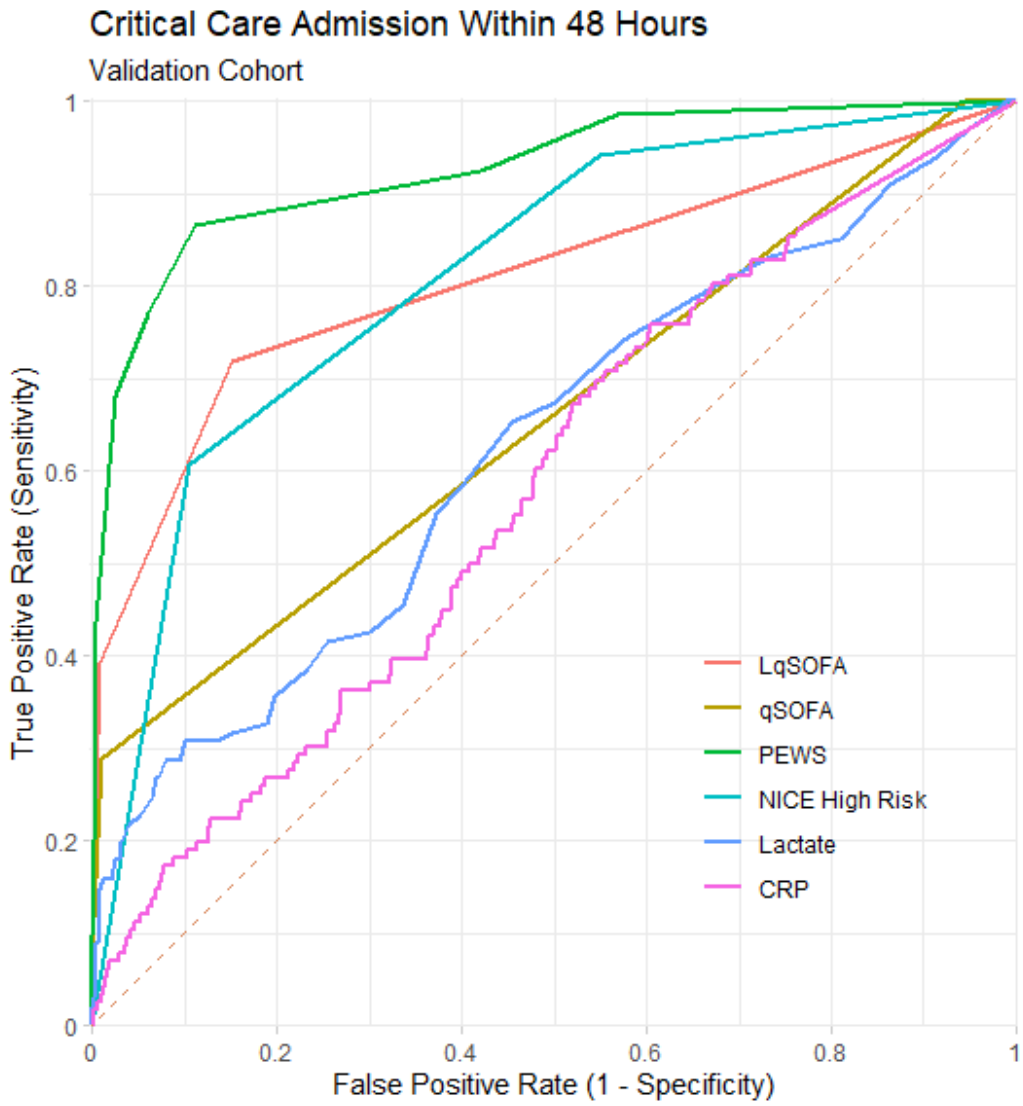

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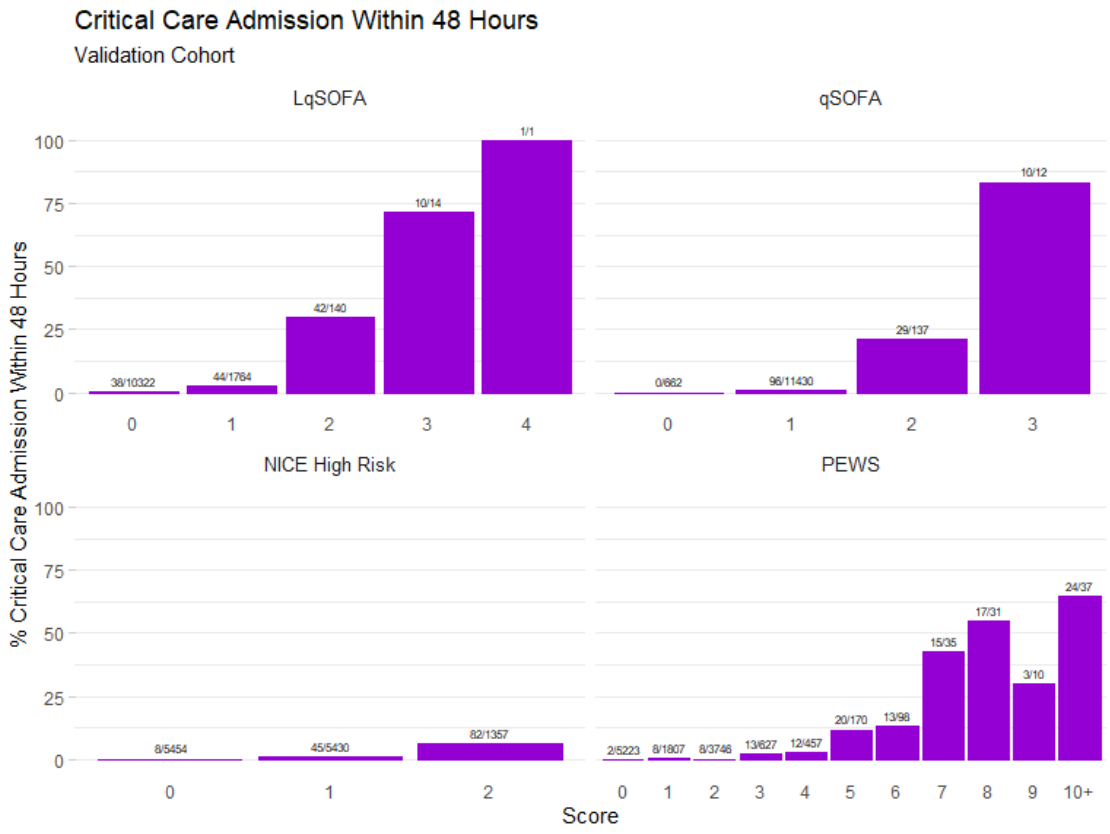


Figure 4: Percentage of validation cohort patients admitted to critical care by LqSOFA score, qSOFA score, NICE High Risk, and PEWS, annotated with raw figures above each bar

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Paediatric Early Warning Score; NICE, National Institute of Health and Care Excellence; CRP, C-reactive protein.

Supplementary Material

Development of the novel LqSOFA score

Study population

A prospective, observational study was undertaken on children (<16 years) admitted to the Emergency Department (ED), at Alder Hey Children's Hospital, with fever >38ºC or a history of fever. The study was conducted between November 2010 and April 2012 and collected data from 1872 eligible patients, of which 1183 were recruited.[1] The data from this published study were used to derive the Liverpool quick Sequential Organ Failure Assessment (LqSOFA) score.

Development of scoring system

The score (Supplementary Table 1) was developed by using quick Sequential Organ Failure Assessment (qSOFA) variables and adapting them to be more pediatric focused, as well as being rapid and easy to measure in children. Capillary refill time (CRT) and heart rate (HR) were selected as alternatives to blood pressure measurements, as hypotension is a late sign in children, and blood pressure measurements are frequently not available in paediatric EDs. Altered mentation was simplified to the Alert, Responds to Voice, Responds to Pain, and Unresponsive (AVPU) scale. Respiratory rate (RR) was retained, as it is easily measurable.

Capillary refill sub score

CRT was used as a surrogate measurement to blood pressure as it is easier to measure in a child, and can be performed as a rapid assessment of perfusion. CRT is a specific "red-flag" sign of serious illness in children: children with prolonged CRT have a four-fold risk of mortality compared to children with normal CRT.[2] NICE sepsis guidelines suggest a CRT> 3 seconds as a moderate to high risk criterion.[3]

Neurological sub score

Altered mentation used in qSOFA can be difficult to assess in children therefore to simplify this variable AVPU was used, as it is frequently used as part of the ED triage, and can be performed rapidly. There is good correlation between simple and fast consciousness AVPU scoring and standard paediatric Glasgow Coma Scale (GCS) in paediatric patients in a prehospital setting.[4]

Heart rate and Respiratory rate sub scores

HR and RR are two quick and easily measurable variables however their normal reference ranges vary with age. We therefore compared two published reference ranges, O'Leary et al.,[5] and Bonafide et al.,[6] to determine which produced the most discriminative age-dependent cut-offs for use in the scoring system (Supplementary Table 2).

Supplementary Table 1. The proposed criteria and thresholds for a novel scoring system

Criterion	Points allocated	
	1 point	0 points
Capillary refill time	≥3 seconds	<3 seconds
AVPU	VPU	A
Heart rate	>99th centile O'Leary et al.[5] age-specific thresholds **Or** >95th centile O'Leary et al.[5] age-specific thresholds **Or** >99th centile Bonafide et al.[6] age-specific thresholds **Or** >95th centile Bonafide et al.[6] age-specific thresholds	≤99th centile O'Leary et al.[5] age-specific thresholds **Or** ≤95th centile O'Leary et al.[5] age-specific thresholds **Or** ≤99th centile Bonafide et al.[6] age-specific thresholds **Or** ≤95th centile Bonafide et al.[6] age-specific thresholds
Respiratory rate	>99th centile O'Leary et al.[5] age-specific thresholds **Or** >95th centile O'Leary et al.[5] age-specific thresholds **Or** >99th centile Bonafide et al.[6] age-specific thresholds **Or** >95th centile Bonafide et al.[6] age-specific thresholds	≤99th centile O'Leary et al.[5] age-specific thresholds **Or** ≤95th centile O'Leary et al.[5] age-specific thresholds **Or** ≤99th centile Bonafide et al.[6] age-specific thresholds **Or** ≤95th centile Bonafide et al.[6] age-specific thresholds

Abbreviations: AVPU, Alert/Voice/Pain/Unresponsive scale.

Supplementary Table 2. O'Leary et al.[5] and Bonafide et al.[6] 99th and 95th centile thresholds for heart rate and respiratory rate

Heart rate (bpm)		>99th centile O'Leary	>95th centile O'Leary		>99th centile Bonafide	>95th centile Bonafide
	0-<3 months	181	171	0-<3 months	186	171
	3-<6 months	174	161	3-<6 months	182	167
	6-<9 months	172	159	6-<9 months	178	163
	9-<12 months	174	160	9-<12 months	176	160
	12-<18 months	176	159	12-<18 months	173	157
	18-<24 months	172	154	18-<24 months	170	154
	2-<3 years	162	146	2-<3 years	167	150
	3-<4 years	152	138	3-<4 years	164	146
	4-<6 years	146	133	4-<6 years	161	142
	6-<8 years	141	128	6-<8 years	155	137
	8-<12 years	135	122	8-<12 years	147	129
	12-<15 years	127	113	12-<15 years	138	121
	15-<16 years	122	111	15-<18 years	132	115
Respiratory rate (breaths/minute)		>99th centile O'Leary	>95th centile O'Leary		>99th centile Bonafide	>95th centile Bonafide
	0-<3 months	60	51	0-<3 months	76	62
	3-<6 months	55	46	3-<6 months	71	58
	6-<9 months	51	42	6-<9 months	67	54
	9-<12 months	46	39	9-<12 months	63	51
	12-<18 months	42	36	12-<18 months	60	48
	18-<24 months	40	34	18-<24 months	57	45
	2-<3 years	38	32	2-<3 years	54	42
	3-<4 years	34	30	3-<4 years	52	40
	4-<6 years	32	28	4-<6 years	50	37
	6-<8 years	31	28	6-<8 years	46	35
	8-<12 years	29	26	8-<12 years	41	31
	12-<15 years	28	24	12-<15 years	35	28
	15-<16 years	28	24	15-<18 years	32	26

Abbreviations: bpm, beats per minute

Calculation of the score

The worst observations recorded during ED stay were used to calculate a score for each patient. The neurological and cardiorespiratory parameters were applied to each patient, using age-specific limits for HR and RR. Each patient received an overall score between 0–4. Scoring significantly on the criterion was defined as an overall score of ≥2, e.g. scoring 1 on two or more of the variables, as this is the method used to calculate qSOFA. A cut-off ≥2 was used to align to the original qSOFA score.

Outcomes and statistics

Admission to ICU/HDU (critical care) was defined as the primary outcome. The performance characteristics of HR and RR cut offs for O'Leary et al.[5] and Bonafide et al.,[6] at both 99th and 95th centiles, were calculated measured against the primary outcome, using area under the receiving operator curve (AUC). The most discriminating cut off points for HR and RR were used for the criteria. The scoring system was applied to the data

set and analysed to determine proportion of cases which fulfilled the criteria (overall score ≥2) in relation to the primary outcome.

Amendment cohort characteristics

Out of the 1183 patients recruited, 62 were excluded due to missing data in the CRT, AVPU, HR, and RR categories. Cases were excluded if two or more variables were missing, if one variable was missing this was deemed to be normal. This left 1121 cases, of which 47 were admitted to critical care.

Comparison of O'Leary and Bonafide 95th and 99th centiles for HR and RR

The 95th and 99th centile reference ranges for Bonafide et al.[6] and O'Leary et al.[5] were applied to the data set for HR and RR; HR/RR >centile = 1 and HR/RR ≤centile = 0. The performance of each set of reference ranges at discriminating critical care admission was assessed using AUC. O'Leary et al.[5] 95th centile was the least discriminative of ICU/HDU admission (AUC=0.764) whereas Bonafide et al.[6] 99th centiles showed the greatest discrimination (AUC=0.783). Bonafide et al.[6] 99th centile reference ranges were therefore used in the score (Supplementary Table 3).

Supplementary Table 3. Thresholds used in LqSOFA including Bonafide et al.[6] 99th centile reference ranges for heart rate and respiratory rate

Criterion		Points allocated	
		1 point	0 points
Capillary refill time		≥3 seconds	<3 seconds
AVPU		VPU	A
Heart rate (bpm)	0-<3 months	>186	≤186
	3-<6 months	>182	≤182
	6-<9 months	>178	≤178
	9-<12 months	>176	≤176
	12-<18 months	>173	≤173
	18-<24 months	>170	≤170
	2-<3 years	>167	≤167
	3-<4 years	>164	≤164
	4-<6 years	>161	≤161
	6-<8 years	>155	≤155
	8-<12 years	>147	≤147
	12-<15 years	>138	≤138
	15-<18 years	>132	≤132
Respiratory rate (breaths/minute)	0-<3 months	>76	≤76
	3-<6 months	>71	≤71
	6-<9 months	>67	≤67
	9-<12 months	>63	≤63
	12-<18 months	>60	≤60
	18-<24 months	>57	≤57
	2-<3 years	>54	≤54
	3-<4 years	>52	≤52
	4-<6 years	>50	≤50
	6-<8 years	>46	≤46
	8-<12 years	>41	≤41
	12-<15 years	>35	≤35
	15-<18 years	>32	≤32

Abbreviations: AVPU, Alert/Voice/Pain/Unresponsive scale; bpm, beats per minute.

Application of scoring system

The scoring system was applied to the data set to give each patient a score of 0 or 1 for each of the four variables (Supplementary Table 3). Of 1121 patients, 64 (5.71%) scored 1 for CRT, 29 (2.59%) scored 1 for AVPU, 290 (25.87%) scored 1 for HR, and 67 (5.98%) scored 1 for RR. This then gave each patient an overall score of minimum 0 and maximum 4 (Supplementary Table 4). A total of 79 (7.05%) patients met the criteria of score ≥2 and of that group, 17 (36.17%) were admitted to ICU/HDU (Supplementary Table 5).

Supplementary Table 4. Distribution of cases scoring 0 or 1 for each variable of LqSOFA

	Capillary refill time		AVPU		Heart rate		Respiratory rate	
	N	%	N	%	N	%	N	%
Cases scoring 1	64	5.71	29	2.59	290	25.87	67	5.98
Cases scoring 0	1057	94.29	1092	97.41	831	74.13	1054	94.02

Abbreviations: AVPU, Alert/Voice/Pain/Unresponsive scale.

Supplementary Table 5. Distribution of patients meeting criteria according to primary outcome

	All cases		Primary outcome: CC admission	
	N	%	N	%
Score ≥2	79	7.05	17	36.17
Score <2	1042	92.95	30	63.83

Abbreviations: CC, critical care.

Performance of each scoring system and biomarker in amendment cohort

Supplementary Table 6. AUCs for primary outcome for LqSOFA, qSOFA, NICE High Risk, lactate, and CRP in amendment cohort

Predictor	**Definition**	**Primary outcome: critical care admission**
		AUC (95% CI)
LqSOFA	LqSOFA score	0.78 (0.71-0.85)
	LqSOFA ≥2	0.65 (0.56-0.75)
	LqSOFA ≥1	0.75 (0.68-0.82)
qSOFA	qSOFA score	0.61 (0.52-0.70)
	qSOFA ≥2	0.59 (0.49-0.68)
	qSOFA ≥1	0.53 (0.45-0.61)
NICE High Risk	NICE High Risk	0.73 (0.65-0.81)
	NICE High Risk ≥2	0.46 (0.38-0.54)
	NICE High Risk ≥1	0.61 (0.54-0.69)
Lactate	Lactate	0.56 (0.45-0.67)
	Lactate ≥4	0.55 (0.43-0.66)
	Lactate ≥2	0.51 (0.40-0.62)
CRP	CRP	0.58 (0.50-0.66)

Abbreviations: AUC, area under receiver operating characteristic curve; CI, confidence interval.
PEWS data not available because it was not in-use at the hospital when amendment cohort data collected.

Criteria and thresholds used in qSOFA, NICE High Risk, and PEWS scoring

For the qSOFA score calculation we used the age-specific cut-offs for RR and systolic blood pressure, as per the corrected 2005 Pediatric Sepsis definitions.[7,8] The AVPU scale was used to assess altered mentation, with readings below Alert given a score of 1 (Supplementary Table 7). The HR and RR components of the NICE High Risk criteria were assessed in the study (Supplementary Table 8). The PEWS used in the present study can be seen in Supplementary Figure 1. As with the LqSOFA, if two or more variables of any scoring system were not recorded, this case was excluded from the study.

Supplementary Table 7. Scoring thresholds for each component of qSOFA as described in corrected 2005 Paediatric Sepsis Definitions[7,8]

Criterion		Points allocated	
		1 point	0 points
AVPU		VPU	A
Systolic blood pressure	0-1 week	<59	≥59
	>1 week-1 month	<79	≥79
	>1 month-1 year	<75	≥75
	>1 year-5 years	<74	≥74
	>5 years-12 years	<83	≥83
	>12 years-<18 years	<90	≥90
Respiratory rate	0-1 week	>50	≤50
	>1 week-1 month	>40	≤40
	>1 month-1 year	>34	≤34
	>1 year-5 years	>22	≤22
	>5 years-12 years	>18	≤18
	>12 years-<18 years	>14	≤14

Abbreviations: AVPU, Alert/Voice/Pain/Unresponsive scale.

Supplementary Table 8. Scoring thresholds for each component of NICE High Risk criteria as described in NICE sepsis guidance[3]

Criterion		Points allocated	
		1 point	0 points
Heart rate (bpm)	0-<1 year	≥160	<160
	1-<3 years	≥150	<150
	3-<5 years	≥140	<140
	5-<6 years	≥130	<130
	6-<8 years	≥120	<120
	8-<12 years	≥115	<115
	≥12 years	≥130	<130
Respiratory rate (breaths/minute)	0-<1 year	≥60	<60
	1-<3 years	≥50	<40
	3-<5 years	≥40	<40
	5-<6 years	≥29	<29
	6-<8 years	≥27	<27
	8-<12 years	≥25	<25
	≥12 years	≥25	<25

Abbreviations: bpm, beats per minute.

Alder Hey Paediatric Early Warning Score-thresholds for alert and response

Respiratory rate	99th centile	90th centile	Acceptable	10th centile	1st centile	Core
Score	2	1	0	1	2	
Age 0-1yr	≥ 70	60 – 69	26-59	20-25	< 20	
Age 1-2yr	≥ 55	50-54	21-49	15-20	<15	
Age 2-7 yr	≥ 40	35-39	21 - 34	15–20	< 15	
Age 7-13yr	≥35	≥30	16-29	≤15	≤10	
All > 13yr	≥35	≥30	11-29	≤10	≤5	

Effort of breathing	Marked subcostal recession, tracheal tug, grunting, nasal flaring, stridor, head bobbing			Core
Score	0= acceptable	1= any one of above	2= any two + of above	

SpO2	≥ 93	88-92	< 88	Core
Score	0	1	2	

O2 delivery	Air	< 28%	29-50%	> 50%	core
	No support	0-2 L/min	3 to 6 L/min	> 6 L/min	
Score	0	1	2	3	

Pulse Score	2	1	0	1	2	Core
Age 0-1yr	≥ 170	160 - 169	101-159	91- 100	≤90	
Age 1-2yr	≥ 165	155 - 164	101-154	81- 100	≤80	
Age 2-7 yr	≥ 140	135 - 139	91-134	81–90	≤80	
Age 7-13yr	> 130	125-130	71 -124	61–70	≤ 60	
All > 13yr	≥ 130	120–129	61-119	51–60	≤ 50	

Blood pressure	Score 10 if systolic BP is on or below 5th centile for age	
Age 0-1yr	≤ Systolic 55	extended
Age 1-2yr	≤ Systolic 65	
Age 2-7 yr	≤ Systolic 70	
Age 7-13yr	≤ Systolic 75	
All > 13yr	≤ Systolic 80	

Capillary refill T	1-2 seconds	3-4 seconds	> 4 seconds	
Score	0	1	2	core

AVPU	Alert	Verbal	Pain	Unresponsive	extended
Score	0	1	3	10	

Nurse concern	Score 1: if nurse concerned child is deteriorating	core
Parent concern	Score 1: if parent is concerned that child is deteriorating	extended

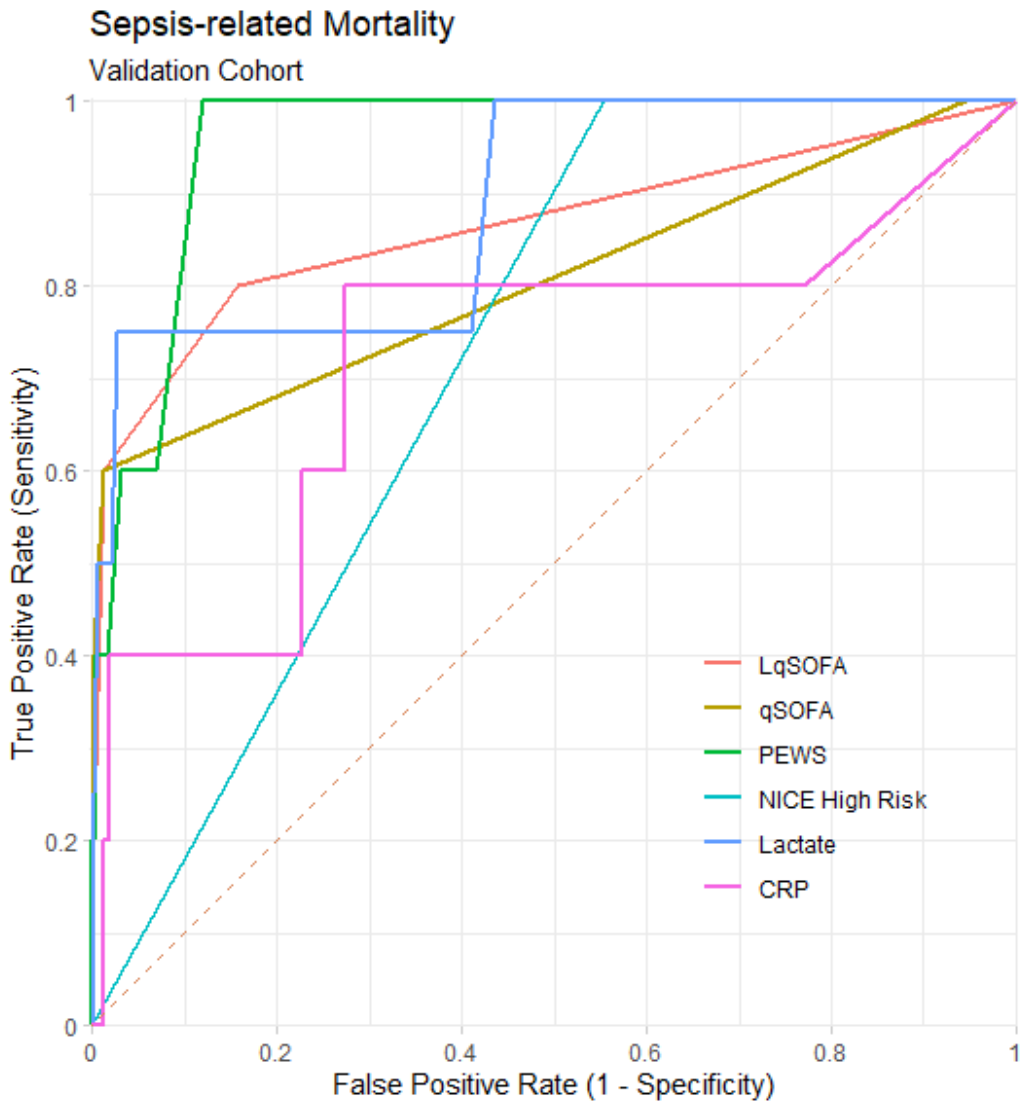
Action to be taken for PEW scores
Score 0 - 2 . Accept as variant of normal. Observations minimum 4 hrly
Score 3- 5. Review by nurse in charge (NIC) of ward. Take a complete set of obs within 1/2 hour If repeat score is 3 -5 , increase the frequency of obs. If the NIC is concerned about the patient get a medical review within one hour. SHO/F2 discuss case with Reg. Agree plan with NIC
Score 6 - 9. Review by nurse in charge (NIC) of ward. Take a complete set of obs within 10 mins If repeat score is 6 -9 , increase the frequency of obs. Start continuous monitoring Get urgent medical review within 30 mins. Agree plan with NIC & Reg
Score 10+. Review by nurse in charge (NIC) of ward. Take a complete set of obs immediately. Continuous monitoring. Urgent review by registrar or above within 10 minutes If cannot contact own team - call 2222
Use SBAR to communicate critical information in a succinct and structured format
Paediatric Early Warning systems do not replace your clinical judgement. It is an adjunct. If a patients is deteriorating rapidly - call 2222

Supplementary Figure 1. Individual components, scoring thresholds, and response to overall score of the PEWS used in the present study

Abbreviations: Yr, year; SpO2, peripheral capillary oxygen saturations; BP, blood pressure; T, time; AVPU, Alert/Voice/Pain/Unresponsive scale; Obs, observations; SHO, Senior House Officer; F2, Foundation Year 2 Doctor; Reg, Specialist Registrar; SBAR, Situation/Background/Assessment/Recommendation communication technique.

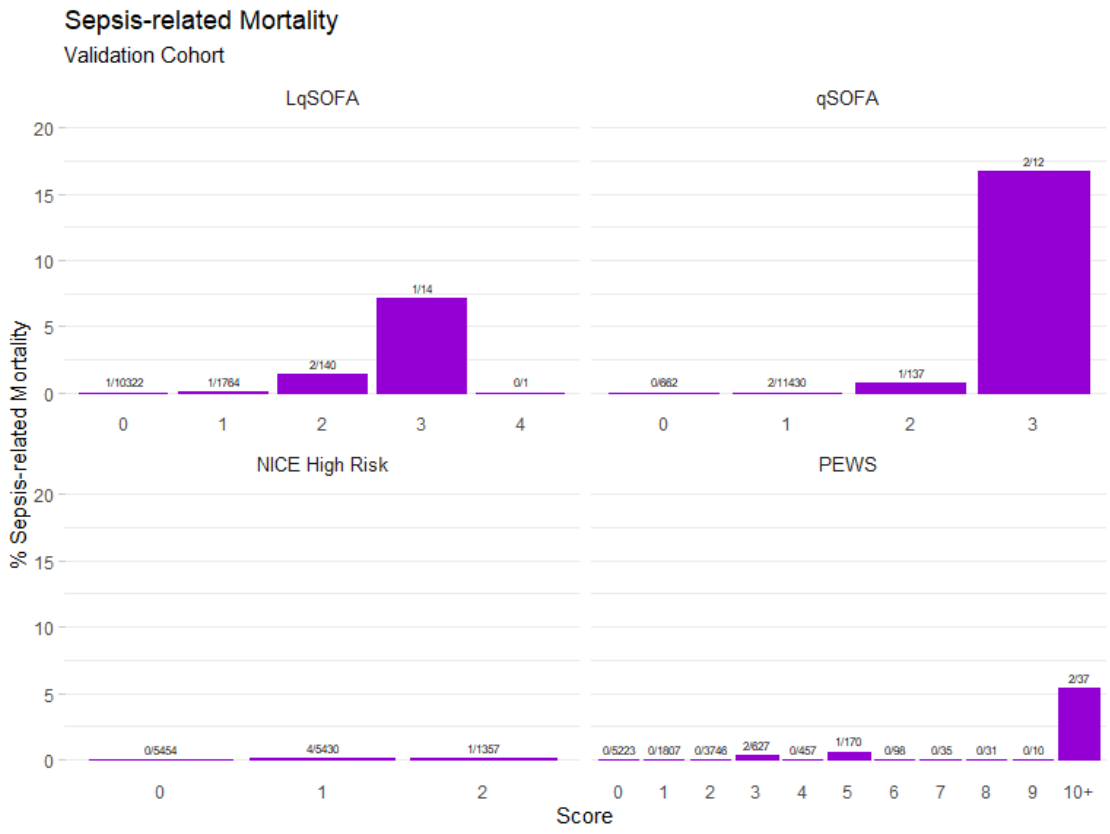
Performance of each scoring system and biomarker in validation cohort

ROC curves for the secondary outcome can be seen in Supplementary Figure 2. Supplementary Figure 3 shows the percentage of patients with sepsis-related mortality, by score, for each of the four systems. Supplementary Figure 4 demonstrates the number of critical care admissions correctly predicted by each scoring system.



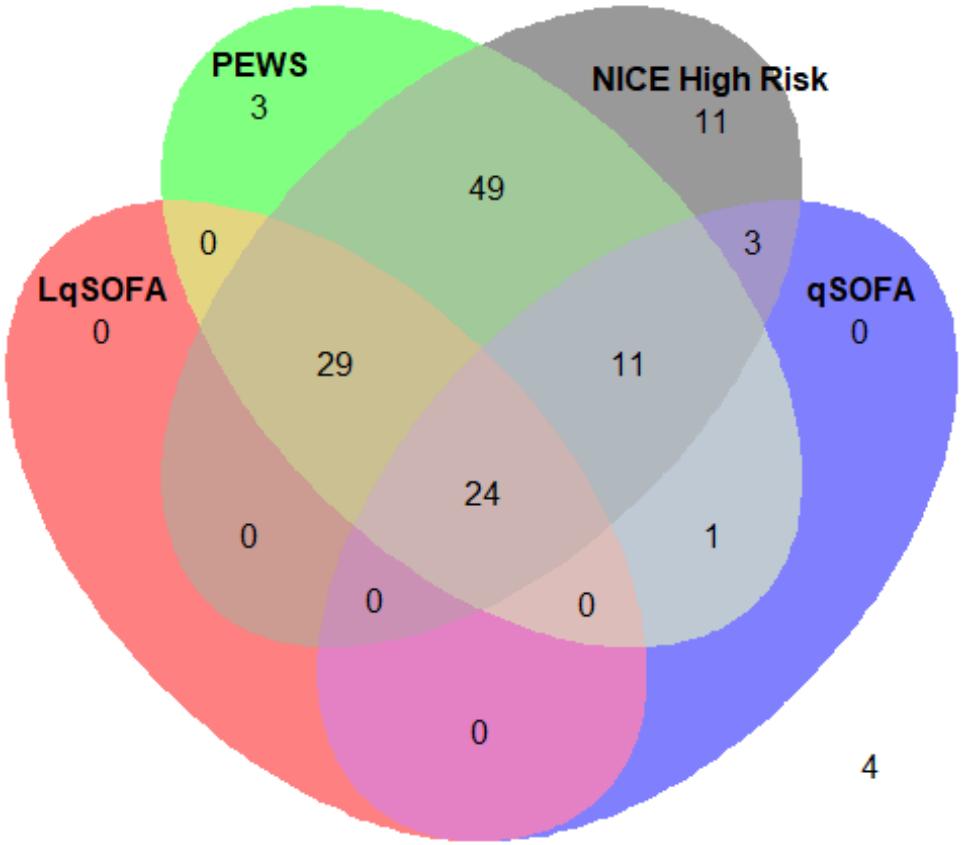
Supplementary Figure 2. Receiver operating characteristic curves for each scoring system or blood biomarker in predicting sepsis-related mortality in the validation cohort

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; PEWS, Paediatric Early Warning Score; NICE, National Institute of Health and Care Excellence; CRP, C-reactive protein.



Supplementary Figure 3: Percentage of validation cohort patients with sepsis-related mortality by LqSOFA score, qSOFA score, NICE High Risk, and PEWS, annotated with raw figures above each bar

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; NICE, National Institute of Health and Care Excellence; PEWS, Paediatric Early Warning Score.



Supplementary Figure 4. Venn diagram demonstrating the number of critical care admissions within 48 hours in the validation cohort that were correctly predicted by each of the four scoring systems or combination thereof

Abbreviations: LqSOFA, Liverpool quick Sequential Organ Failure Assessment; PEWS, Paediatric Early Warning Score; NICE, National Institute of Health and Care Excellence; qSOFA, quick Sequential Organ Failure Assessment.

Thresholds used for each scoring system: LqSOFA ≥2, qSOFA ≥2, PEWS ≥3 and NICE High Risk ≥1. 135 critical care admissions in total. Four critical care admissions were not predicted by any of the scoring systems.

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