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REVIEW ARTICLE

Identification of sepsis in paediatric emergency departments: A scoping review

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Abstract

Aim: Sepsis is an acute illness associated with significant morbidity and mortality. Early detection and time-sensitive management of sepsis has been shown to improve outcomes. We report the results of a scoping review to explore methods evaluated for the identification of sepsis in children presenting to emergency departments.

Methods: A systematic literature search was carried out on two databases, Medline and Web of Science, to identify relevant studies published from 1990 to 2022. Data were extracted for age groups including study design, reference standard used for comparison, sepsis identification method evaluated and study quality.

Results: A total of 89 studies were identified from the literature search. There was significant heterogeneity in the age groups including study design and reference standards used for evaluating the performance of the sepsis identification methods. There has been a substantial increase in the number of published studies in the last 2 years.

Conclusion: Our scoping review identifies marked heterogeneity in approaches to identifying sepsis but demonstrates a recent focus of research on patient outcomes. Using appropriate core outcome sets, developing reference standards, monitoring sepsis prevalence via registries and continuously monitoring process measures will provide robust evidence to identify the best performing identification tools and the impact they have on patient-orientated outcomes.

KEYWORDS

alerts, biomarker, children, paediatric emergency department, risk factors, sepsis

1 | INTRODUCTION

Sepsis is an acute illness seen in all ages. Despite the advances in medical technology and care, the burden of sepsis on global health is significant.[1,2] Time-sensitive management improves outcomes in sepsis,[3–5] with delay in identification and treatment associated with higher mortality.[6] In the absence of a gold standard for identification and diagnosis of sepsis, a definition of sepsis based on systemic inflammatory response syndrome (SIRS) criteria was agreed for the paediatric age groups at the International Pediatric Consensus Conference in 2005.[7] According to this, sepsis is defined as the presence of at least two of the following four criteria—temperature > 38.5°C or < 36°C, tachycardia, increased respiratory rate and abnormal leucocyte count in the presence of suspected or

proven infection. At least one of the four criteria should be either abnormal temperature or leucocyte count. A more recent guidance for the management of septic shock and sepsis-associated organ dysfunction used the same criteria for diagnosis of sepsis. In addition, it recommends systematic screening for septic shock and sepsis-associated organ dysfunction in children with acute illness, for early diagnosis and management. This helps to underscore the identification of sepsis to patient outcomes.[8] The adult 'Sepsis-3' definition of sepsis (Third International Consensus Definitions for Sepsis and Septic Shock, 2016) includes organ dysfunction defined using the Sequential Organ Failure Assessment (SOFA) score or the 'quick' (q)SOFA score, but an equivalent validated for children is yet to be adopted.[9] In children presenting to emergency departments, identifying the proverbial 'needle in the haystack' that is sepsis can be a challenge to clinicians. Multiple national surveys undertaken by research networks such as Paediatric Research in the United Kingdom and Ireland (PERUKI), Research in European Pediatric Emergency Medicine (REPEM) and the Paediatric Research in Emergency Departments International Collaborative (PREDICT) have featured the identification of an appropriate biomarker for sepsis high on the research agenda.[10–12]

1.1 | Aim

Following an initial rapid review (SO), it was agreed by the authors that a scoping review would be appropriate to report clinical research on the identification of sepsis in children presenting to emergency departments. The key objectives of the review were as follows:

In children presenting to emergency departments,

- To provide an overview of the tools used to identify sepsis and the trends in research undertaken to study them.
- To identify any inconsistencies in the objectives and methods of the studies and explore reasons for variation.
- To identify gaps in the relevant literature, novel concepts and methodology of excellence to help guide and enhance future research.

2 | METHODS

The Preferred Reporting Items of Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidance published as part of the Ensuring the QUAlity and Transparency of health Research (EQUATOR) network formed the basis for the initial protocol, which was agreed by the research team for this review a priori.[13] It was agreed to conduct a systematic literature search of two databases: Medline and Web of Science. Web of Science was specifically chosen to capture grey evidence such as studies or quality improvement projects presented in academic conferences and not published in peer-reviewed journals.

KEY POINTS

- This review identifies significant heterogeneity and the need for standardisation within the challenging area of research on identifying sepsis in children presenting to emergency department.
- It highlights the effect of prevalence data and patient risk factors for reporting the performance of sepsis identification tools.
- It discusses the importance of implementing changes in patient care processes to improve outcomes in patients with sepsis.

2.1 | Eligibility criteria

2.1.1 | Inclusion criteria

Research studies which meet all of the criteria below

- Primary studies
- Age: infants, children and young people less than 18 years
- Emergency department/acute assessment setting in secondary care
- Objective of study to identify predictors or describe diagnostic accuracy of a risk-stratifying test
- Predictor studied in relation to sepsis or serious/invasive bacterial infection

2.1.2 | Exclusion criteria

- Adult studies (18 years and over)
- Primary care or inpatient populations
- Aim of study not focussed on identification, prediction or risk stratification
- Predictor in relation to infection but not sepsis or serious/invasive bacterial infection
- Opinion pieces/narrative reviews/case reports

The systematic search of literature was carried out from 1st January 1990, as the first sepsis consensus definition was published in adults in 1992.[14] It was initially up to 31 December 2019, but later updated to include published studies up to April 2022. The literature search strategy in both databases was formulated along with a senior health subject librarian (MH) who then verified the validity before final searches were made.

The search strategy used for Medline is reported in Appendix A. The titles and abstracts were screened independently by two researchers (SO and AJ for Web of Science; JE and TC for Medline) to shortlist articles for detailed review. A data collection chart

was agreed a priori and changes made following a trial of detailed reviews on 10 articles by SO and JE. The data collected from the agreed data collection chart (Appendix B) consisted of information relating to the age of patients selected, study design, diagnostic/screening tool tested, results with accuracy data, standard used for comparing the results and if the study design conforms to the Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines.[15] A detailed review of each article was carried out by a single author (JE, SO, AJ or TC). In case of disagreement during the detailed review, one of the authors (DR) helped to arbitrate any discrepancies. The reviewers were not blinded to either author or journal name.

2.2 | Critical Appraisal

Each study was evaluated for amenability to review against the Standards for Reporting Diagnostic Accuracy (STARD 2015). This was based on the following criteria: clear objectives, study design, eligibility criteria, test methods including details of the index test as well as a reference standard, demographics, clinical characteristics of participants, estimation of diagnostic accuracy of index test and limitations.

2.3 | Synthesis

The synthesis included predominantly quantitative analysis of age groups of participants, screening or diagnostic tools used, reference standards used as well as eligibility criteria for including participants. We aimed to report any observed biases or methodological weaknesses with the help of criteria based on the established guidance for reporting diagnostic accuracy studies. We identified common themes in the quality of reporting of the studies. Studies were presented based on thematic characteristics of the articles.

3 | RESULTS

3.1 | Study selection

Please see the flow chart in Figure 1, which gives the numbers of studies identified during the process up to April 2022. We included a total of 89 studies in the review (see appendix C for citations and Table S1 for details).

3.2 | Date of Publication

The number of studies published annually has increased in recent years, with the highest number of studies published of 13 in each of the years 2020 and 2021. Since 2010, there have been publications related to electronic alerts in emergency departments.

3.3 | Age groups studied in different studies

The most common age group included was from 0 to 18 years (14 studies) followed by <3 months (nine studies). There were 22 variations of age groups under 18 years included in different studies. We did not find a reported justification for selecting the specific age group in any of the studies. A specific numerical age group for inclusion was not reported in 11 studies. Of the 89 studies, Cruz et al (2012) and Balamuth et al (2017) reported age-based variation in the performance of their respective sepsis identification tools.

3.4 | Study setting

The performance of an intervention for early diagnosis of sepsis may depend on factors such as resources available, clinical characteristics of patients presenting to the hospital and the prevalence of sepsis among patients presenting to emergency department. Hence, we collected data on the type of hospital setting for the studies. The majority of the studies reviewed (59 of 89) were set in tertiary paediatric hospitals. Of the studies reviewed, 14 were in multiple centres, out of which four were conducted in a mixture of community and tertiary academic hospital settings. Twenty-eight studies were set in tertiary hospital emergency departments with mixed adult and paediatric services. It was not possible to obtain these data in two studies. In two further studies, these data were not relevant as the study design used was based on a data repository or a modified Delphi method, an iterative method of listing clinical features as ranked by clinicians as significant for identifying sepsis with no involvement of patients attending emergency departments. None of the studies reported epidemiological prevalence data of paediatric sepsis in emergency departments. Verbakel et al (2015) compared the performance of a clinical prediction tool in a variety of settings including general/family practice, clinics and the emergency department. Akech et al (2020) reported the use of procalcitonin to identify serious infections in a resource-challenged setting and used clinical criteria to confirm meningitis. This shows the impact of resources in settings when designing sepsis identification tools.

3.5 | Types of identification tools evaluated

Biomarkers, in isolation, have been the most extensively studied predictors accounting for 39 out of 89 (44%) studies. The numbers and proportions of other methods in decreasing order were clinical variables or parameters during clinician assessments (20 of 89, 22%), methods using a combination of clinical parameters and biomarkers (17 of 89, 19%) and electronic alerts (13 of 89, 15%). (Figure 2). Please see Table 1 for specific identification tools used in each category. There has been an increase in the reporting of studies using electronic prediction tools in the last 4 years. (Table 3).

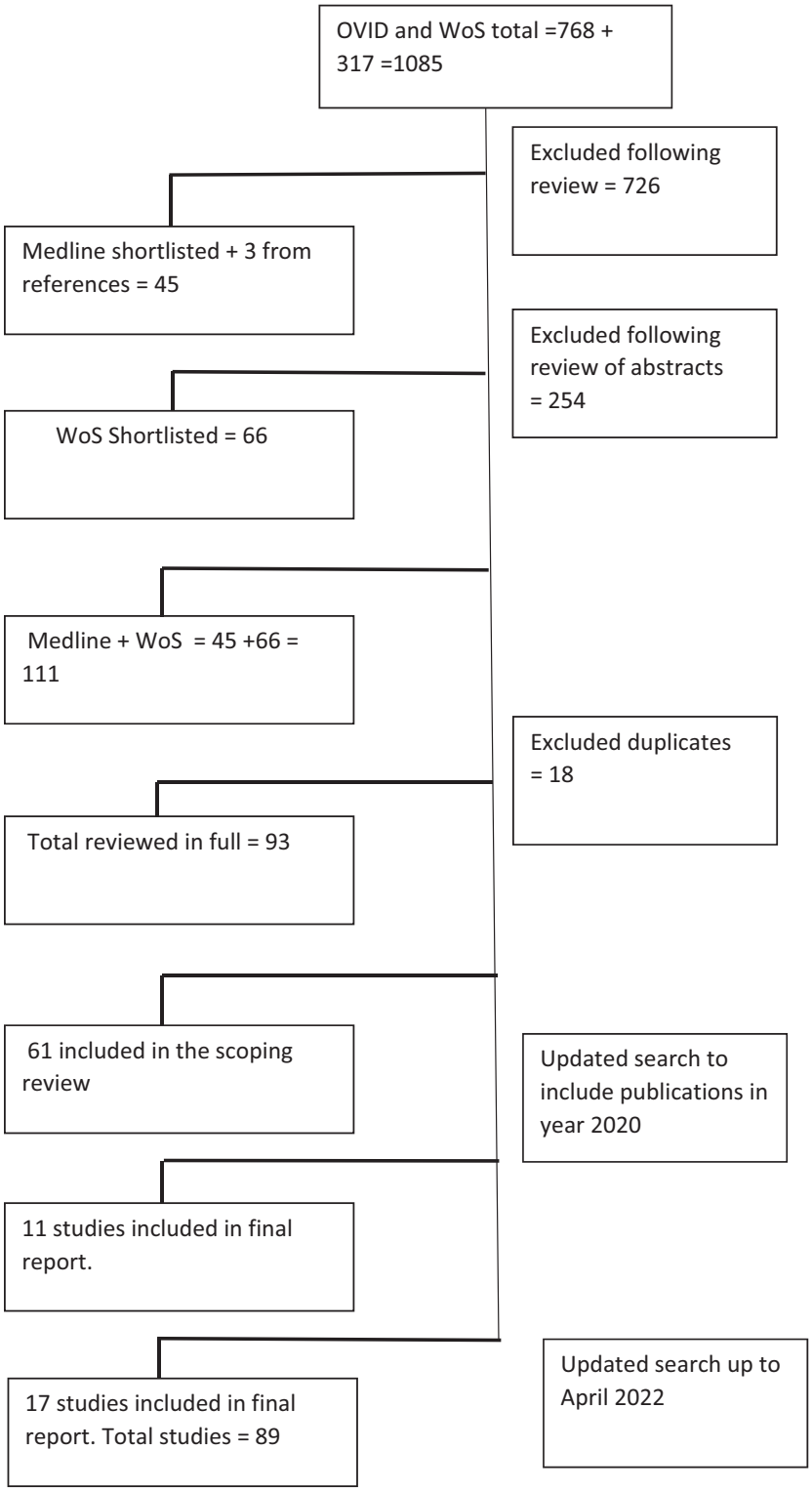

FIGURE 1 Flow chart of search and study selection process. WoS—Web of Science

3.6 | Quality of the Studies

Two studies reported a priori adherence to design and reporting recommendations. (Waterfield et al, 2020—STARD & Long et al, 2020—Strengthening the Reporting of Epidemiology Studies STROBE). Although full systematic critical appraisal was not the objective of this review, the feasibility of reviewing reported studies against the STARD criteria was evaluated for each study. It would have been feasible to appraise the quality of studies against the STARD criteria in 61 of the 89 studies (78%). A total of 85 studies had the objective to evaluate a sepsis detection method or tool, 64 studies reported sensitivity and specificity, and 37 studies reported area under receiver operating characteristic (AUROC) analysis. One aspect of the review process was evaluation of the studies for bias and other methodological limitations. Of the 89 studies reviewed, 40 used retrospective data which introduces observer or recall bias.

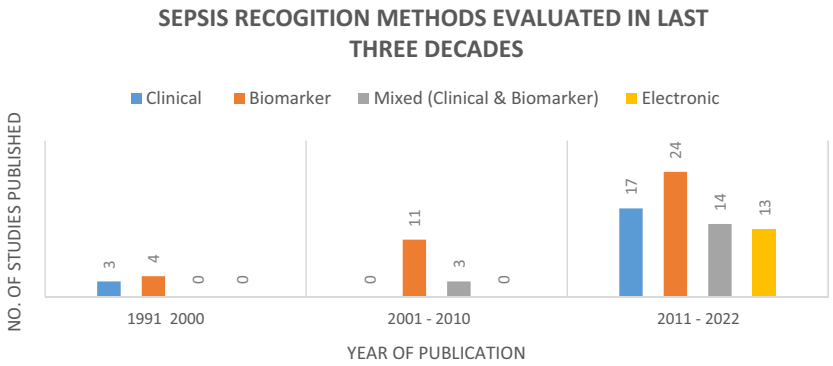

FIGURE 2 Relative frequencies of different methods evaluated in each decade since 1991

Bias inherent in variations in the selection of patients may have led to exclusion of participants with sepsis. An example is the inclusion of only febrile infants, which may miss those infants who are normothermic or hypothermic and have sepsis. As many of the studies using biomarkers or electronic alerts did not blind clinicians to the Index test result, there would have been the risk of a positive result influencing the behaviours and interpretation of the clinical situation. Other examples of bias are the use of the test in making clinical diagnosis (incorporation bias) or variation in the reference standards (Table 2) due to subjective differences in clinicians involved in making the diagnosis (differential verifications). The majority of the studies did not report local prevalence of sepsis in emergency department attendances, leading to difficulties in interpreting external validity due to the likely variable prevalence. Only one study (Nijman et al, 2017) reported the performance of a tool based on combination of clinical parameters and CRP to identify sepsis at different risk thresholds or pre-test probabilities. The methods used in the last 5 years showed 24 of the 45 studies were prospective cohort studies. The variation in age groups included in the studies is less with more studies reporting findings in children under 18 years. There has been an increase in the use of patient-orientated and clinical outcome measures such as admission in intensive care, as reference standards to report performance of the identification tool.

3.7 | Thematic review of the studies

A group of papers highlighted negative association of symptoms or markers with sepsis. Li et al (2019) reported most clinical markers, except pre-existing clinical problems, were associated with false-positive sepsis screens. Edgil et al (2017) reported laboratory markers not associated with sepsis and Snelson et al (2018) used the modified Delphi method to identify patient behaviours not associated with sepsis. Mintegi et al (2018) reported the association of a negative symptom (lack of fever) with invasive bacterial infections. However, there were no reports on specificity and likelihood ratios in these studies, which makes clinical application and interpretation of results challenging. Benito et al (2013), Mickiewicz et al (2018) and Eckerle et al (2017) used multiple biomarkers for the identification of sepsis or serious infections. Waterfield et al (2020), Milcent et al (2016) and Gendrel et al (1999) reported the performance of procalcitonin and CRP at different cut-offs. Rautiainen et al (2019) and Eisenberg et al (2021) reported longitudinal screening of patients, which may have improved the sensitivity of their sepsis identification tool. Studies by Larsen et al (2011) and Cruz et al (2012) reported process and clinical outcomes following the interventions to identify sepsis early. Recent studies (Solé-Ribalta et al 2022, Chong et al 2021 and Romaine et al 2021) reported the performance of sepsis identification tools using clinical outcomes, cost or quality of life years (QALY) as reference standards. We identified some studies, which aimed to evaluate the role of subjective clinical details such as clinician gut feeling, parental concerns or behavioural aspects of children to identify sepsis (Snelson et al, 2018 and Urbane et al, 2019). The study by Waterfield et al in 2020 evaluated the incidence of abnormal vital signs on presentation to the emergency department and the correlation with serious illness. Even though not evaluating a specific tool for the identification of sepsis using recommended methods, it attempted to address some common clinical questions faced by clinicians and would aid the design of further research in the future.

4 | DISCUSSION

This scoping review identified 89 studies which reported outcomes of various prediction, detection or diagnostic tools for sepsis or severe bacterial infections from 1990 to 2022. This has highlighted a recent increase in the reporting of such studies. This review has identified significant heterogeneity in various aspects of the studies including age of subjects, study design, inclusion criteria, type of tools or index tests used, reference standards used for comparison and reporting strategies. Reviewing the collective body of published literature has identified many areas for consideration when planning and implementing paediatric sepsis research.

4.1 | Definition and Reference Standard

There is significant heterogeneity in the use of different reference standards for defining sepsis when reporting the performance of sepsis identification tools. A clear and ubiquitously agreed definition of sepsis would reduce heterogeneity and enable collective

TABLE 1 Specific tools used within the following categories: biomarkers, clinical parameters, clinical and biomarker and electronic alert

Screening or diagnostic Category	Specific tool or method tested (no. of studies)
Biomarkers	Procalcitonin(4); lactate(3); decision tree comprising IL 27, ECC and PCT (1); nCD64 (1); IL-6(1)
	Urine dipstick (1); urinalysis, white Blood Cell count, neutrophils and procalcitonin (1); lab score comprising urine dipstick, PCT and CRP (1)
	WCC (3); WCC, neutrophils and CRP(1); PoCT lacate, WCC and CRP (1)
	CRP (1); compare CRP and serum amyloid A –SAA (1)
	Combined immature granulocyte percentage, WCC and CRP (1); immature granulocytes.
	PCT, interferon-alpha and comparison with Interleukin–6 (IL-6) (1); compare Q-PCT, CRP and WCC (3); compare PCT, WCC and neopterin (1); Compare PCT, CRP, WCC and absolute neutrophil count (1); PCT, CRP, neutrophil–lymphocyte ratio and Urinalysis(1); compare PCT and CRP (1)
	Neutrophil–lymphocyte ratio (NLR), Mean Platelet Volume (MPV) and Platelet-MPV ratio (PLT/MPV (1); compare eosinophil count with neutrophils and WCC (1)
	Pro-adrenomedullin and pro-endothelin and comparison with CTP, WCC and PCT (1)
	Transcriptomics or gene expression markers(1); metabolic and protein mediators(1); Cytokine and chemokine markers (1)
Clinical parameters	PaedCTAS, APLS and Fleming normal reference values (1)
	clinical criteria (2); clinical prediction tool (1)
	Well or ill appearance of child (1); child behaviour (1)
	Clinician gut feeling and parental concern(1)
	Hypothermia in neonates (1); fever (2); temperature–pulse centile charts(1)
	Vital sign measurement (3); SIRS vital signs – heart rate, respiratory rate and temperature-corrected HR(1)
	LiverpoolqSOFA (1)
Clinical and biomarker	Blood culture and paediatric assessment triangle (1)
	Leucocytes in urine, blood leucocyte count, body temperature and age(1)
	Model using clinical parameters and CRP(1); clinical data, PCT and CRP (1); prediction rule using clinical parameters and total WCC (1); Risk Stratification tool using clinical parameter and biomarkers—CRP and WCC (1);
	Pittsburgh criteria for low risk using enhanced urinalysis(1)
	Clinical and biomarker tool (1); temperature and WCC (1)
	Separate evaluation of various clinical and laboratory markers(2)
Electronic alert	Clinical parameters (11)

Abbreviations: APLS, Advanced Pediatric Life Support; CRP, C-reactive protein; HR, Heart Rrate; IL, Interleukin; mSIRS, modified Systermic Inflammatory Response Syndrome criteria; nCD64, neutrophil Cluster of Ddifferentiation; paedCTAS, paediatricpediatric Canadian Triage and Acuity Scale; PCT, Procalcitonin; qSOFA, quick Sequential Organ Failure Assessment score; WCC, white cell count.

interrogation of data such as metanalyses. This has been an ongoing priority posing a significant challenge to gain a widespread international consensus agreement. The variation in the reference standard used reflects the challenge of defining a clinical syndrome lacking a sensitive and specific gold standard test. Measures were taken to address this through adoption of a consensus definition of sepsis for use in research studies and subsequently variably adopted by clinicians in their practice. Despite this, clinicians may find such clearly defined criteria of sepsis inappropriate for use in their daily clinical practice when dealing with an undifferentiated clinical presentation, which can evolve dynamically. This inherent variability in the clinical phenotype based on age and host response, combined with the subjective clinician assessment poses significant challenges to ensuring uniformity in sepsis research. Even though studied in the setting of the paediatric intensive care unit, Weiss et al identified significant discrepancy in the three forms of definitions—research (consensus definition of sepsis), clinician, and administrative (ICD codes).[16] The recommendation by the International Sepsis Forum for research into the use of biomarkers for identification and validation of sepsis is an example of attempts to ensure research is scientifically robust and uniform.[17] Developing an agreed definition of sepsis does not necessarily equate to a less comprehensive description. Some recent studies have adopted a more pragmatic approach of using two or more clinicians independently reviewing the data to set the reference standard. A method adopted by a number of groups recently involves using process and clinical outcome measures, which are

TABLE 2 Reference Standards used

Type of reference standard	Identified methods (no. of studies)
Clinical and laboratory	Meets criteria set by International Paediatric Sepsis Consensus Conference (IPSCC) guideline (8)
Clinical criteria	Clinician diagnosis of sepsis (6)
	Sepsis alert tool (3)
	Septic shock defined as systolic hypotension needing intervention(2)
Laboratory with or without clinical assessment	Serious bacterial infection (or) invasive bacterial infection (or) bacterial infection (or) serious infection (46) Blood culture result (1)
Based on clinical Interventions given to patient	'critical illness requiring intensive care admission except trauma' (5) Fluid bolus or Paediatric Intensive Care Unit admission (1) SIRS with suspected infection and interventions (1) Admission to PICU, death or hospital length of stay (LoS) (1)
Others	Not relevant to study(1)
	Not reported (2)
	ICD = -10 Coding (1); ICD-9 coding (2); both ICD-9 & ICD-10 codes (1)
	Retrospective review of notes (4)
	Sepsis-related mortality(1)
	Combination of paediatric consensus conference sepsis criteria, Paediatric Intensive Care Unit (PICU)/High Dependency Unit (HDU) admission or death (1)
	Combination of IPSCC criteria, intensive care admission or ICD-10 criteria.(1); combination of ICD-9 codes and IPSCC criteria (1)

Note: ICD—International Classification of Diseases coding; *One study used both reference standards of ICCPS definition and ICD-10 code.

patient-oriented. Emergency departments require tools or methods of identifying children who are at risk of serious illness requiring critical care admission, morbidity and mortality, irrespective of them fitting the current strict definition of sepsis. The recent iteration of the definition of sepsis in adults based on the presence of life-threatening organ dysfunction illustrates a focus on patient outcomes.[9] The Pediatric Sepsis Definition Taskforce, convened by the Society of Critical Care Medicine, recognises the need to assess both criteria for the recognition of children with possible sepsis and for the identification of sepsis leading to poor outcomes.[18] This underpins the importance of the early identification of sepsis associated with poor patient outcomes.

The time from birth to 18 years of life is a dynamic and complex phase with significant differences in the biological processes in general and the immune response in particular. A specific age-based evaluation of the various index tests or prediction tools as well as the methods used would be advantageous. Even though we identified high variations in the age groups included in the earlier studies, more recent studies have included all children up to 18 years. With age being one of the strongest risk factors for sepsis, establishing a consensus for reporting the performance of a sepsis identification method with respect to specific age groups would be beneficial.

4.2 | Epidemiology and Collaboration

Prevalence data were seldom reported in the studies reviewed. The performance of any screening or diagnostic tool depends on the prevalence of the medical condition. Therefore, regional and national strategies should include measures to record and share accurate epidemiological data. This would enable tailor-made approaches to sepsis risk stratification, electronic alerts and clinical decision tools, based upon the incidence and risk factors within the local population. One method to achieve this would be the development of national sepsis registries, an example of which is currently being developed in Northern Ireland. High-quality sepsis identification tools, and the research to develop them, will not only need to incorporate this population data but also be adaptable to individual risk factors. Some of the published studies have reported the performance of sepsis identification tools in children with chronic medical problems but this has been inconsistently evaluated. Future research should focus on developing tools that incorporate the impact of known individual risk factors, such as chronic medical problems, at an individual level as well as based on the cohort of patients seen in the local emergency department. Most of the published literature is based in tertiary academic centres where there may be a higher prevalence of patients with co-morbidities. Multicentre studies involving different settings would help evaluate the performance of sepsis identification tools with greater transparency of their projected external validity.

4.3 | Process Measures and Core Outcomes

In the context of sepsis, the goal of any identification tool is to improve outcomes of children attending the emergency department. However, the identification of sepsis forms only one part of multiple processes involved in achieving this goal. Process measures evaluate the steps that should be undertaken for every individual patient encounter in order to achieve a perceived gold standard of care. This

TABLE 3 Electronic alerts—List of articles evaluating electronic alert systems for the identification of sepsis/SBI/IBI

	Author, Year	Methods and objectives	Reference standard used	Results
1.	Cruz et al, 2011	Prospective cohort study. Use of temperature variable heart rate based electronic alert and reported impact on process outcomes – time to first fluid bolus and antibiotic administration from triage	Not specified	Fluid bolus 22 min vs 72 min and Antibiotic administration 38 vs 173 min
2.	Cruz et al 2012	Retrospective study HR and temp adjust HR as per age appropriate norms to identify septic shock, based on ED physician assessment. This formed a Best Practice Alert (BPA) to identify children with sepsis in all children and in those with co-morbidities (Immunodeficiency, asplenia, CV catheter, malignancy or post organ transplant) or looked unwell – poor perfusion and altered mentation.	Clinician diagnosis of sepsis on chart review	Performance of BPA varied based on age in the overall cohort. In the cohort with comorbidities or in those who looked unwell based on perfusion and mentation, the sensitivity and PPV were much better. The PPV was lower (<10%) in the overall group and <50% in the high risk group.
3.	Sepanski et al 2014	Use of IPSCC based tool for HR, RR and WCC and immature granulocytes and refined it using univariate analysis to identify means and 2SD thresholds using data from those with and without sepsis based on the Electronic Medical Records and the gold standard reference diagnosis. The refined tool was based on temperature corrected age based HR and RR. Further validation was done. These changes were generally classifiable into three categories: (1) the addition of new criteria to improve tool sensitivity; (2) the removal or modification of criteria to improve tool specificity; and (3) the use of patient history (triage) information or medica- tion administration data to identify classes of conditions – such as asthma, seizures, diabetic ketoacidosis, and sickle-cell disease (SCD) – that were likely to cause false positive tool firing, and to suppress the firing of portions of the tool for these patients.	Coded discharge diagnosis and physician chart review. Gold standard obtained by chart review to identify those patients with discharge diagnoses of 'sepsis' or 'septic shock', disseminated infection or localised infection with potential for sepsis (Identified from ICD9-CM codes) and who met the IPSCC criteria of SIRS and organ dysfunction during the course of the hospital stay.	The relevant ROC outcomes for the two data sub- sets were as follows: month(#1) *N* D3,713, sensitivity D96.0%, specificityD99.5%, AUC D0.9774, standarderror(SE) D0.02; month(#2) *N* D3,689, sensitivity D100%, specificity D99.5%, AUC D0.9973, and SE D0.0006. The resultant AUC difference of 0.0199 was not statistically significant(*p* D0.32), thus confirming that the tool outcomes were generalizable over the two independent study sub-samples.
4.	Balamuth et al 2015	Retrospective cohort study Comparison of physician judgementl and electronic alert based on the AAP sepsis collaborative criteria[a] to identify sepsis and septic shock	Clinician chart review and confirmation of sepsis.	Combined method had the best performance with ROC curve of 0.9(0.88-0.92) followed by algorithmic method ROC of 0.88 (0.85-0.91). Physician judgement and sequential methods had high PPV 40.25 (39.56–40.94) & 47.6 (46.9–48.3) but lower sensitivity when compared to algorithm and combined method.

(Continues)

TABLE 3 (Continued)

	Author, Year	Methods and objectives	Reference standard used	Results
5.	Balamuth et al 2017	Prospective cohort study. Use of electronic alert based on a modified AAP sepsis criteria to identify sepsis and impact on process outcomes – use of ED sepsis protocol or ICU admission	Initiation of ED sepsis protocol or admission to PICU with sepsis based on IPSCC criteria	electronic sepsis alert alone to detect severe sepsis were sensitivity 86.2% (95% confidence interval [CI] 82.0% to 89.5%), specificity 99.1% (95% CI 99.0% to 99.2%), positive predictive value 25.4% (95% CI 22.8% to 28.0%), and negative predictive value 100% (95% CI 99.9% to 100%). Inclusion of the clinician screen identified 43 additional electronic sepsis alert-negative children, with severe sepsis sensitivity 99.4% (95% CI 97.8% to 99.8%) and specificity 99.1% (95% CI 99.1% to 99.2%). Electronic sepsis alert implementation increased ED sepsis detection from 83% to 96%.
6.	Lloyd et al 2018	Prospective cohort study. Incorporation of the electronic sepsis alert with manual alert to identify sepsis. Used modified American Academy of Paediatrics sepsis collaborative tool. The objective was to compare the time to alert between manual and electronic methods.	Comparison with manual process.	89 vs '15 mins
7.	Eisenberg et al2019	Iterative development of electronic alert system and evaluate its performance. The alert was developed by modifying an alert model and included clinical and laboratory criteria to identify SIRS and organ dysfunction. The alert triggered different levels of severity – SIRS, Sepsis and severe sepsis (based on one or more than one organ dysfunction respectively)	IPSCC criteria for the first iteration and a combination of clinical codes, interventions and outcomes on chart reviews for subsequent iterations.	When only alerts that fell between 48 hours before and 12 hours after sepsis onset were analyzed, the algorithm demonstrated a sensitivity of 72% (CI, 67–77%) for an episode of severe sepsis; specificity 91.8% (CI, 91.5–92.1%); PPV 8.1% (CI, 7.0–9.2%); negative predictive value (NPV) 99.7% (CI, 99.6–99.8%); likelihood ratio 8.8 (CI, 8.1–9.5); and risk ratio 27 (CI, 21–34). In the more restrictive model examining only alerts that fell between 24 hours before and 2 hours after sepsis onset time, the algorithm had the following test characteristics: sensitivity 67% (CI, 62–72%); specificity 91.8% (CI, 91.5–92.1%); PPV 7.5% (CI, 6.5–8.5%); NPV 99.6% (CI, 99.5–99.7%); likelihood ratio 8.1 (CI, 7.4–8.8); and risk ratio 21 (CI, 16–26). Also reported the variation in the PPV based on the location in hospital and severity of illness evaluated as reference standard.
8.	Fesnak et al 2020	Retrospective study Electronic alert based on vital signs and then clinician huddle with report on patient outcomes comparing between those with and without background medical problems.	Local criteria for sepsis	

TABLE 3 (Continued)

	Author, Year	Methods and objectives	Reference standard used	Results
9.	Lee et al 2020	Prospective study. QI project using a digital tool to identify sepsis. Used vital signs – clinical parameters which were developed in developing countries.		
10.	Scott et al 2020	Machine learning on test and validation retrospective cohorts, to predict septic shock in those suspected of having sepsis	Septic shock defined as systolic hypotension with need for vaso-active agents and/or >/=30mls/kg	
11.	Eisenberg et al 2020	Retrospective and Prospective – before and after, Compare an automated alert system and manual screening to identify ?sepsis/?severe sepsis.		Manual tool only used clinical criteria and automated tool used IPSCC criteria. The automated system was more sensitive and specific. It had better Negative Predictive Value. The compliance for screening was much better with the automated system. However it had a low Positive Predictive Value, possibly due to low prevalence of sepsis.
12	Ehwerhemuepha L et al 2021	Retrospective cohort study. Used Machine Learning using clinical data and come up with prediction of sepsis and its complications.	ICD9 and 10 codes	An automated sepsis screening algorithm embedded in the EHR had better sensitivity and specificity, dramatically increased compliance with sepsis screening, and provided continuous surveillance throughout the ED stay when compared with a manual screen
13.	Sepanski et al 2021	Combination of retrospective and prospective study. Used an iterative process and developed a predictive tool that continuously monitors the Electronic Health Record during ED visits. It incorporates new standards for normal/abnormal vital signs based on 1.2 mill children, 82 gold standard sepsis cases, and those with high severity of illness. The process assigned weights to main factors that maximised sensitivity and	Used ICD9, IPSCC as well as bacteremia with organ dysfunction as criteria. Did not report ROC AOC, provided evidence in detail but difficult to understand.	The predictive tool (CAHR-AT*)has high specificity and may help to rule out sepsis and its ensuing complications. The Sensitivity and PPV are low. The positive and negative predictive values for CAHR-AT firing (maximum score ≥5) for high SOI outcomes were 22.5 and 98.7%, respectively. For Gold Standard sepsis cases - sensitivity 77% (67.4, 86.6), Specificity 98.1(97.9, 98.2) and PPV 7.7 (5.8, 9.6).

Note: AAP—American Academy of Pediatrics.

[a]AAP sepsis collaborative criteria—Either three of the following vital signs criteria (Temp, HR, RR & BP) or two of the vital signs criteria and one of either poor perfusion or mental state.*CAHR-AT Children at High Risk Alert Tool.

has been infrequently reported in studies on sepsis identification tools. To achieve the greatest evidence base, it will be important to study and report the dynamics between the processes involved in managing a child in emergency department from screening at triage, identification and post-identification interventions for effective management of sepsis. This poses a logistical challenge and will require a large-scale collaborative multidisciplinary approach. The Paediatric Emergency Medicine community should advocate and lobby for improvements in data acquisition infrastructure to enable progress. Core outcome sets have been identified for a wide range of other paediatric conditions with the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (http://www.cometinitiative.org) uniting researchers interested in the development and application of core outcome sets. Core Outcome Sets act to 'reduce heterogeneity and facilitate meta-analysis. They reduce the risk of reporting bias, and thus ensure that all trials contribute outcome data to meta-analyses. By involving a wide range of stakeholders, such as patients, parents and health professionals, it is more likely that clinically relevant outcomes are identified.' A Core Outcome Set for paediatric sepsis research is of profound importance to draw robust conclusions regarding early sepsis identification.[19] We commend the work of Wooldridge et al. who have published a study protocol for a planned Delphi study to establish a Core Outcome Set for paediatric sepsis in low- and middle-income countries.[20]

4.4 | Digital Risk Calculators and Electronic Alerts

Studies on electronic alerts have increased over recent years. Electronic alerts used in real time, with continuous follow-up longitudinally, provide a trend along the clinical journey. They have the advantage to alert healthcare teams to clinical deterioration as new information becomes available. However, there is a risk of user fatigue and poor compliance with acting on alerts over time, due to the low positive predictive value associated with most at present. Recent studies have used an iterative process to improve performance [Eisenberg 2019] and reported performance to identify sepsis of graded severity. Fesnak et al (2020) used a vital sign-based tool combined with a clinical 'huddle' and reported on outcomes comparing both children with and without underlying medical conditions. It would be feasible to develop a multivariate based risk score that uses red flags from clinical history, clinical signs, vital signs/observations, biomarkers, individual risk factors (e.g. chronic disease and immunisation status) and local incidence. With handheld digital technology, such as mobile phones being almost ubiquitous, this could provide inexperienced healthcare staff with evidence-based risk statistics to aid clinical decision-making.

4.5 | Implementation

Evidence-based medicine takes, on average, more than a decade to be incorporated into routine clinical practice. Implementation of evidence-based strategies into healthcare systems will therefore present a further constraint on rapidly progressing the identification of sepsis in children. In recognition of this, the paediatric national membership bodies and research networks should take ownership to progress implementation of current evidence, with implementation science strategies being considered early and incorporated into study protocols. Quality Improvement Learning Collaboratives are an example of how best practice quality improvement methodology can be identified, shared and utilised collaboratively to embed evidence-based practice and, focus on continual assessment and improvement.[21]

4.6 | Limitations

This scoping review has recognisable limitations. We limited our search to studies published in the English language. Nevertheless, we were able to identify a relevant sample of studies to highlight important issues related to research in this field. In keeping with the scoping review process, we did not attempt to perform a statistical synthesis of the results.

5 | CONCLUSION

The review of available research on the identification of sepsis in children has found that numerous different definitions, methods, biomarkers and approaches to analysis have been utilised. Though, as independent research, each study is highly valuable, the heterogeneity of these approaches makes it difficult to draw conclusions from the body of literature as a whole. A unified and collaborative approach is required to deliver consistent, high-quality studies that provide an evidence base for the early identification of sepsis in children in the acute and emergency care setting. The review highlights concepts worthy of consideration to achieve this. They include defining sepsis, agreeing core outcome sets, the use of patient-orientated outcomes as reference standards, the importance of developing infrastructure to enable sepsis registries and analysis of process measures together with heightening focus on implementation science.

AUTHOR CONTRIBUTIONS

Dr Oruganti conceptualised and designed the study, collected data and drafted the manuscript. Dr Evans contributed to the design of the study, collected data and drafted the manuscript. Dr Cromarty contributed to the design of the study, drafted data collection instruments and collected data. Dr Javaid contributed to collection of data and reviewing of the manuscript. Dr Roland conceptualised and designed the study, contributed to the analysis of the data and review of the manuscript. All the authors have reviewed the manuscript. They have approved the version to be published and are in agreement to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Search strategy for Medline (Sepsis/di [Diagnosis], Sepsis or Sepsis* or septi*) AND (Algorithms, Clinical Alarms or Monitoring, Physiologic, 'Sensitivity and Specificity', screen*, recogni*, diagnos*, assess*, diagnosis predict*, Identif*, tool*, scor*, ROC Curve or Area Under Curve) AND (paediatric* or paediatric*, infant/or paediatric or adolescent, exp Child, teen*) AND (emergency*, exp Emergency Service, Hospital/accident and emergency).

APPENDIX B

Data extraction/charting.

Data were extracted for the following variables.

• Study title • Authors • Year of Publication • Journal of Publication • Reference • DOI • Predictor examined • Classification of predictor (biomarker, clinical, electronic or mixed) • Age range included • Type of hospital • Population • Intervention • Comparison Group • Outcome measure • Definition used for SBI / Sepsis • Study findings • Author's conclusions • Type of study • Level of evidence • Appropriate for STARD review? • Limitations • Risk of bias • Other notes • Personal opinion on quality of paper.

APPENDIX C

List of citations included in the scoping review (alphabetised)

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