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Digital technologies for sepsis prediction in children: A scoping review protocol

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ABSTRACT

Introduction While there have been several literature reviews on the performance of digital sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a knowledge gap examining the development of technologies for sepsis prediction in children for supporting paediatric healthcare. This scoping review will critically analyze the current evidence investigating the design, validation, and implementation of digital technologies to predict paediatric sepsis to advance the development of new technologies for predicting sepsis in clinical settings.

Methods and analysis This scoping review will follow Arksey and O'Malley's framework. We will further develop the protocol using the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews (PRISMA-ScR). We plan to search the following databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Studies will be included on children >90 days post-natal to <21 years old, predicted to have or be at risk of developing sepsis by a digitalized model or algorithm designed for a clinical setting. Two independent reviewers will complete the abstract and full-text screening and the data extraction. Thematic analysis will be used to determine themes and present the narrative findings with descriptive statistics presented in tabular format.

Ethics and dissemination Ethics approval for this scoping review study of the available literature is not required. We anticipate that the scoping review will identify the current evidence

and design characteristics of digital prediction technologies for the timely and accurate prediction of paediatric sepsis and factors influencing implementation and usability by clinicians. We plan to disseminate the preliminary findings from this review at national and international research conferences in global and digital health, gathering critical feedback from multi-disciplinary stakeholders.

Scoping review registration

https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6

Strengths and limitations of this study

- This review is a novel approach to collectively synthesizing current research on designing paediatric sepsis prediction technologies, critically examining the relationships between their design, effectiveness and implementation in clinical settings to identify knowledge gaps requiring further investigation.
- The chosen review strategy will comprehensively evaluate the vast literature across various study types and research disciplines by a multi-disciplinary research team.
- The review will exclude digital prediction technologies for sepsis management and treatment after a diagnosis is confirmed and is limited to peer-reviewed literature written in the English language with a full-text version available.
- Literature focusing on age cohorts <90 days post-natal or >21 years old will be excluded due to significant differences in sepsis etiology and clinical presentation.

INTRODUCTION

Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in 2017, imposing significant health care and societal burden (1). Healthcare costs for severe paediatric sepsis hospitalizations reached approximately $7.31 billion in the United States in 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in low or middle-income countries, specifically sub-Saharan Africa and Southeast Asia (1). Annual global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

	Neonatal (<90 days)	Paediatric (<5 y/o)	Adult (>20 y/o)
Annual Cases (Million)	1.3 – 3.9	20.3	23.7
Annual Mortality (Million)	0.4 – 0.7	2.9	7.7

Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have different sepsis aetiologies (3). For example, children commonly develop sepsis from pneumonia, diarrhea, meningitis, or viral infections, whereas abdominal or genitourinary sources are more common in adults (4). Differences in etiology can also be found between childhood and neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5). Predicting sepsis in children is also significantly more challenging due to maturation-based differences in physiology (including immune system response), limitations in the communication of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction if not identified quickly in children (8), where mortality rates are reduced two-fold if treated within the first hour (4). Prediction of sepsis is confounded by the age-based symptom variations within children, such as their differences in heart rate (4) and commonalities among other

childhood conditions and syndromes like Kawasaki syndrome or bronchiolitis (9). This milieu of complex information combined with significant time pressure provides a significant cognitive burden for healthcare professionals to promptly identify the onset of deterioration that can lead to this serious medical condition.

In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the integration of screening standards in healthcare facilities to support rapid identification of sepsis in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10). Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently, adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA) and neonates (nSOFA) have shown promise in identifying children at risk for mortality with sepsis (12); however, it is controversial whether these scores provide value in low-resource environments (13–15). Development and implementation of algorithms such as the Sepsis Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16). With the call from the World Health Organization to improve sepsis identification and the potential for data-driven and knowledge-based technologies (3,17), digital prediction technologies are becoming more advanced using mathematical, statistical, and machine learning techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and other signs at the bedside (18–21). While recent reviews have explored the literature on the effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there is currently no review on the design and implementation of these predictive tools for children. Considering the pathophysiology and etiology of paediatric sepsis are different from that seen in

adults and neonates (27), combined with the lack of widely accessible digital technologies for children compared to adults (28), it is critically important to review the literature on this age cohort.

Prior reviews on sepsis prediction technologies

Recent narrative reviews discuss machine learning-based technologies for adults and children (20,29,30). However, the exclusion criteria for these reviews result in most of the included literature focusing on technologies to predict adult sepsis, with only two (20) or three (29) articles on paediatric sepsis. Some reviews excluded digital technologies that were not based on "modern" machine learning models (21,30) or involved a broad search on infectious disease prediction beyond sepsis (29). Recent narrative reviews have also limited their investigations to PubMed/Medline, excluding other scientific or engineering databases, which may provide greater insight into the design of digital technologies (20,26,30–32). One narrative review has described the design, implementation, and performance of paediatric sepsis screening technologies (30). However, the review included limited results on technologies based on machine learning while focusing exclusively on US hospitals (30).

Many systematic and scoping reviews have been rigorous in their search strategy but similarly, report on screening tools and technologies for adult patients while excluding paediatrics in their full-review criteria (24,25,28,33–36). They also do not include databases among the engineering disciplines (19,23,37–39), as the objective of these reviews is generally towards understanding the clinical effectiveness of these technologies and not the design methodology. While previously published protocols for systematic reviews do not specify a patient population inclusion or exclusion, some plan to exclude literature on the application of

machine learning models (38,40). This approach may not capture research on certain algorithm types depending on the authors' definitions of artificial intelligence/machine learning. However, the completed reviews from these protocols (38,40) have not been found. While there have been systematic reviews on the performance of neonatal sepsis prediction technologies providing insight into their capabilities (19,23), none are focusing on the specifics of paediatric sepsis, including their design and implementation.

Finally, current systematic reviews that include the paediatric literature as part of their search strategy are limited in their search scope and do not focus on the design and implementation requirements for this specific patient population (22,28,37). Two reviews examine early warning systems for paediatric clinical deterioration, focusing on reporting effectiveness in reducing adverse outcomes and identifying that there remains limited evidence supporting the mandated use of these systems in hospitals (41,42). For sepsis specifically, systematic reviews on automated prediction and decision-support systems have only identified one (37) or three (22,28) related articles specific to children due to the period searched or exclusion restrictions for how the technology was evaluated. One published protocol aims to capture strategies for early recognition of paediatric sepsis from clinical deterioration (39). However, the review focuses on general strategy effectiveness and does not explicitly include engineering databases such as IEEE or ACM Digital Library (39). While the systematic review associated with the protocol mentioned above has not been found, the search strategy approach may not completely capture the breadth of digital technologies developed for paediatric sepsis (39). There is a need for a comprehensive scoping review, understanding the design and evaluation of technologies for sepsis prediction in children, and highlighting where knowledge

gaps exist to inform future development and implementation that supports clinical decision-making.

Purpose of the study

Given the limitations of recent literature reviews and the lack of reviews focused on paediatric sepsis, it is necessary to scope the literature to identify the current evidence describing the development of digital sepsis prediction technologies for this age cohort. The scoping review defined by this protocol will identify and summarize the existing literature on the design, effectiveness, and usability of digital sepsis prediction technologies in the paediatric population. The scoping review, a methodology focusing on answering broader research questions through a systematic search and presenting tabular findings along with a narrative integration (43), was identified as the best approach for this review. We anticipate that this methodology will warrant a meaningful summary of the current development of digital technologies for sepsis prediction that can inform future research towards improving their performance and evidence-based clinical implementation to improve the lives of children globally.

METHODS AND ANALYSIS

The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health researcher/biomedical engineering research librarian, a psychology student, and a paediatric clinician. Our methodology will be guided by the framework developed by Arksey and O'Malley (43), which iterates through six steps: (i) identifying the research question; (ii) searching for relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The

sixth step is optional, and we will modify this step to consult with experts specifically around finding technologies used in hospital or industry settings. Levac's recommendations for independent full-text reviews by at least two reviewers will also be followed (44). This study protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for a scoping review (PRISMA-ScR) (45), with any gaps being filled by the Preferred Reporting Items for Systematic Review and Meta-Analysis extension for protocols (PRISMA-P) [see Additional file 1]. This protocol has been registered on the Open Science Framework (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).

Step 1: **identifying the research question**

The research questions were identified through an initial search of the literature on predictive electronic clinical prediction technologies for sepsis and gaps identified in current systematic and narrative reviews. The following questions maintain a broad scope for understanding the existing evidence on digital sepsis prediction technologies and their clinical implementation in the paediatric context:

1. How are digital sepsis prediction technologies currently designed and developed?
2. What is the effectiveness and usability of digital technologies in predicting sepsis in clinical settings?
3. What gaps exist in understanding how to effectively improve the design and implementation of digital technologies for sepsis prediction?

Step 2: **identifying relevant studies**

We will conduct a comprehensive scoping review that includes a multi-disciplinary group of scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will also be identified using the snowballing technique (46), to identify relevant literature among the references and citations of articles included for the full review. We will additionally hand-search for literature on the design, validation, and implementation of commercial digital technologies for sepsis prediction, which may be approved by governing bodies such as Health Canada (health-products.canada.ca/mdall-limh/), the Food and Drug Administration (accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/textsearch.cfm), and the European Union Medical Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

We have developed a search strategy for each database to support our comprehensive literature search. Our approach employs keywords, medical subject headings (MeSH), key concept subject headings, and Boolean terms. A sample search strategy for PubMed is presented in Table 2.

Table 2. Sample search strategy and results.

Database	Search Terms	Results	Date
PubMed	("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR	15,531	02/15/2022

"electronic*"[All Fields] OR "representation learning"[All Fields] OR "conformal prediction"[All Fields] OR "random forest"[All Fields] OR "naïve bayes"[All Fields] OR "regression" OR "regression analysis"[MeSH Terms] OR "gradient boosting"[All Fields] OR "artificial learning"[All Fields] OR "machine intelligence"[All Fields] OR "probabilistic network*"[All Fields] OR "knowledge representation"[All Fields] OR "bayesian learning"[All Fields] OR "expert system*"[All Fields] OR "technology assisted"[All Fields] OR "computer assisted"[All Fields] OR "statistical"[All Fields] OR "mathematical"[All Fields]) AND ("system"[All Fields] OR "tool"[All Fields] OR "alert*"[All Fields] OR "technology"[All Fields] OR "software"[All Fields] OR "model*"[All Fields] OR "engine"[All Fields] OR "approach*"[All Fields] OR "algorithm"[All Fields] OR "platform"[All Fields] OR "method*"[All Fields] OR "scor*"[All Fields] OR "device"[All Fields]) AND ("sepsis"[All Fields] OR "sepsis"[MeSH Terms] OR "septic shock"[All Fields] OR "systemic inflammatory response syndrome"[All Fields] OR "acute deterioration"[All Fields] OR "patient deterioration"[All Fields] OR "clinical deterioration"[MeSH Terms] OR "clinical deterioration"[All Fields] OR "severe infection"[All Fields] OR "severe bacterial infection"[All Fields] OR "bacterial infections"[MeSH Terms] OR "febrile illness"[All Fields] OR "non-malarial febrile illness"[All Fields] OR "bacteremia"[All Fields] OR "bacteremia"[MeSH Terms]) AND ("diagnos*"[All Fields] OR "detect*"[All Fields] OR "predict*"[All Fields] OR "prognosticate"[All Fields] OR "identif*"[All Fields] OR "infer*"[All Fields] OR "warn*"[All Fields] OR "alert*"[All Fields] OR "recog*"[All Fields] OR "screen*"[All Fields] OR "monitor*"[All Fields] OR "assess*"[All Fields] OR "surveillance"[All Fields] OR "classif*"[All Fields]) AND ("evaluat*"[All Fields] OR "implement*"[All Fields] OR "perform*"[All Fields] OR "design"[All Fields] OR "validat*"[All Fields] OR "usability"[All Fields] OR "effectiveness"[All Fields] OR "efficiency"[All Fields] OR "satisfaction"[All Fields] OR "safety"[All Fields] OR "acceptance"[All Fields] OR "clinical value"[All Fields] OR "interpret*"[All Fields] OR "perception"[All Fields] OR "perspective"[All Fields] OR "opinion"[All Fields] OR "error"[All Fields]) AND ("child*"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR "pediatrics"[MeSH Terms] OR

"toddler*"[All Fields] OR "teen*"[All Fields] OR "youth*"[All Fields] OR "adolescen*"[All Fields] OR "adolescent"[MeSH Terms] OR "infan*"[All Fields] OR "infant"[MeSH Terms] OR "school age*"[All Fields] OR "PICU"[All Fields])

The search results will be imported to Mendeley's reference management software for future referencing and organization (Mendeley Ltd.). A systematic review management software, Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles. A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the inclusion-exclusion requirements are robust in capturing relevant articles related to the design and evaluation of digital prediction technologies for paediatric sepsis. Both reviewers will also ensure that the data extraction items capture valuable and appropriate study details from the articles included in the full-text review, which will be shared with the research team.

Step 3: **study selection**

Inclusion criteria

The proposed review will include articles that meet the following inclusion criteria:

- The article is written in English
- The article is a peer-reviewed journal article, full conference proceeding, or research published on a commercially available digital technology which may be approved by a medical device regulatory body
- The article includes the description of a digital prediction technology indicative of at least one aspect of clinical deterioration that may lead to sepsis in children (>90 days post-natal to <21 years old)

- The article describes how the digital technology was designed, validated for its effectiveness, or evaluated for its usability in the context of a healthcare facility
- The article discusses the features and, if applicable, the dataset used in its design
- There is no specification for publication years

Exclusion criteria

Screened that include any of the following factors will be excluded from this review:

- Commentaries
- Dissertations
- Editorials
- Books and book chapters
- Lectures and addresses
- Study protocols
- Review articles
- Articles inaccessible for full-text review
- Digital technologies informing sepsis treatment strategies
- Digital technologies with proposed use outside a healthcare facility
- Digital technologies that predict mortality risk from sepsis

Selection process

This review will follow the reporting checklist in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco et al. (45). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT

and JG) will independently perform the title and abstract screening using the developed eligibility criteria by classifying them as "Yes," "No." Any article classified as "Yes" by RT or JG will be included in the full-text review during this stage by adding them to an Excel spreadsheet for access by all authors. If a full-text article cannot be accessed, the reviewers will seek assistance from library services at the institution or directly contact the article's corresponding author. Third, two investigators (RT and JG) will independently perform the full-text screening for eligibility using the listed inclusion-exclusion criteria. A third member of the research team will resolve any disagreements on eligibility that occur during the full-text review. After the full-text review, an inter-rater agreement will be calculated using Cohen's kappa coefficient (κ) statistic.

Step 4: **charting the data**

The data extraction form will be developed in Covidence and exported to Excel to capture the relevant information from each article. Two reviewers (RT, JG) will individually extract the relevant data from a sample of eligible articles screened for inclusion in the full-text review to ensure consistency of recording data. Any disagreements on extracted data will be resolved through discussion between the reviewers. The form will be iteratively updated until the authors reach a consensus on the relevant data to extract. We will begin by pulling the following type of data into the form, with additional data included as we screen more articles:

- Author(s) and date published
- Study location
- Document type
- Discipline

- Objective
- Use setting type
    - Prevalence of sepsis in the use setting
- Age cohort
- Number of participants
- Research methodology: retrospective, prospective
- Study design
- Sepsis prediction approach/method
- Design of the digital prediction technology
    - Data source
    - Model type: data-driven, knowledge-based
    - Interface/Platform
    - Data flow: continuous, discrete
    - Prediction objective: sepsis, severe sepsis, septic shock, sepsis severity
    - Definition of the prediction objective
    - Design process/approach
        - Workflow integration: triage, monitoring, discharge
    - Clinical predictors
        - Vital signs
        - Biomarkers
        - Anthropometric data
        - Sociodemographic information
        - Administrative variables

        - Medical history variables
    - Equity considerations (47,48)
        - Bias: quantitative or qualitative misrepresentations of particular patient groups
        - Fairness: impacts on various demographic groups
        - Appropriateness: adaptations for specific patient groups or use contexts
- Measures used for validating the performance and implementation of the digital prediction technology
    - Confirmation method for a true positive sepsis case
    - Quantitative values
        - Firing rate/Proportion positive
        - Specificity
        - Sensitivity
        - Area under the receiver operating curve
        - Positive predictive value
        - Negative predictive value
        - Risk ratio
        - Machine learning performance measures
        - Prediction timing
        - Mortality rates
        - Intervention/Treatment outcomes
        - Method for handling missing data
        - Comparison to other sepsis prediction algorithms

- User focused outcomes
  - Usability: effectiveness, efficiency, satisfaction, safety
  - User feedback
  - User error
  - User acceptance and trust
- Clinical value provided
- Evaluation of bias, fairness or appropriateness

- Conclusion/Primary Findings
  - Future steps/research

Step 5: **collating, summarizing, and reporting the results**

The extracted data will be synthesized within tables that summarize the current digital technology landscape in predicting paediatric sepsis, including characteristics that describe their effectiveness and implementation by health care providers. We will quantitatively identify the number of similar approaches toward model and algorithm development for digital sepsis prediction technologies and their interface and delivery platform. We will also report their quantitative performance and implementation outcomes such as sensitivity and specificity, mortality rates, and impacts on earlier intervention times through descriptive statistics. We will then perform a thematic analysis to identify relevant themes and sub-themes related to our scoping review objectives. The analysis will include an organization of themes on the usability and implementation of digital prediction technologies in clinical contexts related to clinician-system interaction and gaps in improving clinical integration, which will be presented as a narrative. Diagrams will be developed to visualize the relationships and themes between the

design of digital technologies for paediatric sepsis prediction and their influence on system effectiveness and implementation throughout time to highlight further knowledge gaps and opportunities for future investigation.

Step 6: **methodological quality appraisal**

We will consult with experts in paediatric sepsis prediction digital technologies for this review to identify those applied in clinical settings. While critical appraisal of the identified articles is not mandatory in the scoping review methodology, we will consult with stakeholders to inform and validate our findings.

Patient and public involvement

There were no patients or public involvement in the development of this protocol.

ETHICS AND DISSEMINATION

Approval from an ethics review committee is not required for this study because it is a scoping review of previously published literature. Once the review is completed, we plan to disseminate the preliminary findings at national and international research conferences in global and digital health to gather critical feedback from researchers and the public. The finalized results from the review will be submitted for publication in an open access peer-reviewed journal.

DISCUSSION

This scoping review will provide a comprehensive and structured understanding of the digital technologies that have been developed to support the timely prediction of paediatric sepsis. The

results will focus on design, validation, and implementation, which will be analyzed thematically and reported in data summary tables, indicating how the development of these technologies is evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in designing and implementing clinically meaningful digital prediction technologies for paediatric sepsis across various clinical environments. Furthermore, the results are expected to identify critical research aspects requiring further investigation that may contribute toward developing future successful technologies.

Compared to previous reviews, this scoping review focuses on the complexities of paediatric sepsis, with a methodological strength in taking a comprehensive and systematic approach that will provide an overview of the evidence in this digital technology landscape. Inherent in this approach is the limitation of its objective: to summarize the literature and identify meaningful gaps for further research. As this study will include articles with various study designs, it does not aim to answer specific questions about recommending the use or application of certain sepsis prediction technologies for paediatrics. With the results of the pilot search (Table 2), this review is also limited in its scope, where non-English articles or articles without a full-text version will not be included. Finally, digital technologies informing treatment strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21 years old will be excluded because of significant differences in sepsis etiology and clinical presentation. We plan to adequately convey the overall strengths and limitations once the review is completed, including any deviations from the protocol.

In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to outcomes related to clinical implementation and performance, we anticipate that our results will highlight critical research gaps among the medical, engineering, and computer science

disciplines. The results may inform research on identifying relevant predictive indicators best suited for the design of digital technologies in specific use contexts and environments, improvements towards model development for sepsis prediction, and factors supporting the optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review will be critical for advancing knowledge to improve sepsis prediction for children globally.

List of abbreviations

ACM: Association of Computing Machinery

CINAHL: Cumulative Index to Nursing and Allied Health Literature

IEEE: Institute of Electric and Electronic Engineers

nSOFA: neonatal Sequential Organ Assessment Score

PEWS: Paediatric Early Warning Score

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for protocols

PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews

pSOFA: paediatric Sequential Organ Assessment Score

SOFA: Sequential Organ Assessment Score

SPOT: Sepsis Prediction and Optimization Therapy

Author contributions

RT is the guarantor of the review and drafted the initial manuscript. All authors contributed to the development of the search strategy, selection criteria, and data extraction template. MA

provided expertise on paediatric sepsis. All authors critically reviewed the protocol for intellectual content, subsequently revised it for publication, and read and approved the final version.

Availability of data and materials

The datasets used and analyzed during the current study will be available in the Pediatric Sepsis Data CoLab repository: https://dataverse.scholarsportal.info/dataverse/Pedi_SepsisCoLab.

Funding statement

Not applicable.

Competing interests statement

The authors declare that they have no competing interests.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	61, 195
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-28
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	427-432
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	438-439
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	438-439
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	438-446
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	86-166

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	203-207
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	237-263
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	210-220
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	221-226
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	227-229, 268-273
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	266-278
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	232-234, 281-287
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	288-346
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☒	N/A
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☒	N/A
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	349-357,
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	357-363
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	366-369

BMJ Open

Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

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Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

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ABSTRACT

Introduction While there have been several literature reviews on the performance of digital sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a knowledge gap in examining the development of automated technologies for sepsis prediction in children. This scoping review will critically analyze the current evidence on the design and performance of automated digital technologies to predict paediatric sepsis, to advance their development and integration within clinical settings.

Methods and analysis This scoping review will follow Arksey and O'Malley's framework, conducted between February to December 2022. We will further develop the protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR). We plan to search the following databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Studies will be included on children >90 days post-natal to <21 years old, predicted to have or be at risk of developing sepsis by a digitalized model or algorithm designed for a clinical setting. Two independent reviewers will complete the abstract and full-text screening and the data extraction. Thematic analysis will be used to develop overarching concepts and present the narrative findings with quantitative results and descriptive statistics displayed in data tables.

Ethics and dissemination Ethics approval for this scoping review study of the available literature is not required. We anticipate that the scoping review will identify the current evidence

and design characteristics of digital prediction technologies for the timely and accurate prediction of paediatric sepsis and factors influencing clinical integration. We plan to disseminate the preliminary findings from this review at national and international research conferences in global and digital health, gathering critical feedback from multi-disciplinary stakeholders.

Scoping review registration

https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6

Strengths and limitations of this study

- This review is a rigorous approach to collectively synthesizing current research on automated paediatric sepsis prediction technologies, critically examining the relationships between their design, performance, and clinical integration to identify sociotechnical challenges and research gaps.
- The chosen review strategy will comprehensively evaluate the vast literature across various study types and research disciplines by a multi-disciplinary research team.
- The review will exclude digital prediction technologies for paediatric sepsis treatment decisions and is limited to peer-reviewed literature written in the English language with a full-text version available.
- Articles focusing on age cohorts <90 days post-natal or >21 years old will be excluded due to significant differences in sepsis etiology and clinical presentation.

INTRODUCTION

Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in 2017, imposing significant health care and societal burden (1). Healthcare costs for severe paediatric sepsis hospitalizations reached approximately $7.31 billion in the United States in 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in low-middle income countries, specifically those in sub-Saharan Africa and South-East Asia (1). Annual global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

	Neonatal (<90 days)	Paediatric (<5 y/o)	Adult (>20 y/o)
Annual Cases (M)	1.3 – 3.9	20.3	23.7
Annual Mortality (M)	0.4 – 0.7	2.9	7.7

Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have different sepsis aetiologies (3). For example, children commonly develop sepsis from pneumonia, diarrhea, meningitis, or viral infections, where abdominal or genitourinary sources are more common in adults (4). Differences in aetiology can also be found between childhood and neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5). Recognizing sepsis in children is also significantly more challenging due to maturation-based differences in physiology (including immune system response), limitations in the communication of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction if not identified quickly in children (8), where mortality rates are reduced two-fold if treated within the first hour (4). Recognition of sepsis is confounded by the age-based symptom variations within children, such as their differences in blood pressure response, serum lactate

levels (4), and commonalities among other childhood conditions and syndromes like Kawasaki syndrome or bronchiolitis (9). This milieu of complex information combined with significant time pressure provides a significant cognitive burden for healthcare professionals to promptly identify the onset of deterioration that can lead to this serious medical condition.

In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the integration of screening standards in healthcare facilities to support rapid identification of sepsis in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10). Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently, adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA) and neonates (nSOFA) have shown promise in identifying children at risk for mortality with sepsis (12); however, it is controversial whether these scores provide value in low-resource environments (13–15). Development and implementation of algorithms such as the Sepsis Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16). With the call from the World Health Organization to improve sepsis identification and the potential for data-driven and knowledge-based technologies (3,17), digital prediction technologies are becoming more advanced using mathematical, statistical, and machine learning techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and other signs at the bedside (18–21). While recent reviews have explored the literature on the effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there is currently no review on the design and implementation of these predictive technologies for children. Considering the pathophysiology and aetiology for paediatric sepsis are different from

that seen in adults and neonates (27), combined with the lack of widely accessible digital technologies for children compared to adults (28), it is critically important to review the literature on this age cohort.

Prior reviews on sepsis prediction technologies

Recent narrative reviews discuss machine learning-based technologies for adult and paediatric sepsis (20,29,30). However, their eligibility criteria focus primarily on adults, with only two (20) or three (29) articles on children. Some reviews excluded digital technologies that were not based on "modern" machine learning models (21,30), or involved a broad search on infectious disease prediction beyond sepsis (29). Others have also limited their investigations to PubMed/Medline, excluding engineering databases, which may provide greater insight into the design characteristics of digital technologies (20,26,31–33), or they focus exclusively on US hospitals (33).

Many systematic and scoping reviews have been rigorous in their search strategy but similar to the identified narrative reviews, report on screening tools and technologies for adult patients while excluding children (24,25,28,34–37), and the engineering disciplines (19,23,38–40). Currently published protocols plan to exclude literature on the application of machine learning (39,41), which may not capture research on certain relevant technologies. While there have been systematic reviews on the performance of neonatal sepsis prediction and recognition technologies providing insight into their capabilities (19,23), none focus on the specifics of paediatric sepsis.

Current systematic reviews that include the paediatric literature as part of their search strategy are not strictly focused on this patient population (22,28,38), having only identified one

(38) or three (22,28) related articles specific to children. Other reviews broadly examine early warning systems for paediatric clinical deterioration (42,43). We have not identified any systematic or scoping reviews that accurately scope the literature on digital paediatric sepsis prediction technology. While one identified protocol aims to capture strategies for early recognition of paediatric sepsis from clinical deterioration, the focus of the review is general strategy effectiveness and does not explicitly include engineering databases which would describe technical design aspects (40).

Purpose of the study

Given the limitations of recent literature reviews and the lack of reviews focused on paediatric sepsis, it is necessary to synthesize the current research describing the development and evaluation of automated sepsis prediction technologies for this underrepresented age cohort. The scoping review defined by this protocol will identify and summarize the existing literature on the design characteristics, performance, and integration of automated sepsis prediction technologies in paediatric contexts. The scoping review, a methodology focusing on answering broader research questions through a systematic search and presenting tabular findings along with a narrative integration (44), was identified as the best approach for this study. We anticipate that the rigorous methodology will warrant a meaningful summary about the current development of digital technologies for sepsis prediction that can inform future research toward improving their performance and evidence-based clinical implementation to ultimately improve the lives of children globally.

METHODS AND ANALYSIS

The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health researcher/biomedical engineering research librarian, a psychology student, and a paediatric clinician. Our methodology will be guided by the framework developed by Arksey and O'Mally (44), which iterates through six steps: (i) identifying the research questions; (ii) searching for relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The sixth step is optional, and we will modify this step to consult with experts specifically around finding technologies used in hospital or industry settings. Levac's recommendations for independent full-text reviews by at least two reviewers will also be followed (45). This study protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for a scoping review (PRISMA-ScR) (46) with any gaps being filled by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for protocols (PRISMA-P) [see Additional file 1]. This protocol has been registered on the Open Science Framework (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).

Step 1: **identifying the research questions**

The research questions were developed through an initial search of the literature on automated digital technologies for paediatric sepsis recognition and gaps identified in current systematic and narrative reviews in the neonatal and adult context. The Joanna Briggs Institute recommendations of the Population, Concept, and Context model were followed (47), maintaining a broad scope for understanding the existing evidence on paediatric sepsis prediction technologies with respect to their current performance, identified outcome measures, and existing research gaps:

1. How do the design characteristics of automated paediatric sepsis prediction technologies for healthcare facilities (e.g., the recognition task, type, method, demographics, and indicators) influence their performance?
2. What are the impacts of clinically implemented automated paediatric sepsis prediction technologies on decision-making and patient outcome measures?
3. What challenges and research gaps (e.g., evidence, practical knowledge, population, theoretical, methodological) exist for improving the sociotechnical integration of knowledge-based algorithms and data-driven models for predicting paediatric sepsis in healthcare facilities?

Step 2: **identifying relevant studies**

We will conduct a comprehensive scoping review that includes a multi-disciplinary group of scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will further be identified using the snowballing technique (48), to identify relevant literature among the references and citations of articles included for the full review. We will also hand-search for reports on the design, validation, and implementation of commercial digital technologies for sepsis prediction, which may be approved by governing bodies such as Health Canada (health-products.canada.ca/mdall-limh/), the Food and Drug Administration (accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/textsearch.cfm), and the European Union Medical Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

Guided by a University of Waterloo biomedical engineering research librarian, we developed a comprehensive search strategy for each database. The approach employs keywords, medical subject headings (MeSH), key concept subject headings, and Boolean terms broken down into the following parts: the recognition algorithm or model, type of digital technology, health condition, alert type, implementation or validation factors, and patient population. A sample search strategy for PubMed is presented in Table 2.

Table 2. Sample search strategy and results.

Database	Search Terms	Results	Date
PubMed	("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR "electronic*"[All Fields] OR "representation learning"[All Fields] OR "conformal prediction"[All Fields] OR "random forest"[All Fields] OR "naïve bayes"[All Fields] OR "regression" OR "regression analysis"[MeSH Terms] OR "gradient boosting"[All Fields] OR "artificial learning"[All Fields] OR "machine intelligence"[All Fields] OR "probabilistic network*"[All Fields] OR "knowledge representation"[All Fields] OR "bayesian learning"[All Fields] OR "expert system*"[All Fields] OR "technology assisted"[All Fields] OR "computer assisted"[All Fields] OR "statistical"[All Fields] OR "mathematical"[All Fields]) AND ("system"[All Fields] OR "tool"[All Fields] OR "alert*"[All Fields] OR "technology"[All Fields] OR "software"[All Fields] OR "model*"[All Fields] OR "engine"[All Fields] OR "approach*"[All Fields] OR "algorithm"[All Fields] OR "platform"[All Fields] OR "method*"[All Fields] OR "scor*"[All Fields] OR "device"[All Fields]) AND (	15,531	02/15/2022

"sepsis"[All Fields] OR "sepsis"[MeSH Terms] OR "septic shock"[All Fields] OR "systemic inflammatory response syndrome"[All Fields] OR "acute deterioration"[All Fields] OR "patient deterioration"[All Fields] OR "clinical deterioration"[MeSH Terms] OR "clinical deterioration"[All Fields] OR "severe infection"[All Fields] OR "severe bacterial infection"[All Fields] OR "bacterial infections"[MeSH Terms] OR "febrile illness"[All Fields] OR "non-malarial febrile illness"[All Fields] OR "bacteremia"[All Fields]) AND ("diagnos*"[All Fields] OR "detect*"[All Fields] OR "predict*"[All Fields] OR "prognosticate"[All Fields] OR "identif*"[All Fields] OR "infer*"[All Fields] OR "warn*"[All Fields] OR "alert*"[All Fields] OR "recog*"[All Fields] OR "screen*"[All Fields] OR "monitor*"[All Fields] OR "assess*"[All Fields] OR "surveillance"[All Fields] OR "classif*"[All Fields]) AND ("evaluat*"[All Fields] OR "implement*"[All Fields] OR "perform*"[All Fields] OR "design"[All Fields] OR "validat*"[All Fields] OR "usability"[All Fields] OR "effectiveness"[All Fields] OR "efficiency"[All Fields] OR "satisfaction"[All Fields] OR "safety"[All Fields] OR "acceptance"[All Fields] OR "clinical value"[All Fields] OR "interpret*"[All Fields] OR "perception"[All Fields] OR "perspective"[All Fields] OR "opinion"[All Fields] OR "error"[All Fields]) AND ("child*"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR "pediatrics"[MeSH Terms] OR "toddler*"[All Fields] OR "teen*"[All Fields] OR "youth*"[All Fields] OR "adolescen*"[All Fields] OR "adolescent"[MeSH Terms] OR "infan*"[All Fields] OR "infant"[MeSH Terms] OR "school age*"[All Fields] OR "PICU"[All Fields]) LIMIT TO: [Text Availability]: Full text, [Language]: English, [Species]: Human

The search results will be imported to Mendeley's reference management software for future referencing and organization (Mendeley Ltd.). A systematic review management software, Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles. A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the inclusion-exclusion requirements are robust in capturing relevant articles related to the design and evaluation of automated prediction technologies for paediatric sepsis. Both reviewers will

also ensure that the data extraction items capture valuable and appropriate study details from the articles included in the full-text review, which will be shared with the research team.

Step 3: **study selection**

Inclusion criteria

The proposed review will include articles that meet the following inclusion criteria:

- The article is about an automated data-driven or knowledge-based approach toward paediatric sepsis prediction in a healthcare setting, including sepsis, severe sepsis, and septic shock.
- The digital technology is evaluated for its performance through validation testing, experiments, or an observational study.
- Following the American Academy of Pediatrics' definition for late adolescence, more than the majority of data reported will include children aged >90 days post-natal to <21 years old (49).
- The article is written in English.
- The article is a peer-reviewed journal article, full conference proceeding, or research published on a commercially available digital technology which may be approved by a medical device regulatory body.
- There is no specification for publication years.

Exclusion Criteria

Screened articles that that fit within the following categories will be excluded from this review: Commentaries, dissertations, editorials, books and book chapters, lectures and addresses, study

protocols, review articles, and articles inaccessible for full-text review after utilizing library resources. Cohort studies where paediatric sepsis has already been clinically identified, such as articles describing prediction technologies for subsequent sepsis treatment or mortality risk, are outside the scope of this review if predicting sepsis, severe sepsis or septic shock is not a facet of the technology. Also, digital technologies developed for at-home use are also outside the scope of this review, as the context of the protocol is to review the evidence on automated sepsis prediction technologies in regulated healthcare settings.

Selection process

This review will follow the reporting checklist in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco et al. (46). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT and JG) will independently perform the title and abstract screening using the developed eligibility criteria by classifying them as "Yes," "No," or "Maybe." Any article classified as "Yes" or "Maybe" by RT or JG will be included in the full-text review during this stage by adding them to an Excel spreadsheet for access by all authors. If a full-text article cannot be accessed, the reviewers will seek assistance from library services at the institution or directly contact the article's corresponding author. Third, two investigators (RT and JG) will independently perform the full-text screening for eligibility using the listed inclusion-exclusion criteria. A third member of the research team will resolve any disagreements on eligibility that occur during the full-text review. After the full-text review, an inter-rater agreement will be calculated using Cohen's kappa coefficient (κ) statistic.

The first step in identifying relevant studies was performed on February 15, 2022. The planned end date for completing the full-text screening and analysis is December 30th, 2022. We have maintained search alerts for potentially eligible articles to ensure our review remains updated before dissemination through publication.

Step 4: **charting the data**

The data extraction form will be developed in Covidence and exported to Excel to capture the relevant information from each article. Two reviewers (RT, JG) will individually extract the relevant data from a sample of eligible articles screened for inclusion in the full-text review to ensure consistency of recording data. Any disagreements on extracted data will be resolved through discussion between the reviewers. The form will be iteratively updated until the authors reach a consensus on the relevant data to extract. We will begin by pulling the following type of data into the form, with additional data included as we screen more articles:

- Article information: author(s), year published, city, country, discipline(s).
- Prediction task: the definition of sepsis being identified and the use context for recognition in paediatrics.
- Prediction task type:
    - Alerting automation that provides a notification that a patient has met the objective sepsis recognition criteria.
    - Decision support automation that provides assistance in the diagnosis of sepsis.
    - Data automation that collects clinically relevant cues and information on behalf of the user(s), which may be used in combination with alerting and decision support.
- Prediction method:

- Data-driven methods that use retrospective datasets to build a statistical or machine learning-based model.
- Knowledge-based methods that use consensus criteria to build an algorithm with threshold-based criteria.

- Participant demographics: age cohort, number of participants.
- Prediction indicators: vital signs, biomarkers, socio-demographics, treatment, medical history.
- Prediction interface: audible alert, dialog box, provided information
- Validation measures:
  - Reported number of true positives, false positives, and false negatives.
  - Reported sensitivity and specificity.
  - Time to accurate sepsis recognition by the technology and/or the clinician.
  - Measured or expected impact on clinical decisions and patient outcomes.
  - Generalizability of the digital technology in the context of bias, fairness, and appropriateness (50,51).

Step 5: **collating, summarizing, and reporting the results**

The extracted data will be synthesized within tables that summarize the current digital technology landscape in predicting paediatric sepsis, including characteristics that describe their performance and the sociotechnical factors of their integration by health care providers on patient outcomes. Within summary tables, we will present the current approaches toward model and algorithm development for automated sepsis prediction technologies, including the predictive indicators, the prediction timing objective, and how they interface with clinicians.

Quantitative performance and implementation measures such as sensitivity and specificity, and the impacts on intervention timing will also be reported in data tables, including calculations of precision, recall, and F1 score, when possible.

We will then perform a thematic analysis to identify concepts related to our research questions. This analysis will be presented as a narrative, including an organization of themes on the identified design characteristics of automated prediction technologies integrated within clinical contexts. The purpose of the analysis will be to identify the types of research gaps that exist for knowledge-based algorithms and data-driven models to improve sociotechnical integration (i.e., supporting clinical decision-making) and patient outcomes. Challenges with bias, fairness, and appropriateness will also be qualitatively examined with respect to potential generalizability barriers. Diagrams will be developed for the identified relationships and themes among the design characteristics of the automated technologies for paediatric sepsis prediction and their influence on system performance and implementation throughout time to visually highlight the opportunities for future investigations.

Step 6: **methodological quality appraisal**

We will consult with experts in automated paediatric sepsis prediction technologies for this review to identify those applied in clinical settings. While critical appraisal of the identified articles is not mandatory in the scoping review methodology, we will consult with stakeholders to inform and validate our findings.

Patient and public involvement

There were no patients or public involvement in the development of this protocol.

ETHICS AND DISSEMINATION

Approval from an ethics review committee is not required for this study because it is a scoping review of previously published literature. Once the review is completed, we plan to disseminate the preliminary findings at national and international research conferences in global and digital health to gather critical feedback from researchers and the public. The finalized results from the review will be submitted for publication in an open access peer-reviewed journal.

DISCUSSION

This scoping review will provide a comprehensive and structured understanding of the automated digital technologies that have been developed to support the timely prediction of paediatric sepsis. At a high-level, the results will focus on design characteristics, performance validation, and current sociotechnical integration factors, which will be analyzed thematically and reported in data summary tables, indicating how the development of these technologies is evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in developing and implementing clinically meaningful digital prediction technologies for paediatric sepsis across various clinical environments. Furthermore, the results are expected to identify critical research aspects requiring further investigation.

Compared to previous articles, this scoping review focuses on the complexities of paediatric sepsis, with a methodological strength in taking a comprehensive and systematic approach that will provide an overview of the evidence in this digital technology landscape. Inherent in the approach of a scoping review is the limitation of its objective: to summarize the literature and identify meaningful gaps for further research. As this study will include articles

with various study designs, it does not aim to answer specific questions about recommending the use or application of certain sepsis prediction technologies for paediatrics. With the results of the pilot search (Table 2), this review is also limited in its scope, where non-English articles or articles without a full-text version will not be included. Finally, digital technologies informing treatment strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21 years old will be excluded because of significant differences in sepsis etiology and clinical presentation, while capturing literature from geographic areas that provide paediatric healthcare services to this age range. We plan to adequately convey the overall strengths and limitations once the full-text review is completed, including any deviations from the protocol, in the final review.

In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to outcomes related to clinical integration and performance, we anticipate that our results will highlight critical research gaps among the medical, engineering, and computer science disciplines. The results may inform research on identifying relevant predictive indicators best suited for the design of digital technologies in specific use contexts and environments, improvements towards model development for sepsis prediction, and factors supporting the optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review will be critical for advancing knowledge to improve sepsis prediction for children globally.

List of abbreviations

ACM: Association of Computing Machinery

CINAHL: Cumulative Index to Nursing and Allied Health Literature

IEEE: Institute of Electric and Electronic Engineers

nSOFA: neonatal Sequential Organ Assessment Score

PEWS: Paediatric Early Warning Score

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for protocols

PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews

pSOFA: paediatric Sequential Organ Assessment Score

SOFA: Sequential Organ Assessment Score

SPOT: Sepsis Prediction and Optimization Therapy

Author contributions

RT, JG, KM, CMB, and JMA contributed to the development of this manuscript. RT is the guarantor of the review, conceptualized the research questions and methods, and drafted the initial manuscript. All authors contributed to the development of the search strategy, selection criteria, and data extraction template. JMA provided expertise on paediatric sepsis and search terms. All authors critically reviewed the protocol for intellectual content, subsequently revised it for publication, and read and approved the final version for submission.

Availability of data and materials

Not applicable.

Funding statement

Not applicable.

Competing interests statement

The authors declare that they have no competing interests.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	62, 180
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-29
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	396-401
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	414-415
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	408, 414-415
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	408, 414-415
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	87-164

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	183-198
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	230-255
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	201-211
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	218-219, 231-255
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	220-227, 260-264
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	260-274
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	220-227, 231-255
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	277-308
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☒	N/A
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☒	N/A
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	311-319
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	N/A
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	320-330

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	333-336

BMJ Open

Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065429.R2
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Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Paediatrics, Research methods
Keywords:	PAEDIATRICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Paediatric intensive & critical care < PAEDIATRICS

Automated digital technologies for supporting sepsis prediction in children: A scoping review protocol

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Word Count: 3217

ABSTRACT

Introduction While there have been several literature reviews on the performance of digital sepsis prediction technologies and clinical decision-support algorithms for adults, there remains a knowledge gap in examining the development of automated technologies for sepsis prediction in children. This scoping review will critically analyze the current evidence on the design and performance of automated digital technologies to predict paediatric sepsis, to advance their development and integration within clinical settings.

Methods and analysis This scoping review will follow Arksey and O'Malley's framework, conducted between February to December 2022. We will further develop the protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR). We plan to search the following databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Studies will be included on children >90 days post-natal to <21 years old, predicted to have or be at risk of developing sepsis by a digitalized model or algorithm designed for a clinical setting. Two independent reviewers will complete the abstract and full-text screening and the data extraction. Thematic analysis will be used to develop overarching concepts and present the narrative findings with quantitative results and descriptive statistics displayed in data tables.

Ethics and dissemination Ethics approval for this scoping review study of the available literature is not required. We anticipate that the scoping review will identify the current evidence

and design characteristics of digital prediction technologies for the timely and accurate prediction of paediatric sepsis and factors influencing clinical integration. We plan to disseminate the preliminary findings from this review at national and international research conferences in global and digital health, gathering critical feedback from multi-disciplinary stakeholders.

Scoping review registration

https://osf.io/veqha/?view_only=f560d4892d7c459ea4cff6dcdfacb086

Strengths and limitations of this study

- This review is a rigorous approach to collectively synthesizing current research on automated paediatric sepsis prediction technologies, critically examining the relationships between their design, performance, and clinical integration to identify sociotechnical challenges and research gaps.
- The chosen review strategy will comprehensively evaluate the vast literature across various study types and research disciplines by a multi-disciplinary research team.
- The review will exclude digital prediction technologies for paediatric sepsis treatment decisions and is limited to peer-reviewed literature written in the English language with a full-text version available.
- Articles focusing on age cohorts <90 days post-natal or >21 years old will be excluded due to significant differences in sepsis etiology and clinical presentation.

INTRODUCTION

Globally, it is estimated there were a total of 25.2 million cases of sepsis in children (<19) in 2017, imposing significant health care and societal burden (1). Healthcare costs for severe paediatric sepsis hospitalizations reached approximately $7.31 billion in the United States in 2016, accounting for almost 20% of total paediatric hospitalization costs (2). However, about 85% of global sepsis cases and 84.5% of sepsis-related deaths among all age groups occur in low-middle income countries, specifically those in sub-Saharan Africa and South-East Asia (1). Annual global mortality rates for children (<5) are approximately 2.9 million (Table 1) (3).

Table 1. Differences between global neonatal, paediatric, and adult sepsis (3).

	Neonatal (<90 days)	Paediatric (<5 y/o)	Adult (>20 y/o)
Annual Cases (M)	1.3 – 3.9	20.3	23.7
Annual Mortality (M)	0.4 – 0.7	2.9	7.7

Early recognition of sepsis in children is challenging. Unlike adult sepsis, children have different sepsis aetiologies (3). For example, children commonly develop sepsis from pneumonia, diarrhea, meningitis, or viral infections, where abdominal or genitourinary sources are more common in adults (4). Differences in aetiology can also be found between childhood and neonatal sepsis, with early-onset neonatal sepsis having a distinct microbial pattern (5). Recognizing sepsis in children is also significantly more challenging due to maturation-based differences in physiology (including immune system response), limitations in the communication of symptoms, and diagnostic modalities (4,6,7). Sepsis can lead to life-altering organ dysfunction if not identified quickly in children (8), where mortality rates are reduced two-fold if treated within the first hour (4). Recognition of sepsis is confounded by the age-based symptom variations within children, such as their differences in blood pressure response, serum lactate

levels (4), and commonalities among other childhood conditions and syndromes like Kawasaki syndrome or bronchiolitis (9). This milieu of complex information combined with significant time pressure provides a significant cognitive burden for healthcare professionals to promptly identify the onset of deterioration that can lead to this serious medical condition.

In 2020, updated Paediatric Sepsis Survival guidelines were published calling for the integration of screening standards in healthcare facilities to support rapid identification of sepsis in children (10) and provide the appropriate antimicrobial therapy at the proper time (5,10). Established screening tools such as the Paediatric Early Warning Score (PEWS) may support the timeliness of detecting clinical deterioration in children that can lead to sepsis (11). Recently, adaptations to the Sequential Organ Assessment Score (SOFA) for paediatric patients (pSOFA) and neonates (nSOFA) have shown promise in identifying children at risk for mortality with sepsis (12); however, it is controversial whether these scores provide value in low-resource environments (13–15). Development and implementation of algorithms such as the Sepsis Prediction and Optimization Therapy (SPOT) that can analyze electronic health data in real-time to provide a rule-based approach to initiate a physical sepsis screen have also been reported (16). With the call from the World Health Organization to improve sepsis identification and the potential for data-driven and knowledge-based technologies (3,17), digital prediction technologies are becoming more advanced using mathematical, statistical, and machine learning techniques to support sepsis prediction utilizing clinical information, symptoms, biomarkers, and other signs at the bedside (18–21). While recent reviews have explored the literature on the effectiveness of digital technologies for adult and neonate sepsis prediction (18,19,22–26), there is currently no review on the design and implementation of these predictive technologies for children. Considering the pathophysiology and aetiology for paediatric sepsis are different from

that seen in adults and neonates (27), combined with the lack of widely accessible digital technologies for children compared to adults (28), it is critically important to review the literature on this age cohort.

Prior reviews on sepsis prediction technologies

Recent narrative reviews discuss machine learning-based technologies for adult and paediatric sepsis (20,29,30). However, their eligibility criteria focus primarily on adults, with only two (20) or three (29) articles on children. Some reviews excluded digital technologies that were not based on "modern" machine learning models (21,30), or involved a broad search on infectious disease prediction beyond sepsis (29). Others have also limited their investigations to PubMed/Medline, excluding engineering databases, which may provide greater insight into the design characteristics of digital technologies (20,26,31–33), or they focus exclusively on US hospitals (33).

Many systematic and scoping reviews have been rigorous in their search strategy but similar to the identified narrative reviews, report on screening tools and technologies for adult patients while excluding children (24,25,28,34–37), and the engineering disciplines (19,23,38–40). Currently published protocols plan to exclude literature on the application of machine learning (39,41), which may not capture research on certain relevant technologies. While there have been systematic reviews on the performance of neonatal sepsis prediction and recognition technologies providing insight into their capabilities (19,23), none focus on the specifics of paediatric sepsis.

Current systematic reviews that include the paediatric literature as part of their search strategy are not strictly focused on this patient population (22,28,38), having only identified one

(38) or three (22,28) related articles specific to children. Other reviews broadly examine early warning systems for paediatric clinical deterioration (42,43). We have not identified any systematic or scoping reviews that accurately scope the literature on digital paediatric sepsis prediction technology. While one identified protocol aims to capture strategies for early recognition of paediatric sepsis from clinical deterioration, the focus of the review is general strategy effectiveness and does not explicitly include engineering databases which would describe technical design aspects (40).

Purpose of the study

Given the limitations of recent literature reviews and the lack of reviews focused on paediatric sepsis, it is necessary to synthesize the current research describing the development and evaluation of automated sepsis prediction technologies for this underrepresented age cohort. The scoping review defined by this protocol will identify and summarize the existing literature on the design characteristics, performance, and integration of automated sepsis prediction technologies in paediatric contexts. The scoping review, a methodology focusing on answering broader research questions through a systematic search and presenting tabular findings along with a narrative integration (44), was identified as the best approach for this study. We anticipate that the rigorous methodology will warrant a meaningful summary about the current development of digital technologies for sepsis prediction that can inform future research toward improving their performance and evidence-based clinical implementation to ultimately improve the lives of children globally.

METHODS AND ANALYSIS

The reviewers on this scoping review consist of a multi-disciplinary team of engineers, a health researcher/biomedical engineering research librarian, a psychology student, and a paediatric clinician. Our methodology will be guided by the framework developed by Arksey and O'Mally (44), which iterates through six steps: (i) identifying the research questions; (ii) searching for relevant studies; (iii) selecting the studies; (iv) charting the data; (v) collating, summarizing, and reporting the results; and (vi) consulting with stakeholders to inform or validate findings. The sixth step is optional, and we will modify this step to consult with experts specifically around finding technologies used in hospital or industry settings. Levac's recommendations for independent full-text reviews by at least two reviewers will also be followed (45). This study protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for a scoping review (PRISMA-ScR) (46) with any gaps being filled by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for protocols (PRISMA-P) (47). This protocol has been registered on the Open Science Framework (https://osf.io/nh6qz/?view_only=8c840412a2a44117ac16fdf76e06abd6).

Step 1: **identifying the research questions**

The research questions were developed through an initial search of the literature on automated digital technologies for paediatric sepsis recognition and gaps identified in current systematic and narrative reviews in the neonatal and adult context. The Joanna Briggs Institute recommendations of the Population, Concept, and Context model were followed (48), maintaining a broad scope for understanding the existing evidence on paediatric sepsis prediction technologies with respect to their current performance, identified outcome measures, and existing research gaps:

1. How do the design characteristics of automated paediatric sepsis prediction technologies for healthcare facilities (e.g., the recognition task, type, method, demographics, and indicators) influence their performance?
2. What are the impacts of clinically implemented automated paediatric sepsis prediction technologies on decision-making and patient outcome measures?
3. What challenges and research gaps (e.g., evidence, practical knowledge, population, theoretical, methodological) exist for improving the sociotechnical integration of knowledge-based algorithms and data-driven models for predicting paediatric sepsis in healthcare facilities?

Step 2: **identifying relevant studies**

We will conduct a comprehensive scoping review that includes a multi-disciplinary group of scholarly databases: Association of Computing Machinery (ACM) Digital Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Google Scholar, Institute of Electric and Electronic Engineers (IEEE), PubMed, Scopus, and Web of Science. Articles will further be identified using the snowballing technique (49), to identify relevant literature among the references and citations of articles included for the full review. We will also hand-search for reports on the design, validation, and implementation of commercial digital technologies for sepsis prediction, which may be approved by governing bodies such as Health Canada (health-products.canada.ca/mdall-limh/), the Food and Drug Administration (accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/textsearch.cfm), and the European Union Medical Device Regulation (ec.europa.eu/tools/eudamed/#/screen/home).

Guided by a University of Waterloo biomedical engineering research librarian, we developed a comprehensive search strategy for each database. The approach employs keywords, medical subject headings (MeSH), key concept subject headings, and Boolean terms broken down into the following parts: the recognition algorithm or model, type of digital technology, health condition, alert type, implementation or validation factors, and patient population. A sample search strategy for PubMed is presented in Table 2.

Table 2. Sample search strategy and results.

Database	Search Terms	Results	Date
PubMed	("decision support"[All Fields] OR "decision-support"[All Fields] OR "early warning score"[MeSH Terms] OR "early warning score"[All Fields] OR "smart system*"[All Fields] OR "electronic alert*"[All Fields] OR "artificial intelligence"[All Fields] OR "artificial intelligence"[MeSH Terms] "machine learning"[All Fields] OR "deep learning"[All Fields] OR "neural network*"[All Fields] OR "support vector machine"[All Fields] OR "hidden markov model"[All Fields] OR "statistical learning"[All Fields] OR "predictive function"[All Fields] OR "algorithm"[All Fields] OR "algorithms"[MeSH Terms] OR "automat*"[All Fields] OR "comput*"[All Fields] OR "decision making, computer assisted"[MeSH Terms] OR "electronic*"[All Fields] OR "representation learning"[All Fields] OR "conformal prediction"[All Fields] OR "random forest"[All Fields] OR "naïve bayes"[All Fields] OR "regression" OR "regression analysis"[MeSH Terms] OR "gradient boosting"[All Fields] OR "artificial learning"[All Fields] OR "machine intelligence"[All Fields] OR "probabilistic network*"[All Fields] OR "knowledge representation"[All Fields] OR "bayesian learning"[All Fields] OR "expert system*"[All Fields] OR "technology assisted"[All Fields] OR "computer assisted"[All Fields] OR "statistical"[All Fields] OR "mathematical"[All Fields]) AND ("system"[All Fields] OR "tool"[All Fields] OR "alert*"[All Fields] OR "technology"[All Fields] OR "software"[All Fields] OR "model*"[All Fields] OR "engine"[All Fields] OR "approach*"[All Fields] OR "algorithm"[All Fields] OR "platform"[All Fields] OR "method*"[All Fields] OR "scor*"[All Fields] OR "device"[All Fields]) AND (	15,531	02/15/2022

"sepsis"[All Fields] OR "sepsis"[MeSH Terms] OR "septic shock"[All Fields] OR "systemic inflammatory response syndrome"[All Fields] OR "acute deterioration"[All Fields] OR "patient deterioration"[All Fields] OR "clinical deterioration"[MeSH Terms] OR "clinical deterioration"[All Fields] OR "severe infection"[All Fields] OR "severe bacterial infection"[All Fields] OR "bacterial infections"[MeSH Terms] OR "febrile illness"[All Fields] OR "non-malarial febrile illness"[All Fields] OR "bacteremia"[All Fields]) AND ("diagnos*"[All Fields] OR "detect*"[All Fields] OR "predict*"[All Fields] OR "prognosticate"[All Fields] OR "identif*"[All Fields] OR "infer*"[All Fields] OR "warn*"[All Fields] OR "alert*"[All Fields] OR "recog*"[All Fields] OR "screen*"[All Fields] OR "monitor*"[All Fields] OR "assess*"[All Fields] OR "surveillance"[All Fields] OR "classif*"[All Fields]) AND ("evaluat*"[All Fields] OR "implement*"[All Fields] OR "perform*"[All Fields] OR "design"[All Fields] OR "validat*"[All Fields] OR "usability"[All Fields] OR "effectiveness"[All Fields] OR "efficiency"[All Fields] OR "satisfaction"[All Fields] OR "safety"[All Fields] OR "acceptance"[All Fields] OR "clinical value"[All Fields] OR "interpret*"[All Fields] OR "perception"[All Fields] OR "perspective"[All Fields] OR "opinion"[All Fields] OR "error"[All Fields]) AND ("child*"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields] OR "pediatrics"[MeSH Terms] OR "toddler*"[All Fields] OR "teen*"[All Fields] OR "youth*"[All Fields] OR "adolescen*"[All Fields] OR "adolescent"[MeSH Terms] OR "infan*"[All Fields] OR "infant"[MeSH Terms] OR "school age*"[All Fields] OR "PICU"[All Fields]) LIMIT TO: [Text Availability]: Full text, [Language]: English, [Species]: Human

The search results will be imported to Mendeley's reference management software for future referencing and organization (Mendeley Ltd.). A systematic review management software, Covidence (Veritas Health Innovation Ltd.), will be used to identify and merge duplicate articles. A sample of 20 abstracts will be initially screened by two reviewers (RT and JG), ensuring the inclusion-exclusion requirements are robust in capturing relevant articles related to the design and evaluation of automated prediction technologies for paediatric sepsis. Both reviewers will

also ensure that the data extraction items capture valuable and appropriate study details from the articles included in the full-text review, which will be shared with the research team.

Step 3: **study selection**

Inclusion criteria

The proposed review will include articles that meet the following inclusion criteria:

- The article is written in English.
- The article is a peer-reviewed journal article, full conference proceeding, or research published on a commercially available digital technology which may be approved by a medical device regulatory body.
- Following the American Academy of Pediatrics' definition for late adolescence, more than the majority of data reported will include children aged >90 days post-natal to <21 years old (50).
- The article is about an automated data-driven or knowledge-based approach toward paediatric sepsis prediction in a healthcare setting, including sepsis risk, severe sepsis, septic shock, or sepsis mortality risk.
- The digital technology is evaluated for its performance through validation testing, experiments, or an observational study.
- There is no specification for publication years.

Exclusion Criteria

Screened articles that fit within the following categories will be excluded from this review: Commentaries, dissertations, editorials, books and book chapters, lectures and addresses, study

protocols, review articles, and articles inaccessible for full-text review after utilizing library resources. Articles that describe digital technologies informing sepsis treatment strategy selection are outside the scope of this review, because this study is focused on technologies supporting clinical decision-making and screening that occurs before fluid resuscitation or antibiotic selection for confirmed sepsis patients. Digital technologies developed for at-home use are also outside the scope of this review, as the context of the protocol is to review the evidence on automated sepsis prediction technologies in regulated healthcare settings.

Selection process

This review will follow the reporting checklist in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), provided by Tricco et al. (46). First, all relevant articles will be imported into Covidence. Second, two reviewers (RT and JG) will independently perform the title and abstract screening using the developed eligibility criteria by classifying them as "Yes," "No," or "Maybe." Any article classified as "Yes" or "Maybe" by RT or JG will be included in the full-text review during this stage by adding them to an Excel spreadsheet for access by all authors. If a full-text article cannot be accessed, the reviewers will seek assistance from library services at the institution or directly contact the article's corresponding author. Third, two investigators (RT and JG) will independently perform the full-text screening for eligibility using the listed inclusion-exclusion criteria. A third member of the research team will resolve any disagreements on eligibility that occur during the full-text review. After the full-text review, an inter-rater agreement will be calculated using Cohen's kappa coefficient (κ) statistic.

The first step in identifying relevant studies was performed on February 15, 2022. The planned end date for completing the full-text screening and analysis is December 30th, 2022. We have maintained search alerts for potentially eligible articles to ensure our review remains updated before dissemination through publication.

Step 4: **charting the data**

The data extraction form will be developed in Covidence and exported to Excel to capture the relevant information from each article. Two reviewers (RT, JG) will individually extract the relevant data from a sample of eligible articles screened for inclusion in the full-text review to ensure consistency of recording data. Any disagreements on extracted data will be resolved through discussion between the reviewers. The form will be iteratively updated until the authors reach a consensus on the relevant data to extract. We will begin by pulling the following type of data into the form, with additional data included as we screen more articles:

- Article information: author(s), year published, city, country, discipline(s).
- Prediction task: the definition of sepsis being identified and the use context for recognition in paediatrics.
- Prediction task type:
    - Alerting automation that provides a notification that a patient has met the objective sepsis recognition criteria.
    - Decision support automation that provides assistance in the diagnosis of sepsis.
    - Data automation that collects clinically relevant cues and information on behalf of the user(s), which may be used in combination with alerting and decision support.
- Prediction method:

- Data-driven methods that use retrospective datasets to build a statistical or machine learning-based model.
- Knowledge-based methods that use consensus criteria to build an algorithm with threshold-based criteria.

- Participant demographics: age cohort, number of participants.
- Prediction indicators: vital signs, biomarkers, socio-demographics, prior treatments, medical history.
- Prediction interface: audible alert, dialog box, provided information
- Validation measures:
  - Reported number of true positives, false positives, and false negatives.
  - Reported sensitivity and specificity.
  - Time to accurate sepsis recognition by the technology and/or the clinician.
  - Measured or expected impact on clinical decisions and patient outcomes.
  - Generalizability of the digital technology in the context of bias, fairness, and appropriateness (51,52).

Step 5: **collating, summarizing, and reporting the results**

The extracted data will be synthesized within tables that summarize the current digital technology landscape in predicting paediatric sepsis, including characteristics that describe their performance and the sociotechnical factors of their integration by health care providers on patient outcomes. Within summary tables, we will present the current approaches toward model and algorithm development for automated sepsis prediction technologies, including the predictive indicators, the prediction timing objective, and how they interface with clinicians.

Quantitative performance and implementation measures such as sensitivity and specificity, and the impacts on intervention timing will also be reported in data tables, including calculations of precision, recall, and F1 score, when possible.

We will then perform a thematic analysis to identify concepts related to our research questions. This analysis will be presented as a narrative, including an organization of themes on the identified design characteristics of automated prediction technologies integrated within clinical contexts. The purpose of the analysis will be to identify the types of research gaps that exist for knowledge-based algorithms and data-driven models to improve sociotechnical integration (i.e., supporting clinical decision-making) and patient outcomes. Challenges with bias, fairness, and appropriateness will also be qualitatively examined with respect to potential generalizability barriers. Diagrams will be developed for the identified relationships and themes among the design characteristics of the automated technologies for paediatric sepsis prediction and their influence on system performance and implementation throughout time to visually highlight the opportunities for future investigations.

Step 6: **methodological quality appraisal**

We will consult with experts in automated paediatric sepsis prediction technologies for this review to identify those applied in clinical settings. While critical appraisal of the identified articles is not mandatory in the scoping review methodology, we will consult with stakeholders to inform and validate our findings.

Patient and public involvement

There were no patients or public involvement in the development of this protocol.

ETHICS AND DISSEMINATION

Approval from an ethics review committee is not required for this study because it is a scoping review of previously published literature. Once the review is completed, we plan to disseminate the preliminary findings at national and international research conferences in global and digital health to gather critical feedback from researchers and the public. The finalized results from the review will be submitted for publication in an open access peer-reviewed journal.

DISCUSSION

This scoping review will provide a comprehensive and structured understanding of the automated digital technologies that have been developed to support the timely prediction of paediatric sepsis. At a high-level, the results will focus on design characteristics, performance validation, and current sociotechnical integration factors, which will be analyzed thematically and reported in data summary tables, indicating how the development of these technologies is evolving throughout time. It is anticipated that the outcomes will reveal the current challenges in developing and implementing clinically meaningful digital prediction technologies for paediatric sepsis across various clinical environments. Furthermore, the results are expected to identify critical research aspects requiring further investigation.

Compared to previous articles, this scoping review focuses on the complexities of paediatric sepsis, with a methodological strength in taking a comprehensive and systematic approach that will provide an overview of the evidence in this digital technology landscape. Inherent in the approach of a scoping review is the limitation of its objective: to summarize the literature and identify meaningful gaps for further research. As this study will include articles

with various study designs, it does not aim to answer specific questions about recommending the use or application of certain sepsis prediction technologies for paediatrics. With the results of the pilot search (Table 2), this review is also limited in its scope, where non-English articles or articles without a full-text version will not be included. Finally, digital technologies informing treatment strategies for sepsis and studies looking at age cohorts <90 days post-natal or >21 years old will be excluded because of significant differences in sepsis etiology and clinical presentation, while capturing literature from geographic areas that provide paediatric healthcare services to this age range. We plan to adequately convey the overall strengths and limitations once the full-text review is completed, including any deviations from the protocol, in the final review.

In conclusion, by mapping the attributes of paediatric sepsis prediction technologies to outcomes related to clinical integration and performance, we anticipate that our results will highlight critical research gaps among the medical, engineering, and computer science disciplines. The results may inform research on identifying relevant predictive indicators best suited for the design of digital technologies in specific use contexts and environments, improvements towards model development for sepsis prediction, and factors supporting the optimal workflow integration of digital prediction systems by clinicians. Ultimately, this review will be critical for advancing knowledge to improve sepsis prediction for children globally.

List of abbreviations

ACM: Association of Computing Machinery

CINAHL: Cumulative Index to Nursing and Allied Health Literature

IEEE: Institute of Electric and Electronic Engineers

nSOFA: neonatal Sequential Organ Assessment Score

PEWS: Paediatric Early Warning Score

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for protocols

PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews

pSOFA: paediatric Sequential Organ Assessment Score

SOFA: Sequential Organ Assessment Score

SPOT: Sepsis Prediction and Optimization Therapy

Author contributions

RT, JG, KM, CMB, and JMA contributed to the development of this manuscript. RT is the guarantor of the review, conceptualized the research questions and methods, and drafted the initial manuscript. All authors contributed to the development of the search strategy, selection criteria, and data extraction template. JMA provided expertise on paediatric sepsis and search terms. All authors critically reviewed the protocol for intellectual content, subsequently revised it for publication, and read and approved the final version for submission.

Availability of data and materials

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Competing interests statement

The authors declare that they have no competing interests.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	62, 180
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-29
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	396-401
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	414-415
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	408, 414-415
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	408, 414-415
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	87-164

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	183-198
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	230-255
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	201-211
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	218-219, 231-255
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	220-227, 260-264
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	260-274
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	220-227, 231-255
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	277-308
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐	☒	N/A
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐	☒	N/A
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	311-319
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	320-330
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	333-336