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Advanced Machine Learning Approaches for Sepsis Prediction: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2023 and was last updated on 18 December 2023.

INTRODUCTION

Review question / Objective The aim of our study is to conduct the network meta-analysis to explore the use of ML models for predicting the onset of sepsis, and to utilize meta-regression for evaluating factors that affect model quality, thereby establishing conditions for developing an optimal sepsis prediction model.
(i) population: adult patients (without restrictions on age, sex, race, or ethnicity). Patients suspected of having sepsis or presenting with signs and symptoms indicative of sepsis.
(ii) intervention (index test): Machine Learning (ML) models developed for the prediction, detection, or diagnosis of sepsis (right alignment). Traditional Scoring Systems used for sepsis diagnosis or prediction, such as SOFA (Sequential Organ Failure Assessment), qSOFA (quick SOFA), NEWS/NEWS2 (National Early Warning Score), MEWS (Modified Early Warning Score), SAPS II (Simplified Acute Physiology Score), SIRS (Systemic Inflammatory Response Syndrome).
(iii) comparator (Reference test): sepsis-3 definition or other operational definitions of sepsis used in clinical settings.
(iv) outcomes: Area Under the Receiver Operating Characteristic Curve (AUC-ROC), assessing the diagnostic accuracy of the ML models and traditional scoring systems in identifying or predicting sepsis.
(v) study design: prospective and retrospective diagnostic test accuracy studies.

Rationale The rationale for our study is grounded in the critical nature of sepsis, a condition with high mortality risk, where early detection and prompt treatment are crucial for reducing hospital mortality. The 2021 Surviving Sepsis Campaign emphasizes rapid antibiotic therapy for high-risk patients and systematic screening for early detection. However, the current clinical scales and diagnostic methods for sepsis prediction are not highly accurate, leading to delayed interventions. This highlights the need for more precise tools, with a growing focus on machine learning models. These models, particularly right-aligned ones, have shown potential in predicting sepsis development hours before clinical confirmation, offering advantages over traditional scoring systems. Despite previous meta-analyses in this field, significant heterogeneity and varying approaches in studies have limited definitive conclusions about the efficacy of machine learning models in sepsis prognosis. Our study aims to address these challenges through a network meta-analysis and meta-regression, seeking to identify key factors for an effective predictive model suitable for the complex clinical scenarios of sepsis prognosis.

Condition being studied Sepsis.

METHODS

Search strategy A systematic literature search of studies published within the last 10 years (from 2013 to 2023) was performed in Medline, PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) by two independent investigators.

Participant or population Adult patients (without restrictions on age, sex, race, or ethnicity).Patients suspected of having sepsis or presenting with signs and symptoms indicative of sepsis.

Intervention ML models developed for the prediction, detection, or diagnosis of sepsis (right alignment). Traditional Scoring Systems used for sepsis diagnosis or prediction, such as SOFA, qSOFA, NEWS/NEWS2, MEWS, SAPS II, SIRS.

Comparator Sepsis-3 definition or other operational definitions of sepsis used in clinical settings.

Study designs to be included We will include prospective and retrospective diagnostic test accuracy studies.

Eligibility criteria Inclusion criteria: studies aimed to predict the onset of sepsis in real time (right alignment) using ML models, in adult patients in any hospital setting.Studies were excluded if they met one of the following criteria: 1) review articles, case reports or case series; 2) no sepsis definition criteria; 3) no relevant outcomes; 4) other outcomes (mortality); 5) pediatric patients; 6) no data on patient cohort; 7) conference papers or preprints.

Information sources PubMed, MEDLINE, Google Scholar, CENTRAL, PROSPERO.

Main outcome(s) Area Under the Receiver Operating Characteristic Curve (AUC-ROC), assessing the diagnostic accuracy of the ML models and traditional scoring systems in identifying or predicting sepsis.

Data management Data extraction was performed by two independent authors. These data included: (1) Basic study details such as the first author, publication year, country, journal, study design, data collection period, mean age, sex, hospital mortality, prediction method, and sample size; (2) ML model characteristics: data source, prediction model, sepsis definition criteria, department, prediction window, external validation, imputation, features; (3) Outcome data: area under the curve of the receiver operating characteristic (AUC) as performance metric.

Quality assessment / Risk of bias analysis The internal validity and risk of bias will be assessed by three independent reviewers using the 'Quality Assessment of Diagnostic Accuracy Studies' (QUADAS-2) tool combined with an adapted version of the 'Joanna Briggs Institute Critical Appraisal checklist for analytical cross-sectional studies'. Publication bias and small-study effects will be assessed using Bayesian NMA meta-regression and funnel plot analysis (for comparisons with 10 or more studies). The certainty of evidence will be assessed with GRADE methodology integrated in CINeMA approach.

Strategy of data synthesis Traditional meta-analysis will be conducted to calculate pooled AUCs. Inter-study heterogeneity will be evaluated using the I-squared (I2) statistic and the Cochrane Q test; random-effects model (restricted maximum–likelihood, REML) will be used. We will conduct a meta-regression analysis, leveraging the REML random-effects model, to ascertain if the AUC metrics might be affected by covariates such as study design and ML model characteristics.
We will use a frequentist, random-effects Network Meta-Analysis (NMA) using CINeMA (Confidence in Network Meta-Analysis) approach and STATA 17.0 (StataCorp, College Station, TX) software. Articles will be included in the NMA if they compared any two ML models with different ML models or any ML model with a traditional scoring system. The

Mean Difference (MD) with corresponding 95% CI will be calculated for AUCs.

Subgroup analysis We will compare the following groups:
(1) NNM (Neural Network Models) = LSTM (Long Short-Term Memory), CNN (Convolutional Neural Networks), DNN (Deep Neural Networks), GRU (Gated Recurrent Unit), TCN (Temporal Convolutional Networks), MLP (Multilayer Perceptron); (2) DT (Decision Trees) = RF (Random Forest), AdaBoost, XGBoost, LightGBM, ET (Extremely Randomized Trees); (3) LR (Regression methods) = Logistic Regression, Cox Regression, Non-linear Regression; (4) SVM (Support Vector Machine); (5) KNN (K-Nearest Neighbors); (6) GLM (Generalized Linear Model); (7) NB (Naive Bayes); (8) Traditional Scoring Systems used for sepsis diagnosis or prediction, such as SOFA, qSOFA, NEWS/NEWS2, MEWS, SAPS II, SIRS.

Sensitivity analysis Sensitivity analysis will be conducted by using studies with low to moderate risk of bias.

Language restriction No language limitation.

Country(ies) involved Russian Federation.

Keywords Sepsis; Machine Learning; Network Meta-Analysis; Decision Trees; Predictive Modeling.

Contributions of each author
Author 1 - Mikhail Yadgarov - collected the data, contributed data and analysis tools, performed the analysis, assessed risk of bias, certainty of evidence rating, wrote the paper.
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