Prognosis, Deterioration Monitoring, and Predisposing Factors for Sepsis: A Rapid Scan

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Conflicts of Interest

The authors declare no conflicts of interest.

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Key Findings

- Machine learning and AI algorithms consistently outperform traditional clinical scoring systems (SOFA, APACHE II, SAPS II) in predicting sepsis progression, sepsis-associated acute kidney injury, and mortality, with XGBoost often demonstrating the highest predictive accuracy
- Biomarkers such as lactate, procalcitonin, albumin, and inflammatory markers are strongly associated with both the incidence and severity of sepsis, and they enhance risk stratification when combined with ML/AI and clinical scoring systems
- Echocardiographic parameters, including global longitudinal strain (GLS), left ventricular outflow tract velocity time integral (LVOT VTI), and systolic/diastolic dysfunction, are significant predictors of fluid responsiveness and short-term mortality in septic patients
- Predisposing/risk factors for sepsis include age, sex, chronic comorbidities (diabetes, cancer, chronic kidney disease, COPD, hypertension), catheter-associated interventions, ICU length of stay, mechanical ventilation, ECMO, and nutritional support, with many showing high odds ratios for both incidence and mortality
- Genetic polymorphisms, such as IL-6 572C/G, may increase susceptibility to sepsis, although evidence for other genetic variants (for example, Asp299Gly, IL-8) is mixed
- Infection-related factors, particularly multi-drug-resistant organisms and hypermucoviscous bacterial phenotypes, significantly elevate the risk of bloodstream infections and mortality
- Hospital-acquired sepsis is associated with higher mortality and longer ICU/hospital stays compared with community-acquired sepsis

Abstract

Background

Sepsis is a complex life-threatening condition driven by a dysregulated host response to infection and remains a leading cause of morbidity and mortality worldwide. Accurate early prediction and risk stratification are critical to guiding timely interventions, optimising resource allocation, and improving patient outcomes. This rapid scan aims to synthesise evidence from systematic reviews on deterioration monitoring, prognostic indicators, and predisposing risk factors associated with sepsis incidence and mortality.

Method

A rapid scan was conducted using a structured search strategy in Embase (Ovid). Records were initially screened using a large language model (LLM)–assisted approach to support efficient identification of potentially relevant studies, followed by independent manual screening by reviewers to confirm eligibility. Priority was given to systematic reviews with or without meta-analysis to maximise methodological rigour while enabling timely synthesis. Data were extracted on study populations, clinical settings, measured parameters, and outcomes related to sepsis risk and prognosis. Extracted data were organised into categories, including machine learning/AI-based predictive models, clinical scoring systems, biomarkers, laboratory tests, predisposing risk factors, and other prognostic indicators.

Results

We identified a total of 76 systematic reviews, the majority of which focused on prognostic indicators and deterioration monitoring in sepsis, with others examining predisposing/risk factors across diverse patient populations and clinical settings. The included reviews demonstrate that machine learning/artificial intelligence (ML/AI) models, particularly gradient boosting approaches such as XGBoost, generally outperform traditional clinical scoring systems (for example, SOFA, APACHE II, SAPS II) in predicting mortality and sepsis-associated complications, including acute kidney injury. Prognostic biomarkers such as lactate, procalcitonin, albumin, and inflammatory markers were consistently associated with disease severity and mortality, particularly when used in combination with clinical scoring systems. Echocardiographic measures, including global longitudinal strain and left ventricular outflow tract velocity time integral, provided additional prognostic value in assessing cardiovascular dysfunction and fluid responsiveness. Predisposing/risk factors for sepsis and adverse outcomes included age, comorbidities (such as diabetes, chronic kidney disease, and cancer), catheter-associated interventions, prolonged ICU stay, mechanical ventilation, and infection with multidrug-resistant organisms. Hospital-acquired sepsis was associated with higher mortality and longer lengths of ICU stay compared to community-acquired sepsis.

Conclusion

Combining ML/AI models with established clinical scoring systems, biomarkers, and echocardiographic assessment has the potential to reduce mortality, improve patient

outcomes, and optimise ICU resource utilisation. Future research should place stronger emphasis on well-designed prospective studies, together with standardisation of biomarkers, scoring systems, and model evaluation methods, to support robust validation and facilitate equitable translation of these approaches into routine clinical practice.

Background

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and remains a major global health challenge, contributing to substantial morbidity, mortality, and healthcare burden worldwide.[1,2] Estimates from the Global Burden of Diseases 2017 study suggest that sepsis accounts for nearly 49 million cases and 11 million deaths worldwide, representing one in five deaths globally.[3] In 2016, updated definitions for sepsis and septic shock were released as part of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). These definitions place greater emphasis on recognising early organ dysfunction (such as respiratory, renal or cardiovascular impairment) and identifying patients at high risk of clinical deterioration. They highlight the critical need for tools and approaches that enable reliable prognostic assessment and timely monitoring to guide clinical interventions. [4]

Accurate prediction of sepsis outcomes and early identification of patient deterioration are critical for guiding clinical decision-making, optimising resource allocation, and improving survival.[1,5] A wide array of systems and markers, ranging from clinical scoring systems such as the quick Sequential Organ Failure Assessment (qSOFA) and National Early Warning Score 2 (NEWS2), to physiological and laboratory parameters, inflammatory and immune biomarkers, and more recently machine learning algorithms, have been proposed to aid prognosis and monitoring. Despite this, the performance, feasibility, and generalisability of these approaches vary significantly across healthcare settings, patient populations, and stages of illness.[1]

In parallel, a clearer understanding of the factors that predispose individuals to developing sepsis or experiencing severe disease is essential for prevention and early intervention. Established risk factors include advanced age, underlying comorbidities, immunosuppression, genetic susceptibility, and environmental or healthcare-related exposures. Improved characterisation of these risk factors can support targeted screening, earlier recognition, and more personalised approaches to sepsis management.[2]

Aim

This rapid scan synthesises current evidence on prognostic indicators, deterioration monitoring tests, and predisposing factors for sepsis. The findings aim to inform decision-making by NHS England (NHS E) and the Innovation, Research and Life Sciences Strategy (IRLSS) teams, supporting the AMR Diagnostic Programme. By identifying approaches that enable earlier recognition of sepsis, better stratification of risk, and more targeted clinical responses, this work directly contributes to the objectives of the UK's National Action Plan for Antimicrobial Resistance 2024–2029, published in May 2024. This report contributes to the development of the sepsis Modern Service Frameworks (MSF), which aim to support long-term planning, sustainable investment, and the consistent delivery of high-quality, evidence-based, and digitally enabled care. MSFs are collaboratively designed with input from clinicians, individuals with lived experience, and system partners, focusing on conditions where substantial and rapid improvements in quality and productivity can be achieved.

This project has been commissioned by the Horizon Scanning, Demand Signalling and Business Development team in the NHSE Innovation Research and Life Science Strategy Group to support the NHSE Antimicrobial Resistance Diagnostics Programme.

Method

Scope

This rapid scan focuses on identifying and synthesising evidence related to prognostic indicators, deterioration monitoring tests, and predisposing factors for sepsis in children and adult patient populations. The scan was limited to studies indexed in Embase (Ovid), selected for its comprehensive coverage of biomedical and clinical literature, including international observational studies, clinical trials, and emerging technologies.

Eligibility criteria

The inclusion criteria were defined using the PICOS framework:

- **Population:** children or adults with sepsis, septic shock, bloodstream infections or sepsis-related organ dysfunction
- **Intervention/Exposure:** Prognostic indicators such as organ dysfunction, biomarkers; deterioration monitoring tests such as laboratory tests, scoring systems; predisposing factors for sepsis such as age, chronic medical conditions, or indwelling devices
- **Comparator:** Any comparator, including standard care, alternative prognostic tools, or no comparator
- **Outcomes:** Mortality, clinical deterioration, predictive performance measures, organ failure, intensive care unit (ICU) admission, or identification of predisposing factors associated with sepsis onset or severity
- **Study design:** Systematic reviews with or without meta-analysis

Studies focusing on infections unrelated to sepsis were excluded. Studies were also excluded when they did not report prognostic, deterioration, or risk-factor outcomes relevant to sepsis. In addition, any records that were not systematic reviews such as primary studies (randomised trials, observational studies) were excluded.

Search Strategy

Our search was restricted to studies published from January 2024 to November 2025 to ensure that the scan captured the most recent evidence reflecting current clinical practice, technological developments, and emerging methodologies (see Appendix A). Searches were

designed to identify systematic reviews relevant to sepsis prognosis, predisposing factors and deterioration monitoring, including clinical scoring systems, physiological and biomarker-based measures, and machine learning or algorithmic approaches. The scan includes studies published in English. The findings reflect the evidence available within Embase (Ovid) data source and timeframe.

Title and Abstract Screening

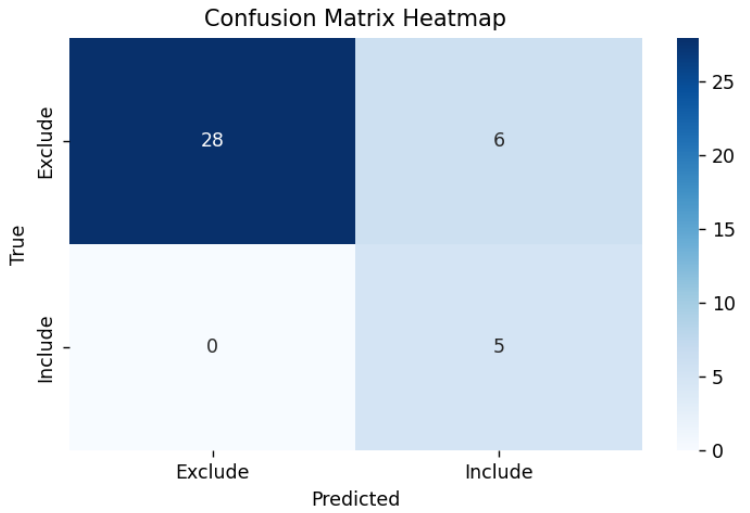
Following completion of the searches, a sample of records was screened independently by three reviewers using Rayyan, an online screening tool. This sample was used to develop and validate a large language model (LLM) tool to support the title and abstract screening process. Title and abstract screening for the remaining records was assisted by gpt-4o-mini-2024-07-18 (https://platform.openai.com/docs/models/gpt-4o-mini) (accessed via OpenAI on 5 December 2025).

A sample of 101 records was manually screened to support the development and validation of the LLM screening tool. From these, a random 40% of includes and 40% of excludes were used as prompt development dataset. The final prompt is the following:

"You are a researcher screening references for inclusion in a literature analysis that aims to identify literature reviews related to sepsis, including systematic reviews on the topics of sepsis prognosis, sepsis deterioration monitoring and sepsis predisposing factors. Answer YES if the following record is a systematic review or a literature review with a meta-analysis AND if it is about sepsis. Answer YES if the record meets these inclusion criteria or if you are unsure. Otherwise, answer NO. Then reproduce the exact context from the text that contained the information on which basis you made the decision. Here is the text of the record:"

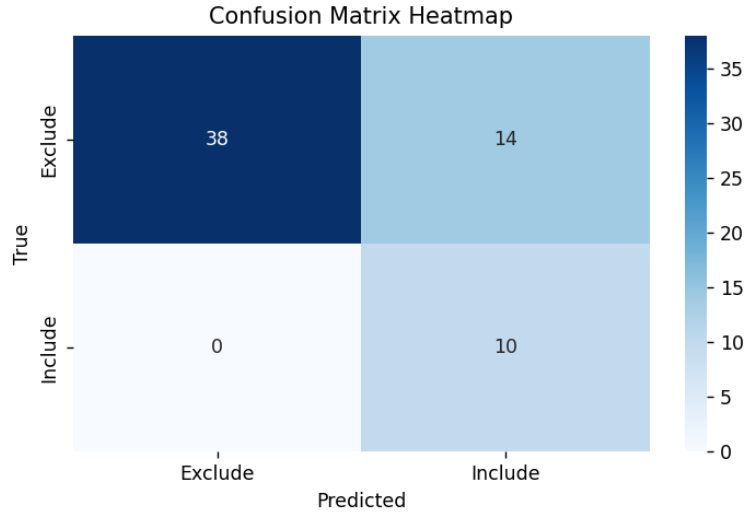
On the development set, initially 7 records were labelled as included but upon discussing eligibility criteria during the prompt development, only 5 included records remained. These are the scores on the development dataset:

Precision 0.45 and sensitivity 1.00



The remaining 60% includes and 60% excludes from the pilot screening were used for the final and independent evaluation of the LLM prompt. The results are the following:

Precision 0.42, recall 1.00



As part of an error analysis of two false-negative predictions, inclusion labels were changed in order to achieve the final scores.

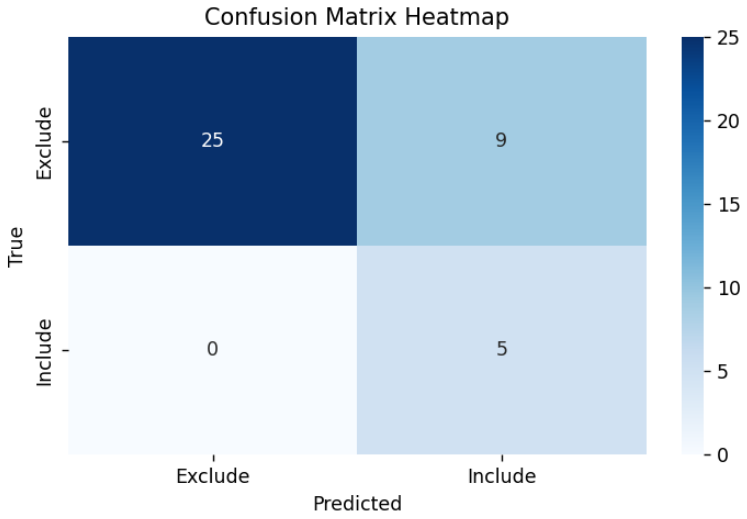
After discussing the error analyses and achieving 100% sensitivity on both the development and evaluation datasets we decided to develop an additional prompt that considers bloodstream infections in addition to sepsis. Starting over on the prompt development dataset, the final updated prompt is shown below, with edited text printed in bold:

"You are a researcher screening references for inclusion in a literature analysis that aims to identify literature reviews related to sepsis ***and bloodstream infections****, including systematic reviews on the topics of sepsis* ***and bloodstream infection*** *prognosis, sepsis* ***and bloodstream infection*** *deterioration*

*monitoring and sepsis **and bloodstream infection** predisposing factors. Answer YES if the following record is a systematic review or a literature review with a meta-analysis AND if it is about sepsis or bloodstream infections. Answer YES if the record meets these inclusion criteria or if you are unsure. Otherwise, answer NO. Then reproduce the exact context from the text that contained the information on which basis you made the decision. Here is the text of the record:"*

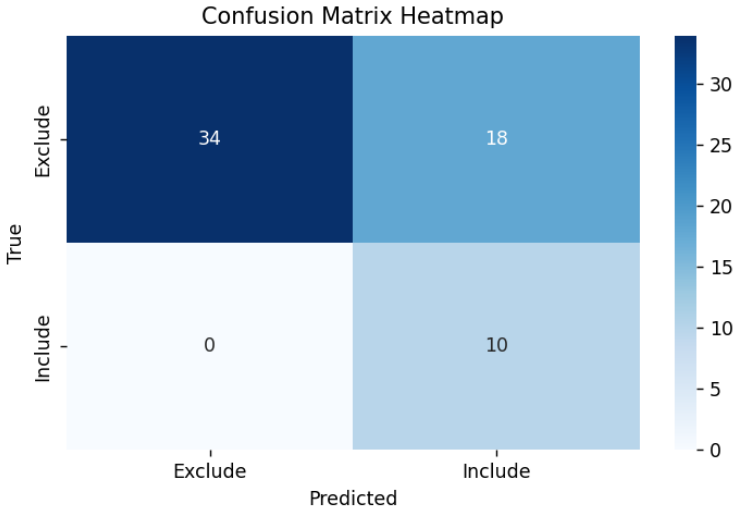
It reached the following scores:

Precision 0.36 (-0.09 compared with first prompt) and remained at a sensitivity of 1.00



When applied to the evaluation dataset, it reached the following scores:

Precision 0.36 (-0.06 compared with previous prompt) and sensitivity 1.00.



The updated prompt including bloodstream infections as concept did not impact sensitivity, thus indicating that the LLM is still able to correctly include relevant articles. Declining precision values by 9% on the development dataset and 6% on the evaluation set indicate that this

prompt leads to more irrelevant articles being falsely included. However, due to sepsis and bloodstream infections being used to describe the same concept it was deemed safer to proceed with the updated prompt and to accept the additional screening workload created by this.

We then applied the second prompt (with bloodstream infections concept) to 681 unscreened records from the literature search. This resulted in 314 records being progressed to manual screening labelled as 'included' by the LLM, and 367 records excluded automatically, thus leading to work-savings of 54%.

Following the LLM-assisted screening, the review team conducted comprehensive quality assurance checks to verify the accuracy of the model's decisions. This entailed reassessing titles and abstracts for all studies identified as potentially relevant to ensure that no ineligible or irrelevant records were retained. These checks were essential to maintain methodological rigour and strengthen the reliability of the final evidence base.

Full-text Screening

Subsequently, full-text articles were retrieved and assessed against predefined eligibility criteria. To appraise the methodological quality of included systematic reviews, the review team applied the DARE (Database of Abstracts of Reviews of Effects) criteria.[6] These criteria provide a widely accepted, objective framework for the rapid and consistent assessment of systematic review quality. At full-text screening, studies were evaluated according to the following five components:

1. Were inclusion and exclusion criteria reported?
2. Was the search adequate?
3. Were the included studies synthesised?
4. Was the quality of the included studies assessed?
5. Were sufficient details about the individual included studies presented?

Systematic reviews that did not meet at least four of the five DARE criteria were classified as *"Reviews not meeting DARE criteria"* and listed in Appendix B for transparency.

Data Extraction

Data extraction for all included records was carried out using a structured Excel data extraction form developed specifically for this scan. One reviewer independently extracted the relevant information from each record, and a second reviewer checked the extracted data for completeness and accuracy. Any uncertainties, discrepancies, or interpretive issues were resolved through discussion within the review team to ensure consistency in decision-making.

The project lead performed overarching quality assurance checks to confirm the accuracy of the final extracted data and ensure that all fields were populated according to the predefined extraction criteria. This approach helped ensure that the final dataset was robust, internally consistent, and suitable for synthesis.

The following data fields were extracted from each of the included studies:

- Study Identification & Focus
    - Primary research focus
    - Parameter / risk factor / outcome measured
    - Test, tool, or innovation assessed
    - Description of test/tool
    - Key reportable outcomes
    - Developer or sponsoring organisation
- Population & Clinical Context
    - Population
    - Age
    - Clinical setting
    - Infection type associated with sepsis (if stated)
- Review Characteristics
    - Total number of studies included in the review
    - Meta-analysis performed?
    - Geographical distribution of included studies
- Additional Analytical Features
    - Use of artificial intelligence

Relevant information for each data field was captured wherever available to ensure a consistent and comprehensive dataset. When specific details were missing or not disclosed in the source material, “Not reported” was recorded. This method helped maintain transparency in the data extraction process.

Data Analysis

Analysis was undertaken to classify the included studies into two overarching evidence domains: clinical deterioration monitoring/use of prognostic indicators and predisposing or risk factors for sepsis. Studies were mapped to these domains based on their primary aims and outcome measures. Within each category, key themes, outcome measures, and assessment tools were extracted and synthesised to identify areas of consistency, divergence, and evidence gaps.

Results

Our search identified a total of 782 records. Following the LLM-assisted screening, a total of 314 records were manually screened by three reviewers at the title and abstract level to confirm eligibility. In total, 151 records were labelled as eligible and retrieved for full-text assessment. After full-text screening against the predefined eligibility and DARE quality criteria, 76 records were ultimately included for data extraction (Figure 1).

Figure 1 illustrates the flow diagram outlining the process of record identification, screening, and selection for inclusion.

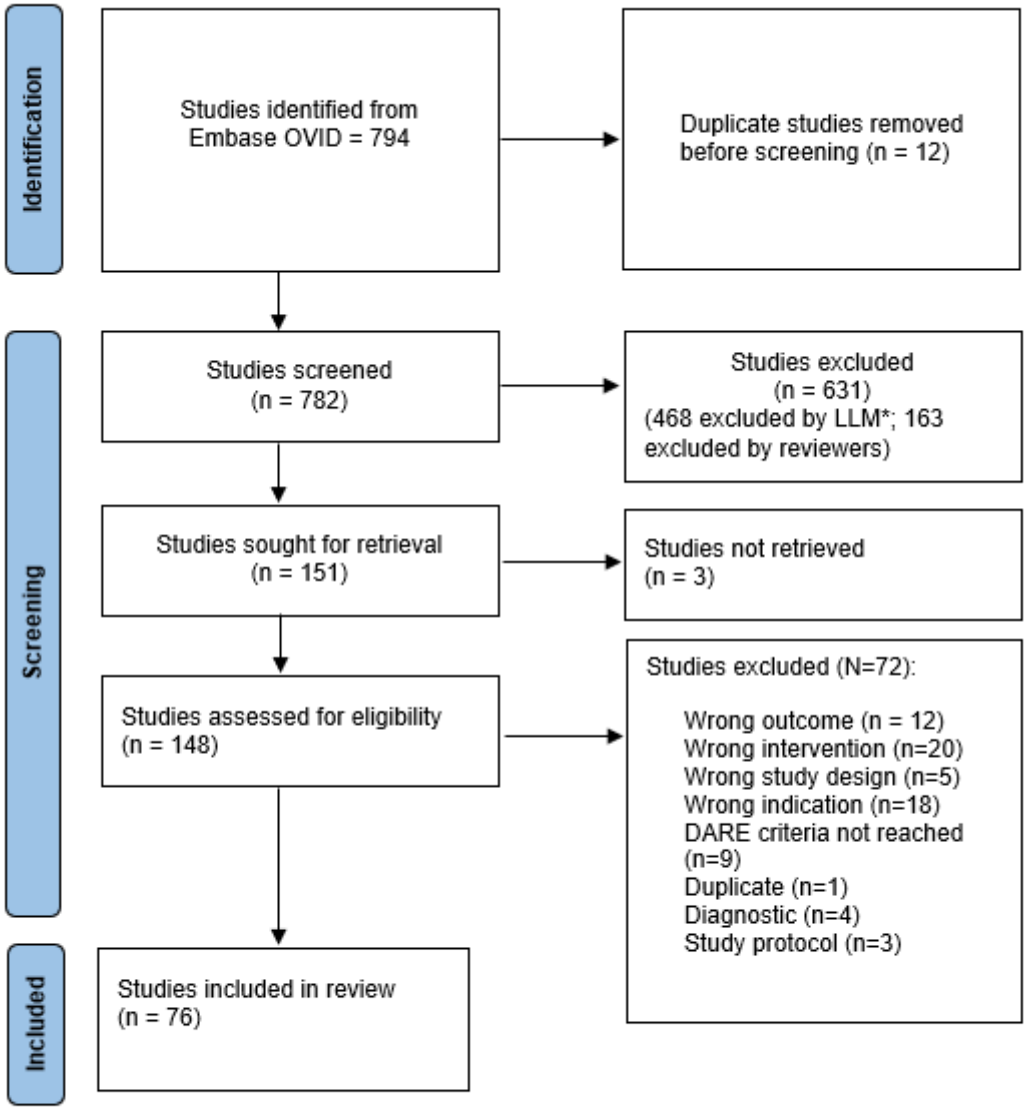


Figure 1. Flow diagram showing the final number of included technology records

Overview of Eligible Records

Due to the rapid nature of this scan, we prioritised systematic reviews with or without meta-analysis, rather than individual primary studies to draw from prior syntheses of existing evidence. This approach was chosen to save time; while still maintaining the quality and relevance of the scan, as systematic reviews use structured methods to summarise the best available evidence in a topic area.[7]

Of the 76 systematic reviews included in this scan, 53 focused on clinical deterioration monitoring and prognostic indicators of sepsis, some of which include the use of biomarkers, clinical scores, and machine learning/AI tools. Twenty-three others reviewed predisposing/risk factors for sepsis, including comorbidities (Figure 2).

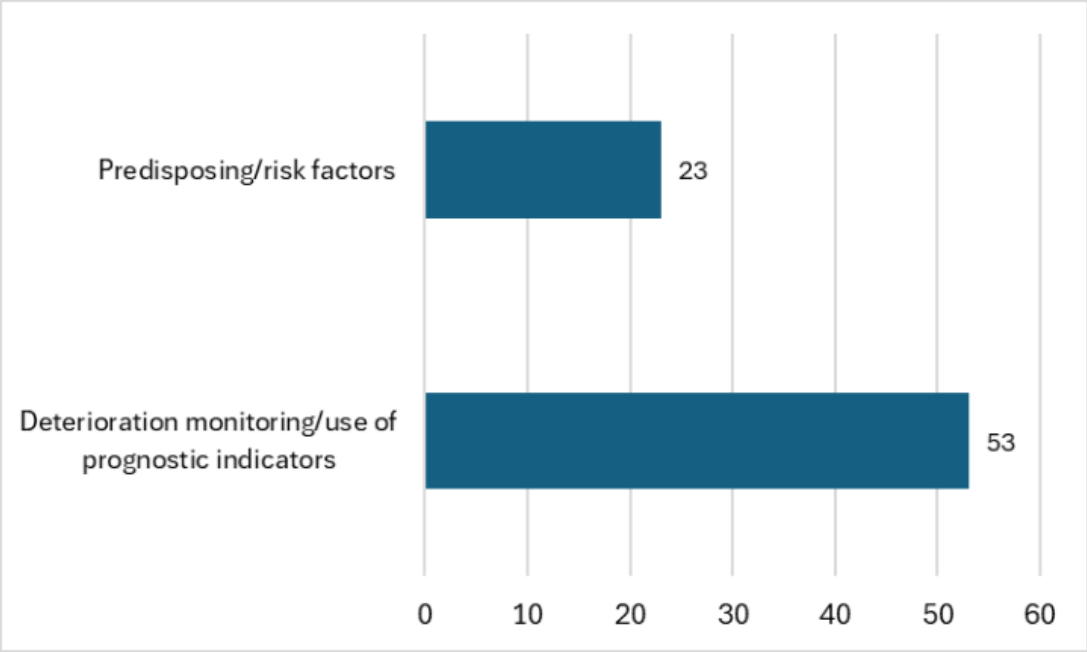


Figure 2. Graph showing the research focus of the included reviews

Most of the reviews (n=46) focused on adult patients, while 19 reviews were carried out in adults and children. There were only 2 reviews focused on children (<18 years), and 1 in the elderly.[8] Eight reviews did not specify the ages of the included population.

The majority of reviews (n=32) included studies conducted across multiple clinical settings, such as hospitals and ICUs, while others were limited to hospital-only (n=21) or ICU-only (n=12) settings. In a smaller number of reviews, the clinical setting was not reported (n=11).

Most reviews (n=59) included fewer than 40 primary studies, with the number of studies ranging from 3 to 38. Fifteen reviews included more than 40 studies, ranging from 47 to 189. The largest systematic review, comprising 189 studies, focused on sepsis-associated acute kidney injury in ICU patients with sepsis.[9]

Study locations were reported in 55 reviews, while 21 did not provide this information. Among those reporting locations, 43 included at least one European country, and eight included at least one study conducted in the UK (Figure 3).[10-17]

The majority of reviews (n=69) did not involve the use of artificial intelligence (AI) to determine prognosis, predisposing factors, or deterioration monitoring in sepsis. Only seven reviews reported the use of AI, and these will be discussed in detail in the following sections.[18-24]

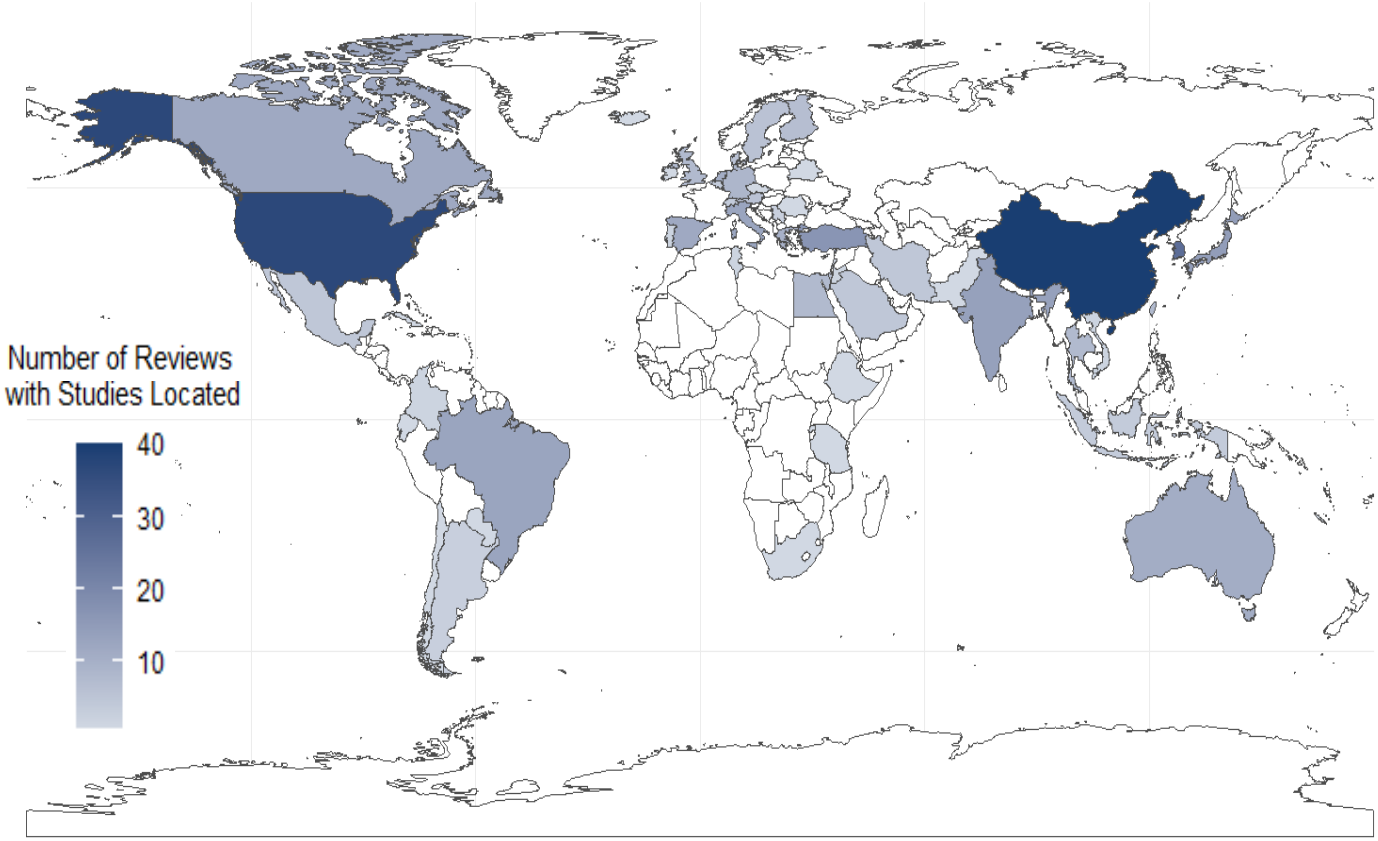


Figure 3. Global map showing the geographical distribution of the included studies in the systematic reviews

Clinical Deterioration Monitoring and Use of Prognostic Indicators

A total of 53 systematic reviews assessed the use of deterioration monitoring tests and prognostic indicators to identify patients at high risk of clinical deterioration. Identifying patients at high risk of clinical deterioration is a critical component of effective clinical care. Early recognition of those likely to worsen allows timely intervention and improved outcomes, underscoring the need for reliable prognostic indicators to support informed clinical decision-making.

The reviews that assessed the use of deterioration monitoring tests/prognostic indicators were grouped into the following subcategories:

- Biomarkers (n=23)
- Clinical scores/systems (n=10)

- Machine learning/artificial Intelligence (n=7)
- Left ventricular function tests (n=4)
- Laboratory tests (n=3)
- Other (n=7)

One review examined both biomarkers and clinical scoring systems and was therefore included and analysed in both categories.

Biomarkers

Of the 53 reviews that assessed deterioration monitoring/prognostic indicators, 23 focused on prognostic biomarkers. These covered patients with suspected infection (n=1), sepsis (n=15), and sepsis and/or septic shock (n=7). Adults only were studied in 14 reviews, seven included both adults and children, and age was unreported in two reviews.

Among the sepsis studies including children, settings were hospital (n=3), ICU (n=1), or mixed hospital/ICU (multiple) (n=3). Adult-only sepsis reviews were mainly multiple settings (n=5), with one ICU-based and one not reporting setting. Adult-only sepsis and/or septic shock reviews were conducted in hospital (n=4) or multiple settings (n=2), while the suspected infection review also used multiple settings. Reviews that did not report age similarly did not report clinical setting. Figure 4 summarises the biomarkers, age groups and clinical settings across included reviews.

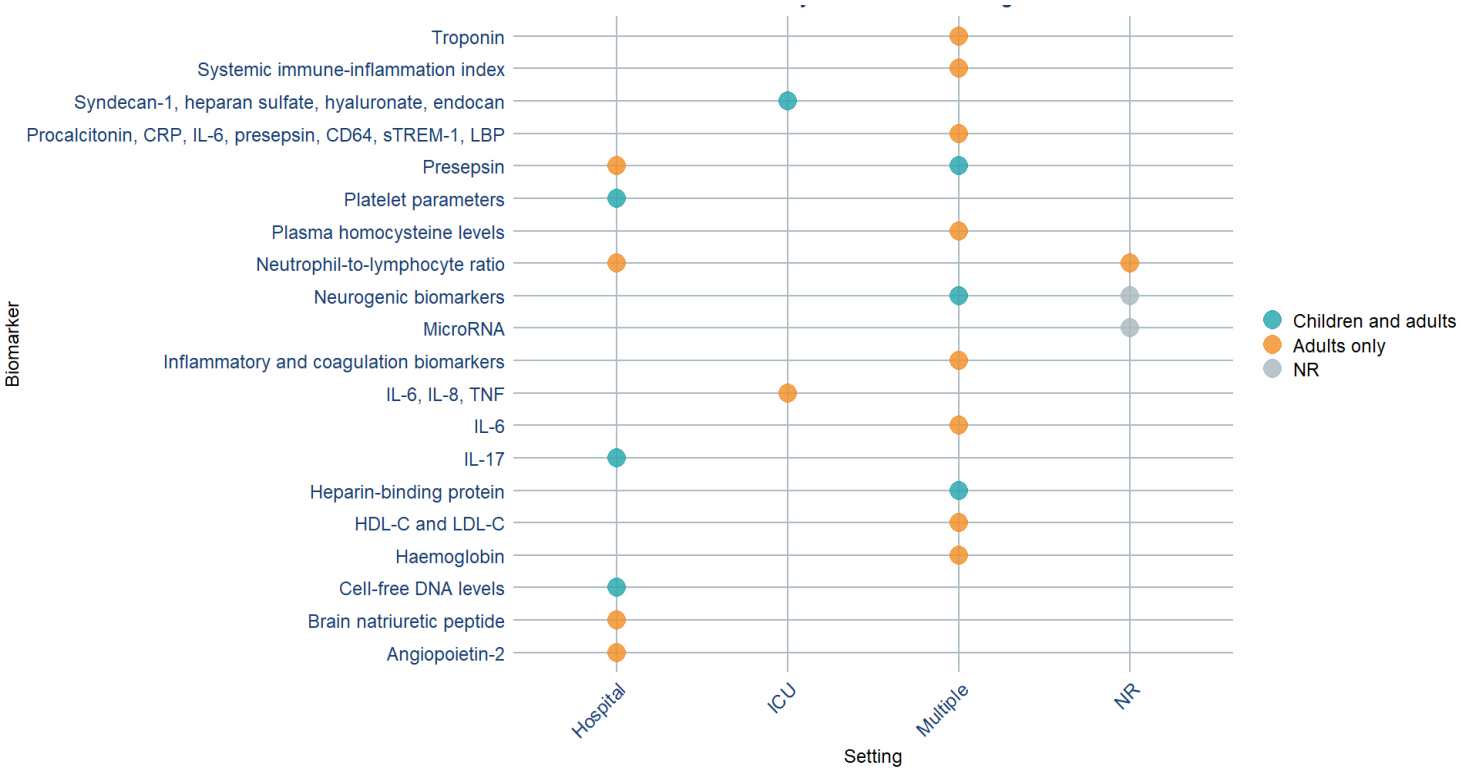


Figure 4. Graph showing the specific biomarkers, clinical settings and age groups of the prognostic biomarker-focused sepsis studies. CRP, C-reactive protein; IL-6, interleukin-6; CD64, Fc gamma receptor I; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; LBP, lipopolysaccharide-binding protein; NLR, neutrophil-to-lymphocyte ratio; IL-8, interleukin-8; TNF, tumour necrosis factor; IL-17, interleukin-17; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide.

The majority of the reviews (n=19) evaluated mortality as the primary outcome. The remaining studies examined other prognostic outcomes related to clinical deterioration, including cytokine levels and survival status, biomarker concentrations and clinical outcomes, infection severity, and diagnostic odds ratios. Table 1 summaries the reportable outcomes from each review.

Table 1. Table of biomarkers from each review and the reportable outcomes

Prognostic Indicators: Biomarkers	**Reportable Outcomes**
Interleukin-17 (IL-17)	Patients with 28 days of death (non-survivors) had higher IL-17 levels of 5.96 times compared to patients who were alive (survivors) (4 studies; n=194 patients; RoM = 5.96; 95% CI, 3.51-10.13; p <0.00001; I2 = 92%).[25]
Brain natriuretic peptide (BNP)	Elevated levels of BNP and N-terminal pro B-type natriuretic peptide were significantly related to the mortality of patients with sepsis and had a moderate prognostic value in predicting the mortality of patients with sepsis.[26]
Heparin-binding protein (HBP)	HBP demonstrated moderate prognostic accuracy for mortality at a cutoff value of 161.415 ng/mL, with a sensitivity and specificity of 72%, and for severe sepsis outcomes at a cutoff value of 58.907 ng/mL, with a sensitivity and specificity of 71%.[11]
Low circulatory levels of total cholesterol, HDL-C and LDL-C	Non-survivors had distinctly lower HDL-C at ICU admission −7.06 mg/dL (95% CI −9.21 to −4.91, p < 0.0001) in comparison with survivors.[27]
Troponin	The pooled OR for elevated high-sensitivity cardiac troponin was 1.78 (95% confidence interval (CI): 1.41–2.25), which suggests that individuals in the elevated troponin group had 78% higher odds of death.[28]
Neutrophil-to-lymphocyte ratio (NLR)	Higher NLR level were associated with a poor Prognosis. Significantly greater mortality rate in the high NLR group in comparison to the low NLR group (OR: 1.11; 95% CI: 1.08, 1.14; p<0.00001).[29]
Serum neurogenic biomarkers (NSE, UCH-L1, Tau, S100β, and GFAP)	Statistically significant difference between serum NSE levels in SAE patients and NE patients [SMD 1.98 (95% CI 1.55–2.42), P < 0.00001].[30]
microRNA	The pooled sensitivity was 0.76 (95% CI: 0.74–0.77), accompanied by significant heterogeneity (p < 0.0001, χ2 = 357.42, I2 = 75.4%, Figure 2A). The pooled specificity was 0.72 (95% CI: 0.71–0.73), also exhibiting notable heterogeneity (p < 0.0001, χ2 = 901.34, I2 = 90.2%, Figure 2B). The pooled diagnostic odds ratio (DOR) was 10.21 (95% CI: 8.60–12.14), with substantial heterogeneity (p < 0.0001, Cochran Q = 218.42, I2 = 59.7%, Figure 2C). The area under the curve (AUC) value was 0.83.[31]
Inflammatory and coagulation biomarkers: C-reactive protein (CRP)	There is evidence that C-reactive protein (CRP) is associated with NOAF, with hazard ratios 3.33 (3.32–3.35) p = 0.001 and odds ratios of 1.011 (1.008–1.014) p<0.001. International Normalised Ratio (INR) and fibrinogen may be associated with NOAF with odds ratios reported as 1.837 (1.270–2.656) p = 0.001 and 1.535(1.232–1.914) p<0.001 respectively.[32]

Cell-free DNA (cfDNA) levels	cfDNA levels were higher in septic patients compared to healthy controls (SMD = 3.303; 95%-CI [2.461-4.145], p<0.01). Furthermore, cfDNA levels were higher in non-survivors than survivors (SMD = 1.554; 95%-CI [0.905-2.202], p<0.01). Prognostic studies demonstrated a pooled sensitivity and specificity of 0.78.[15]
Glycocalyx-associated biomarkers (syndecan-1, heparan sulfate, hyaluronate) and the endothelial activation marker (endocan)	Elevated syndecan-1 was significantly associated with increased mortality (nine studies, n = 2167; OR 2.04, 95% CI, 1.66–2.51; p < 0.05; I^2 = 84%). Similarly, elevated endocan predicted mortality with a stronger effect size (six studies, n = 435; OR 5.06, 95% CI,2.52–10.18; p < 0.05) and low heterogeneity.[33]
Mean platelet volume-to-platelet count, MPV/PLT; platelet distribution width-to-platelet count, PDW/PLT; and platelet distribution width-to-plateletcrit, PDW/PCT	For predicting mortality, neonatal sepsis showed higher sensitivity (89%) and specificity (73%) than adult sepsis (63%, 58%). In LMICs, MPV/PLT was elevated at admission in both age groups but was linked to survival only in neonates.[34]
Interleukin-6 (IL-6)	While not a strong independent predictor, IL-6 demonstrates some discriminatory ability, suggesting its potential value in conjunction with other biomarkers.[35]
Neutrophil-to-lymphocyte ratio	The pooled results indicated that patients with a higher NLR level were associated with a poor prognosis (Random-effects model, HR: 1.6273, 95% CI: 1.3951-1.8981). Heterogeneity testing showed significant heterogeneity (I2 = 87.2%, 95% CI: 79.5-92, p<0.0001).[36]
Presepsin	Presepsin showed moderate accuracy for predicting the risk of mortality. The pooled sensitivity and specificity were 76% (95% CI: 69-82%) and 70% (95% CI: 59-78%), respectively. Sensitivity was notably higher in patients with septic shock (90%) compared to those with sepsis (75%), whereas specificity was comparatively lower (50% vs. 77%).[37]
Haemoglobin	This meta-analysis showed that haemoglobin levels on admission were associated with the prognosis of sepsis patients, and the mortality of sepsis patients increased with decreasing haemoglobin levels.[38]
Angiopoietin-2	In comparison to survivors, the levels of Ang-2 in non-survivors were markedly elevated [standardized mean difference (SMD) = 1.08, 95% confidence intervals (CI) 0.68-1.49, P < 0.001], and the same results were also observed in the subgroup that met sepsis 3.0 diagnosis criteria (SMD = 0.63, 95% CI 0.11-1.14, P = 0.017). The results comparing Ang-2 levels between non-survivors and survivors were independent of duration of follow-up, sample sources, type of study, and region. Ang-2 was a risk factor for mortality [odds ratios (OR) = 1.16, 95% CI 1.09-1.23, P < 0.001]. Ang-2 was demonstrated to be able to predict mortality in septic adult patients [area under the curve (AUC) = 0.76, 95% CI 0.70-0.82, P < 0.001]. Ang-2 level was positively correlated with risk of death in sepsis patients. Ang-2 might be a useful and valuable biomarker for predicting mortality in septic adult patients.[39]
Procalcitonin, C-reactive protein (CRP), interleukin-6 (IL-6), presepsin (cluster of differentiation 14 subtypes), CD64, soluble triggering	CD64 demonstrated the highest superiority index, followed by sTREM-1 and presepsin (diagnostic odds ratio: 20.17 vs 18.73 and 10.04, 95 % credible interval [CrI]: 8.39–38.61 vs

receptor expressed on myeloid cells-1 (sTREM-1), and lipopolysaccharide-binding protein (LBP).	1.31–83.98 and 6.71–14.24; quality of evidence: moderate vs low and low). CD64, presepsin, procalcitonin, IL-6, CRP.[40]
Cytokine biomarkers: IL-6, IL-8, TNF	Cytokine levels (IL-6, IL-8, IL-10, TNF-α and IL-1β) in survival groups were substantially lower than those in non-survival groups (ALL $P < 0.00001$).[40]
Systemic immune-inflammation index (SII)	A high SII at admission was significantly associated with an increased risk of all-cause short-term mortality in sepsis patients (RR: 1.51, 95% CI: 1.31-1.67, $P < 0.001$), with moderate heterogeneity ($I^2 = 43\%$).[41]
Neurogenic biomarkers: NSE, S100β, GFAP, TAU, and UCH-L1	Random-effects analysis revealed significant differences in serum NSE levels between SAE and NE adult patients (WMD = 6.82; 95% CI: 5.43, 8.21; $P < 0.001$), S100β levels (WMD = 0.48; 95% CI: 0.37, 0.60; $P < 0.001$), GFAP levels in the SAE group (WMD = 62.28; 95% CI: 45.42, 79.14; $P < 0.001$), TAU levels in the SAE individuals (WMD = 1.73; 95% CI: 0.95, 2.51; $P < 0.001$), UCH-L1 levels in SAE patients (WMD = 1.73; 95% CI: 0.95, 2.51; $P < 0.001$), APACHE II scores in the SAE group (WMD = 6.30; 95% CI: 4.61, 7.99; $P < 0.001$), and SOFA scores in SAE (WMD = 3.65; 95% CI: 2.96, 4.34; $P < 0.001$).[42]
Plasma homocysteine levels	High plasma Hcy at enrolment was not associated with an increased risk of death in patients with sepsis (OR per 1-unitincrement of Hcy=1.03, 95% CI: 0.95–1.11, P=0.51; I2=72%.[43]
Presepsin	Pooled sensitivity of 75% and specificity of 80% in cirrhotic patients with suspected infection. Presepsin may become a valuable addition to clinical decision-making tools, particularly in hepatology-focused sepsis management.[44]

Clinical Scores/Systems

Ten reviews focused on clinical scores or systems. These reviews addressed three patient populations: patients with suspected infection (n=2), patients with sepsis (n=7), and patients with sepsis and/or septic shock (n=1). Adults were the sole population studied in seven reviews across these groups, including suspected infection (n=2), sepsis (n=4), and sepsis and/or septic shock (n=1). Two sepsis-focused reviews included both adults and children, while one review focused exclusively on children under 18 years of age, also within a sepsis population.

Adult-only sepsis reviews reported multiple (n=5) or hospital-only (n=2) settings, while adult-only suspected infection reviews reported hospital (n=1) or multiple settings (n=1). As above, 'multiple' settings refer to studies conducted in both hospital and ICU environments. The adult sepsis/septic shock review reported multiple settings. Of the two sepsis reviews including adults and children, one was hospital-based and one in multiple settings. The children-only sepsis review did not report a setting. Figure 5 shows the clinical scores/systems, settings and age groups of the included reviews.

Most studies (n=9) focused on mortality, assessing either sensitivity and specificity for predicting mortality or overall predictive efficacy. The remaining study examined other prognostic outcomes of clinical deterioration, such as the diagnostic odds ratio.

The majority of these studies evaluated the Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), lactate-enhanced qSOFA (LqSOFA), or Sepsis Prediction Score (pSOFA).

Overall, these scores demonstrated clinically significant sensitivity and specificity and often outperformed other scoring systems, such as the Systemic Inflammatory Response Syndrome (SIRS) criteria and the Paediatric Logistic Organ Dysfunction score (PELOD-2), in predicting mortality and sepsis outcomes. However, findings were not entirely consistent, with some studies showing no difference between scores or even opposite results, for example, one study reported that SIRS had significantly higher pooled sensitivity than qSOFA.

Table 2 summaries the reportable outcomes for each clinical score/system identified from the reviews.

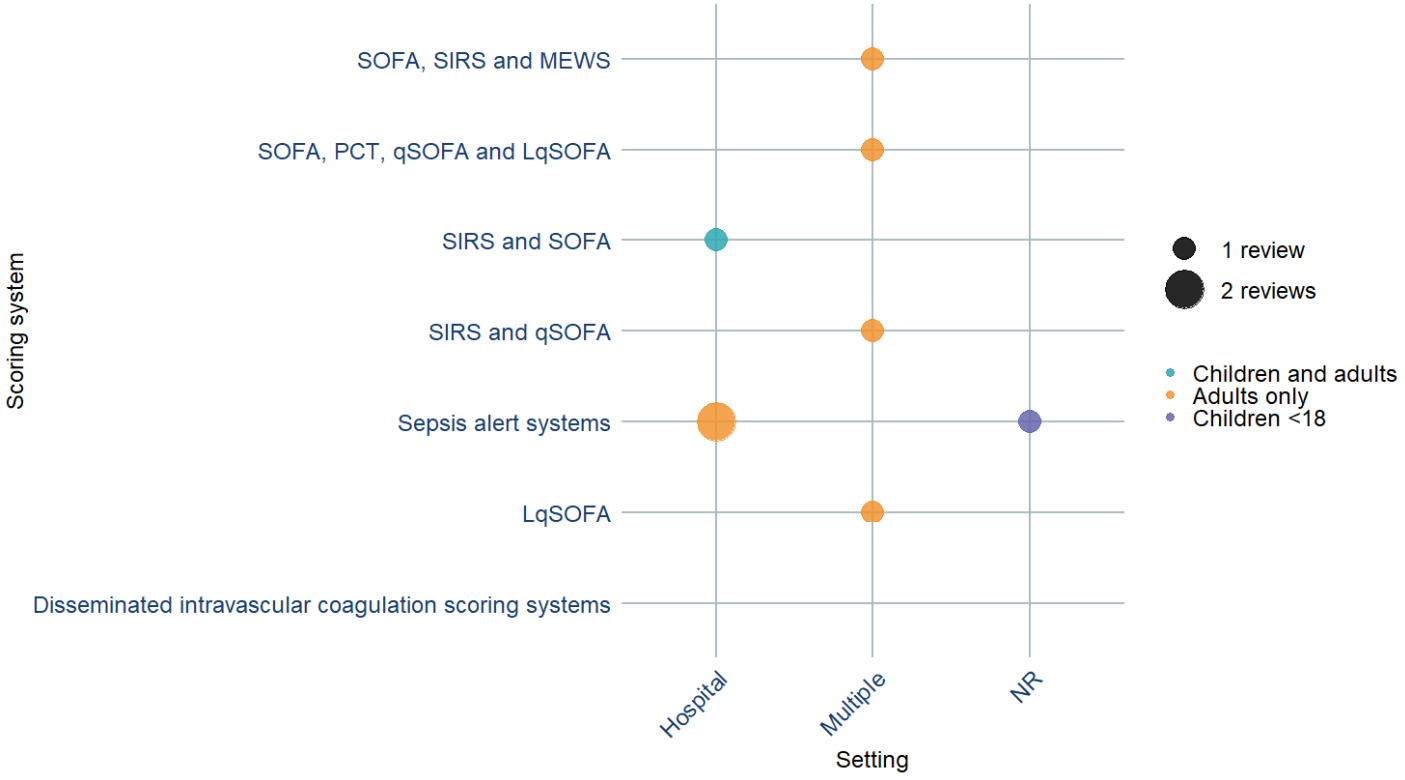


Figure 5. Clinical scoring systems, clinical settings, and age groups of sepsis-focused clinical score/system studies. SOFA, Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; LqSOFA, Lactate enhanced qSOFA; SIRS, Systemic Inflammatory Response Syndrome; MEWS, Modified Early Warning Score; PCT, Procalcitonin.

Table 2. Table of clinical scores/systems from each review and the reportable outcomes

Clinical Score/ System	**Reportable Outcomes**
Systemic Inflammatory Response Syndrome (SIRS) and sequential organ failure (SOFA)	The overall estimate of the pooled area under the ROC curve (AUC) was 0.67 (95% CI: 0.60-0.73) for SIRS and 0.79 (95% CI: 0.73-0.84) for SOFA. The SOFA score outperformed the SIRS criteria in predicting mortality.[45]
Lactate-enhanced-qSOFA (LqSOFA) score	The LqSOFA score demonstrates a good predictive capacity for in-hospital mortality in septic patients, showing clinically significant levels of sensitivity (69%) and specificity (79%).[46]

Quick Sequential Organ Failure Assessment (qSOFA)	For predicting sepsis diagnosis, the pooled sensitivity of (early warning system) EWS (65%) was similar to SIRS ≥2 (70%) and higher than qSOFA ≥2 (37%). The pooled specificity of EWS (77%) was higher than SIRS ≥2 (62%) but lower than qSOFA ≥2 (94%).[47]
Sepsis prediction score (pSOFA)	pSOFA performed the best in predicting prognosis with a pooled AUC of 0.86 (CI) compared to the Paediatric Logistic Organ Dysfunction score (PELOD-2) with a pooled AUC of 0.83 (CI).[48]
Sepsis alert systems	Sepsis alert systems were associated with reduced mortality risk (risk ratio [RR], 0.81; 95% CI, 0.71 to 0.91) and length of hospital stay (standardised mean difference [SMD], −0.15; 95% CI, −0.20 to −0.11). These systems were also associated with better adherence to sepsis bundle elements, notably in terms of shorter time to fluid administration (SMD, −0.42; 95% CI, −0.52 to −0.32), blood culture (SMD, −0.31; 95% CI, −0.40 to −0.21), antibiotic administration (SMD, −0.34; 95% CI, −0.39 to −0.29), and lactate measurement (SMD, −0.15; 95% CI, −0.22 to −0.08).[17]
Disseminated intravascular coagulation (DIC) scoring systems: The International Society on Thrombosis and Haemostasis DIC (ISTH-DIC) criteria, the Japanese association for acute medicine DIC (JAAM-DIC) criteria, and the sepsis-induced coagulopathy (SIC) criteria	The pooled mortality rates when using ISTH-DIC criteria, JAAM-DIC criteria, and SIC were 44% (95% CI:33–53%), 37% (95% CI: 29–46%), and 35% (95% CI: 29–41%), respectively. The pooled sensitivity and specificity of ISTH-DIC to predict mortality were 0.43 (95% CI: 0.34–0.52), and 0.81 (95% CI: 0.74–0.87), respectively, while for JAAM-DIC it was 0.73 (95% CI: 0.57–0.85) and 0.46 (95% CI: 0.28–0.65), respectively. Pooled sensitivity and specificity for SIC were 0.71 (95% CI: 0.57–0.82) and 0.49 (95% CI: 0.31–0.66), respectively.[49]
Scoring systems: qSOFA, and systemic inflammatory response syndrome (SIRS) criteria	SIRS displayed the significantly higher pooled sensitivity than the qSOFA score.[40]
Sequential Organ Failure Assessment (SOFA) score, Modified Early Warning Score (MEWS), and Systemic Inflammatory Response Syndrome (SIRS) criteria	SOFA had an intermediate sensitivity of 0.73 (95% CI: 0.67–0.78) and a specificity of 0.70 (0.63–0.76). SIRS criteria had the highest sensitivity of 0.75 (0.66–0.82) and the lowest specificity of 0.40 (0.29–0.52). MEWS had the lowest sensitivity of 0.49 (0.40–0.59) and the highest specificity of 0.82 (0.78–0.86).[50]
Sequential Organ Failure Assessment (SOFA), procalcitonin (PCT), lactate, quick Sequential Organ Failure Assessment (qSOFA), and lactate-adjusted qSOFA (LqSOFA)	SOFA demonstrated superior predictive efficacy (AUROC = 0.819, 95% CI: 0.783–0.850; sensitivity = 0.77, 95% CI: 0.71–0.82; specificity = 0.73, 95% CI: 0.67–0.79), significantly outperforming PCT (ΔAUROC = 0.10, 95% CI: 0.04–0.16), lactate (ΔAUROC = 0.07, 95% CI: 0.03–0.11), and qSOFA (ΔAUROC = 0.08, 95% CI: 0.05–0.11). LqSOFA (AUROC = 0.823, 95% CI: 0.787–0.854) demonstrated efficacy comparable to SOFA (ΔAUROC = 0.02, 95% CI: −0.02–0.06) and significantly superior to qSOFA (ΔAUROC = 0.06, 95% CI: 0.04–0.08), with a sensitivity of 0.46 (0.24–0.69) and specificity of 0.88 (0.80–0.93).[51]

Early Warning Systems for Sepsis (Unspecified)	Pooled OR 0.84 (95% CI, 0.60, 1.18). Early warning systems were associated with reduced mortality and improved process measures.[52]

Machine learning/Artificial Intelligence

Seven reviews focused on synthesising evidence for machine learning/AI approaches to deterioration monitoring/prognosis (Table 3). Six of which focused on innovations that are able to predict mortality outcomes. One review looked at machine learning approaches to predict acute kidney injury whereas three other studies involved patients that already had sepsis-associated acute kidney injury. The remaining studies (n=4) involved patients with sepsis (n=2), septic shock (n=1), or sepsis and bloodstream infections (n=1). All these reviews involved adults only apart from one review which did not report the age requirements for inclusion. Most reviews included studies that took place in ICU (n=3) or hospital (n=2), with one review involving a mix of locations and one failing to report clinical location.

Three of these reviews reported that machine learning algorithms were found to be superior in terms of specificity and other performance measures than conventional scoring systems such as the sequential organ failure assessment (SOFA), the simplified acute physiology score (SAPS) and the Acute Physiology and Chronic Health Evaluation (APACHE).[23,53,54] Two reviews highlighted the impressive performance of XGBoost which one review found consistently outperformed other machine learning techniques in reliably predicting the onset, progression, and mortality of acute kidney injury in critically ill septic patients (Table 3).[22,53] Despite many positive findings that support the application of machine learning/AI algorithms, there was also some criticism around the application. Some reviews reported mixed findings; one noted that during training, the model achieved strong discrimination (C-index = 0.81) with very high specificity (92%) but low sensitivity (39%), while in validation, performance declined slightly (C-index = 0.73) yet maintained high specificity (90%) and moderate sensitivity (54%)[24]. Another review shared concerns regarding data limitations as although models exhibit promise in advanced disease stages such as sepsis, early stages remain underexplored (Table 3).[55]

Table 3 summaries the reportable outcomes for each machine learning/AI innovation identified from the reviews.

Table 3. Table of machine learning/AI models from each review and the reportable outcomes

Machine Learning	Reportable Outcomes
Machine learning models (such as Gradient Boosting Decision Tree (GBDT), Blending model)	Machine learning models showed a slight improvement in predicting sepsis-associated mortality compared to conventional severity scoring systems like sequential organ failure assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE), and Simplified Acute Physiology Score (SAPS).[53]
Machine Learning-Based Prediction models (such as random forest, extreme gradient boost (XGBoost), support vector machine (SVM), Light Gradient Boosting Machinen (LightGBM))	ML models outperform conventional scoring systems, such as the SOFA and the SAPS II. XGBoost consistently outperformed other machine learning techniques in reliably predicting the onset, progression, and mortality of acute kidney injury in critically ill septic patients.[55]

Machine learning techniques (feature engineering, feature scaling)	While machine learning (ML) models exhibit promise in advanced disease stages such as sepsis, early stages remain underexplored due to data limitations.[55]
ML algorithms (such as XGBoost, MiceForest, Random Forest, K-nearest neighbor, MiceForest)	The predictive models demonstrated varying levels of performance, with area under the receiver operating characteristic curve (AUROC) values ranging from 0.60 to 0.87. Algorithms such as extreme gradient boosting (XGBoost), random forest (RF), and logistic regression (LR) showed the best performance in terms of accuracy. The findings of this study show that ML models hold immense ability to identify high-risk patients, predict the progression of AKI early, and improve survival rates. However, the lack of fairness in ML models for predicting mortality in critically ill patients with sepsis-associated AKI could perpetuate existing healthcare disparities.[21]
Machine learning models (such as Random Forest and Extreme Gradient Boosting)	The performance of various ML models in prediction tasks showed that the AUC on the training set mostly ranged from 0.75 to 0.99, with RF, XGBoost, and CatBoost performing particularly well.[22]
AI for mortality risk stratification	Compared to traditional clinical scoring systems, AI demonstrated significantly higher specificity (0.81 vs. 0.66, P < 0.05) and AUC (0.80 vs. 0.69, P < 0.05). AI demonstrates promising discrimination and higher specificity than traditional clinical scoring systems.[23]
Machine learning models (such as Multilayer perceptron (MLP), Naive Bayes (NB), Adaptive Boosting (AdaBoost), Categorical Boosting (CatBoost), Decision Tree (DT), Gradient Boosting Machines (GBM))	The overall C index in the training set was 0.81 (95% CI: 0.78–0.84), sensitivity was 0.39 (0.32–0.47), and specificity was 0.92 (95% CI: 0.89–0.95). The overall C-index in the validation set was 0.73 (95% CI: 0.71–0.74), sensitivity was 0.54 (95% CI: 0.48–0.60) and specificity was 0.90 (95% CI: 0.88–0.91). Machine learning has been shown to be an effective tool for predicting sepsis-associated acute kidney injury deaths.[24]

Left Ventricular Function test

Four reviews investigated the impact of left ventricular flow and other cardiac factors on outcomes for patients with sepsis.[10,56-58] Most (n=3) assessed the impact on mortality, one of which determined the prognostic effect of left ventricular global longitudinal strain (GLS) on both mortality and length of hospital stay.[10,56,57] One review included patients with sepsis, while the others involved patients with both sepsis and septic shock. All patients were adults and two were conducted in a mix of clinical settings and the other two involved studies conducted at a hospital.[10,56-58]

Across the included reviews, several echocardiographic parameters demonstrated significant associations with outcomes in sepsis (Table 4). Global longitudinal strain (GLS) was linked to survival, with survivors exhibiting more negative strain values compared to non-survivors (mean difference: −1.45%, $p < 0.0001$).[56] Left ventricular outflow tract velocity time integral (LVOT VTI) showed excellent predictive accuracy for fluid responsiveness, with reported AUC values approaching 1.0.[58] Hyperdynamic left ventricular systolic function was associated with increased short-term mortality, with a pooled odds ratio of 2.37.[10] Furthermore, patients exhibiting echocardiographic phenotypes such as left ventricular systolic dysfunction, left

ventricular diastolic dysfunction, and right ventricular dysfunction were at significantly higher risk of mortality.[57]

Table 4. Table of reviews focussed on left ventricular function and the reportable outcomes

Left Ventricular Function test	Reportable Outcomes
Association between left ventricular global longitudinal strain (GLS) and mortality in septic patients	The forest plot shows the mean difference in GLS values between survivors and non-survivors of sepsis. The analysis found that survivors had more negative (better) GLS values compared to non-survivors, with a mean difference of -1.45% ($p < 0.0001$). The results consolidated previous findings where more negative GLS values had a positive prognostic association with survival.[56]
Left Ventricular Outflow Tract Velocity Time Integral (LVOT VTI)	The three studies reported different cut-offs with an AUC reported close to 1.0, specificity of 90%, and a sensitivity of 85% across patients with septic shock and 75% across septic patients. LVOT VTI is a reliable, non-invasive parameter for assessing fluid responsiveness in sepsis and septic shock.[58]
Left ventricular systolic function effect on mortality	All the four studies included in the meta-analysis reported short-term mortality which was significantly higher for hyperdynamic left ventricular (LV) function as compared to normal LV systolic function, with an OR of 2.37 (95%CI 1.47, 3.80; $I2 = 79\%$; $P < 0.01$).[10]
Echocardiographic phenotypes	Patients with left ventricular systolic dysfunction (LVSD), left ventricular diastolic dysfunction (LVDD), or right ventricular dysfunction (RVD) showed a higher risk of death (LVSD: relative risk [RR], 1.57 [95% CI, 1.29–1.91], $p < 0.0001$; LVDD: RR, 1.36 [95% CI, 1.05–1.75], $p = 0.02$; and RVD: RR, 1.62 [95% CI, 1.35–1.95], $p < 0.0001$).LVSD, LVDD, and RVD are significant risk factors for mortality in sepsis.[57]

Laboratory tests

Three systematic reviews evaluated the use of laboratory or physiology-based tests in the context of sepsis. Two reviews focused on stone culture, both examining hospital-based patient populations at increased risk of developing sepsis, with an emphasis on prevention rather than prognosis. The third review investigated sublingual microcirculation as a monitoring tool in patients with established sepsis, drawing on studies conducted across hospital wards and ICU settings. All three reviews included mixed populations of children and adults. In terms of outcomes, two reviews assessed the ability of these tests to predict the development of sepsis, while one evaluated their association with mortality. These characteristics and outcomes are summarised in Table 5.

Table 5. Table of Laboratory tests from each review and the reportable outcomes

Laboratory test	Reportable outcomes
Stone Culture	Stone cultures had a log odds ratio of 5.79 for predicting post-operative SIRS/sepsis vs. only 2.30 for pre-operative urine culture.[59]

Stone Culture	Stone cultures showed a higher sensitivity (0.52 vs 0.32) and higher positive predictive value (0.28 vs 0.21) in predicting post-operative sepsis, compared to bladder urine cultures. The pool-weighted logarithmic odd risk (LOR) for BUC was 2.30 (95% CI 1.51–3.49, p < 0.001); the LOR for stone cultures (SC) in predicting post-operative sepsis was 5.79 (95% CI 3.58–9.38, p < 0.001).[60]
Sublingual Microcirculation	TVD, PVD, PPV, and MFI of severe sepsis patients and non-surviving patients were lower than those of non-severe sepsis patients and surviving patients. Microcirculatory blood flow heterogeneity was greater in non-survivors and patients with severe disease than in survivors and patients with non-severe disease.[34]

Other reviews

Seven reviews were classified as 'Other' because they did not fit within the existing subcategories. Five examined sepsis populations (impact of sepsis-associated acute kidney injury, neurologic complications, sepsis and upper gastrointestinal bleeding, heart rate variability, and location of onset), one focused on septic shock (point-of-care echocardiography), and one included sepsis and/or septic shock (fibrinolytic impairment). Three sepsis studies involved adults only, while the other two included both adults and children. The septic shock study included both age groups, while the sepsis and/or septic shock study involved adults only. Four studies were ICU-based, two spanned hospital and ICU settings, and one did not report setting. Most studies (n=5) assessed mortality, with others examining prognostic outcomes such as neurocognitive impairment and upper gastrointestinal bleeding. Table 6 summarises reported outcomes for this subcategory.

Table 6. Table of the uncategorised tests/tools and their reportable outcomes

Test/Innovation/Tool	**Reportable outcomes**
Fibrinolytic impairment	Fibrinolytic assessment provides important prognostic information in sepsis, despite methodological challenges. The integration of point-of-care viscoelastic testing with modified protocols shows promise for real-time evaluation. Future research should focus on developing standardised, automated assays suitable for routine clinical practice, enabling personalised therapeutic interventions that target fibrinolytic dysfunction in sepsis.[61]
Assessing the impact of Sepsis-Associated Acute Kidney Injury (SA-AKI)	Pooled mortality ORs: ICU mortality (0.40, 0.32–0.49) Hospital mortality (0.47, 0.38–0.56) Mortality at final follow up (0.48, 0.43–0.53). SA-AKI is common in ICU patients with sepsis and carries a high risk of death and persisting kidney impairment.[9]
Neurologic complications in patients with sepsis	A meta-regression was performed and showed that patients who had pulmonary infection (RR = 1.12; 95% CI, 1.04–1.20), or sepsis from a gram-

	positive organism (RR = 1.06; 95% CI, 1.02–1.09) were associated with a higher risk of developing septic encephalopathy. Studies of patients with septic encephalopathy had a higher mean Sequential Organ Failure Assessment score (7 vs 5, p = 0.002), and Acute Physiology and Chronic Health Evaluation II score (21 vs 17, p = 0.016) at admission and longer ICU length of stay (10 d vs 5 d, p < 0.001). However, the admission Simplified Acute Physiology Score II, length of sedation, and mechanical ventilation did not differ between the two cohorts (Fig. 4). Studies of patients who suffered from septic encephalopathy are at a higher risk of death compared with those without septic encephalopathy (78% vs 55%; RR = 1.64; 95% CI, 1.1–2.4) after adjusting for follow-up time.[62]
Upper gastrointestinal bleeding (UGIB)	The findings highlight the need for vigilant monitoring and proactive management of septic ICU patients to mitigate the risk of UGIB. The meta-analysis reveals a significant association between sepsis and an increased risk of UGIB in ICU patients, particularly in adults.[14]
Heart rate variability analysis	Non-surviving patients with sepsis had lower LFnu, LF/HF ratio, SD2, DFAα1, and DFAα2, while survivors exhibited higher HFnu, RMSSD, SDNN, HTI, and SD1.[63]
Point of care echocardiography	POC echocardiography guided septic shock management was associated with lower in-hospital and 28-day mortality (sOR = 0.82 [95%CI: 0.71–0.95], p = 0.01), more frequent initiation of inotropic support (sOR = 2.42 [95%CI 1.92–3.03], p < 0.0001) and shorter time to achieve lactate clearance (SMD = – 0.87 h [95%CI − 1.23 h to − 0.51 h], p < 0.0001).[64]
Location of onset (hospital or community)	The risk of death in patients with hospital-acquired sepsis was significantly higher than that in patients with community-acquired sepsis (OR = 2.19, 95% CI = 1.82-2.63, P < 0.001). Likewise, patients admitted due to hospital-acquired sepsis were likely to have a longer length of stay in the ICU than patients with community-acquired sepsis (Hedge's g = 1.27, 95% CI = 0.67-1.87, P < 0.001). The length of total hospital stay was also significantly higher in patients with hospital-acquired sepsis (Hedge's g = 0.71, 95% CI = 0.20–1.13, P < 0.001).[65]

Predisposing/Risk Factors for Sepsis

Sepsis arises from a dysregulated host response to infection, and its development is influenced by a range of predisposing/risk factors. These factors affect an individual's susceptibility to infection, the ability to mount an effective immune response, and the likelihood of progression to severe disease.

Out of the 23 systematic reviews investigating predisposing or risk factors for sepsis, six focused on comorbidities, four on genetic factors, five on clinical risk factors, one on infection type, and seven covered multiple risk factors (Figure 6). The number of reviews found per risk factor category followed the same pattern as the total number of primary studies included within these reviews, except that infection type was supported by a larger number of primary studies than genetic factors, despite being addressed in only one review. Table 7 outlines the risk factors for each broad category.

Table 7. Risk factors for sepsis and bloodstream infections, grouped by broad categories for analysis

Broad category	**Risk factors**
Clinical risk factor	Age, sex, serum iron levels, transferrin saturation, iron-binding capacity, body weight, history of catheter-associated infection, dialysis duration, catheter-associated infection, catheter placement site, catheter duration, number of catheterizations, catheter types, use of multiple-lumen catheters, times of tube indwelling, length of ICU stay, CD4+ cells, albumin, C-reactive protein, haemoglobin, procalcitonin, inadequate hand hygiene, APACE II scores, SAPS II score, tracheal intubation, mechanical ventilation, ECMO, central venous cannulation, methylprednisolone use, combination of methylprednisolone and Tocilizumab, elevated lactate, white blood cell count, neutropenia, place of infection acquisition, acute disease severity, methicillin susceptibility, intravenous drug use
Comorbidities	Diabetes, cancer, postoperative biliary complications, history of biliary atresia, severe mental illness, chronic obstructive pulmonary disease, hypertension, coronary artery disease, congestive heart failure, chronic kidney disease, chronic liver disease, kidney disease
Genetic factors	Asp299Gly variant, interleukin-8 gene polymorphism, IL and 6 572C/G polymorphism, VDR gene polymorphism
Infection type	Multi-drug-resistant organisms, hypermucoviscous (HM)-phenotype (characteristic of certain bacteria)
Multiple risk factors	Reviews that explored more than one of the risk factors above

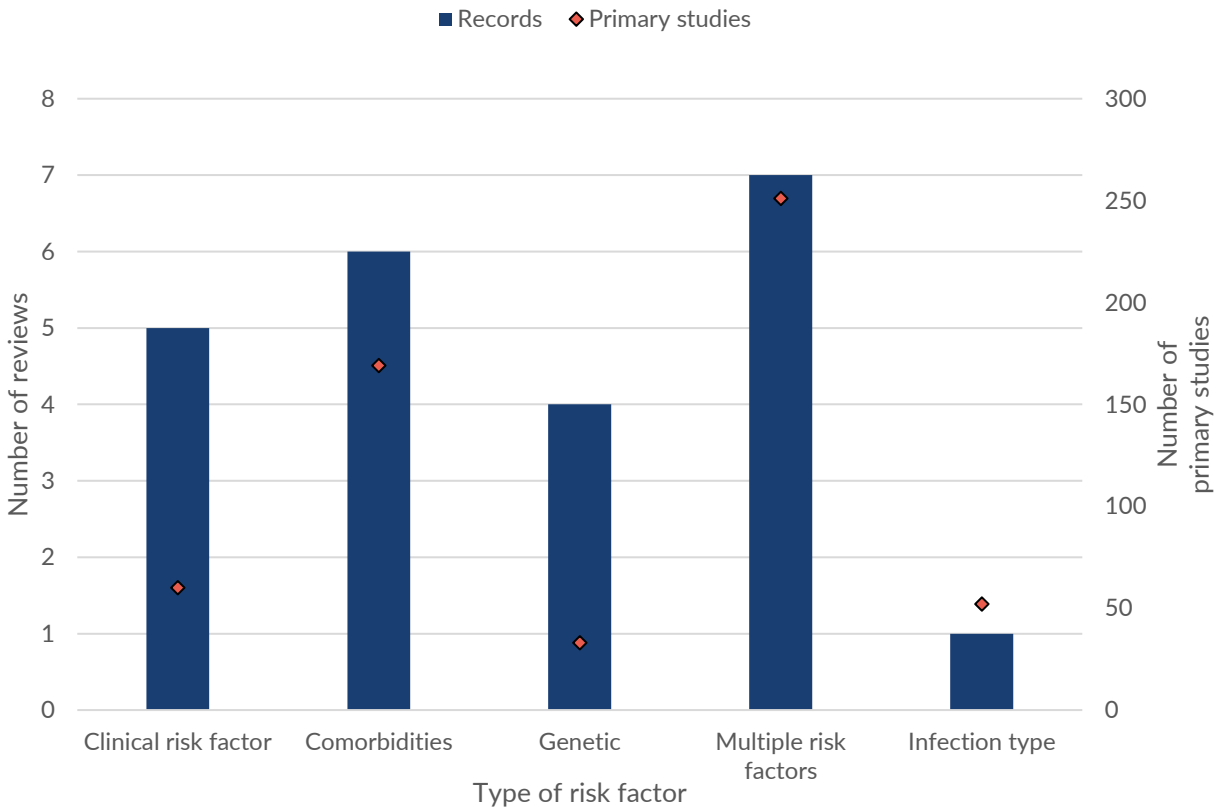


Figure 6. Types of risk factors explored by included reviews, and the sum of the primary studies included within these reviews

The most common age group investigated was adults, with 12 reviews focusing exclusively on adults and four investigating children and adults. One review focused solely on children, one on the elderly and five reviews did not report age group. Reviews examining genetic factors primarily included both children and adults (n = 2) and older adults (n=1). The single review focusing solely on children was looking at comorbidities (Figure 7).

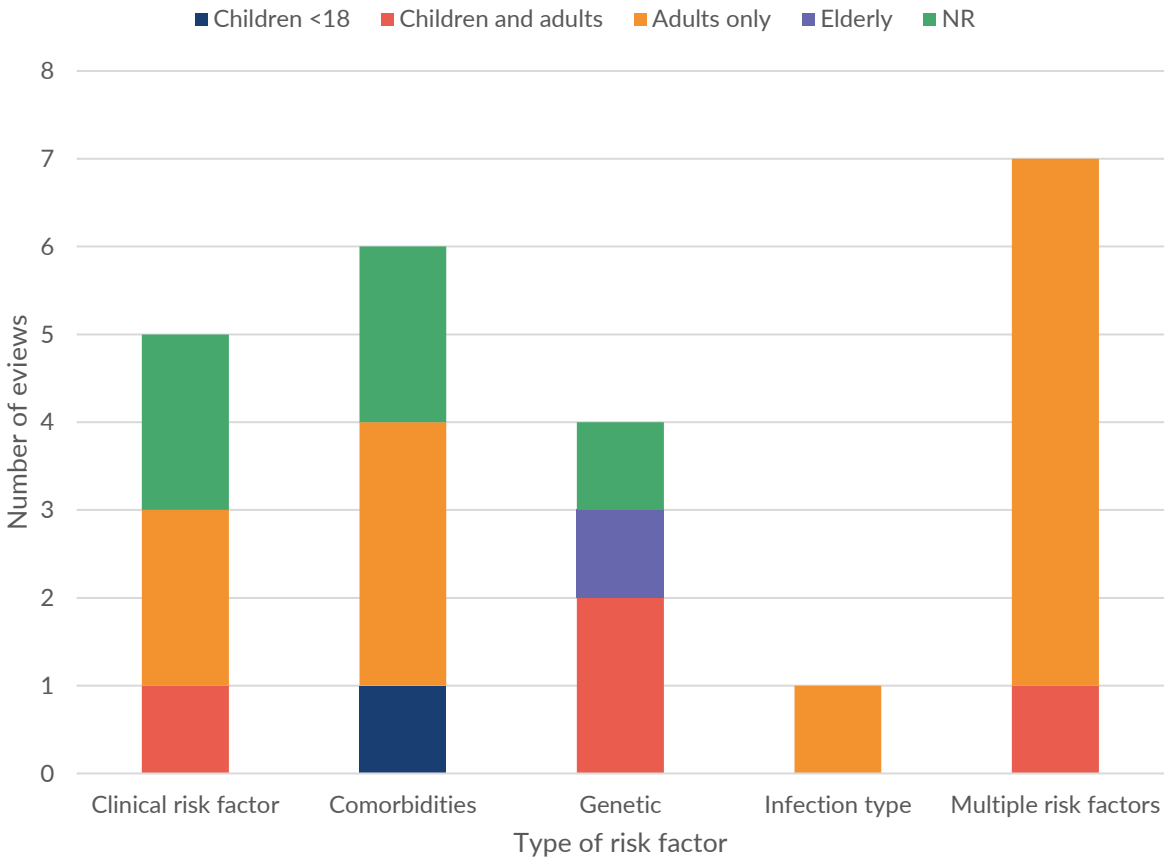


Figure 7. Risk factors and age groups investigated in included reviews

The most frequently reported clinical setting was 'multiple' (n = 10), referring to reviews that included studies conducted across more than one setting, such as hospital wards, intensive care units (ICUs), or other healthcare environments (Figure 8). This highlights the broad applicability of the findings across diverse clinical contexts. The number of reviews per clinical setting followed the same pattern as the total number of primary studies included within these reviews.

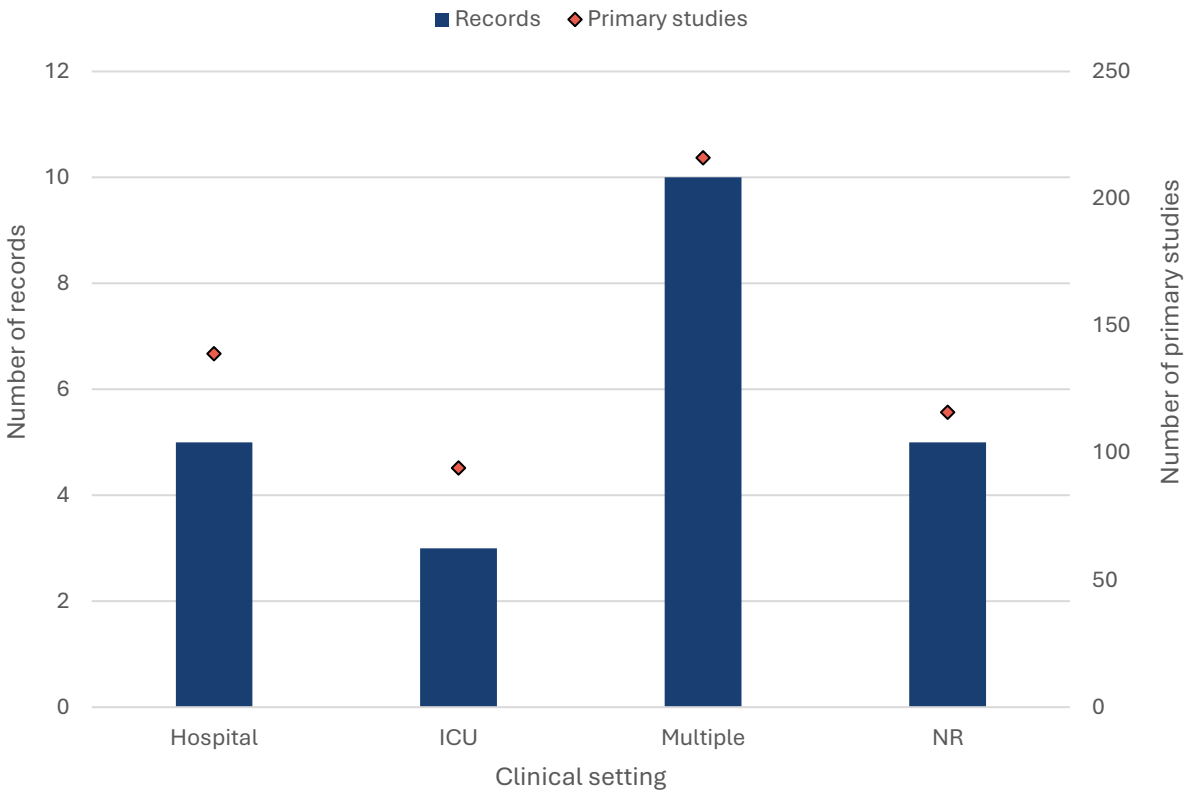


Figure 8. Clinical setting investigated in included predisposing or risk factor reviews, and the sum of the primary studies included within these reviews

Risk factors for incidence of sepsis or bloodstream infections

Comorbidities identified as risk factors for sepsis or blood stream infections (BSI) incidence included diabetes mellitus (studied in two reviews), chronic pulmonary disease, kidney disease and hypertension (Table 8). Two reviews investigated the use of a catheter, concluding that catheter placement site, duration, type and number of catheterisations were risk factors for BSI. One review reported an odds ratio (OR) of 4.22 for the association between the number of catheterisations and BSI, and another reported an OR of 4.285 for catheterisation lasting at least 14 days and BSI. Evidence on genetic risk factors was mixed: one review identified the IL-6 572C/G polymorphism as a risk factor, while others found no increased risk associated with an interleukin-8 gene polymorphism or protective effect from the Asp299Gly variant. Other risk factors with high reported ORs (>4) were the hypermucoviscous-phenotype, inadequate hand hygiene and length of ICU stay.

*Table 8.7 Studies investigating risk factors for the **incidence** of sepsis and bloodstream infections, and their reportable outcomes. Abbreviations: BSI = bloodstream infections; OR = Odds ratio*

Outcome tested	Risk factor	Reportable outcomes
Incidence of sepsis	Asp299Gly variant (protective effect)	The TLR4 Asp299Gly variant may potentially offer a limited protective effect against sepsis, although this outcome is not statistically substantial.[66]
	Diabetes	Diabetes as a risk factor (OR = 1.56).[67]

Incidence of Hypervirulent *Klebsiella pneumoniae* (HvKp) infections	CA-Kp (community-acquired *Klebsiella pneumoniae)*	CA-Kp as a risk factor (OR = 2.59).[67]
	Hypermucoviscous (HM)-phenotype	HM-phenotype as a risk factor (OR = 29.79).[67]
Incidence of BSI	Postoperative biliary complications, a medical history of biliary atresia, and younger age were the risk factors most commonly associated with BSI (no meta-analysis).[68]	
Incidence of BSI	Age	Age as a risk factor (OR = 1.52, 95% CI [0.49, 4.68]).[69]
	Diabetes	Diabetes as a risk factor (OR = 2.52, 95% CI [1.95, 3.25]).[69]
	Kidney disease	Kidney disease as a risk factor (OR = 3.45, 95% CI [1.71, 6.96]).[69]
	History of catheter-associated infection	History of catheter-associated infection as a risk factor (OR = 2.79, 95% CI [1.96, 3.98]).[69]
	Hypertension	Hypertension as a risk factor (OR = 1.43, 95% CI [1.08, 1.91]).[69]
	Dialysis duration	Increased dialysis duration as a risk factor (OR = 3.06, 95% CI [1.70, 5.50]).[69]
	Catheter placement site	Catheter placement site as a risk factor (OR = 1.91, 95%CI [1.35, 2.70]).[69]
	Catheter duration	Catheter duration as a risk factor (OR = 2.06, 95% CI [1.17, 3.60]).[69]
	Number of catheterisations	Increased number of catheterisations as a risk factor (OR = 4.22, 95% CI [3.32, 5.37]).[69]
	Catheter types	Catheter types as a risk factor (OR = 3.83, 95% CI [2.13, 6.87]).[69]
	CD4+ cells	CD4+ cells as a risk factor (OR = 0.33, 95% CI [0.18, 0.63]).[69]
	Albumin	Albumin as a risk factor (OR = 2.12, 95% CI [1.15, 3.91]).[69]
	C-reactive protein	C-reactive protein as a risk factor (OR = 1.73, 95% CI [1.47, 2.03]).[69]
	Haemoglobin	Haemoglobin as a risk factor (OR = 1.48, 95% CI [0.54, 4.07]).[69]
	Procalcitonin	Procalcitonin as a risk factor (OR = 1.05, 95% CI [1.03, 1.06]).[69]
	Inadequate hand hygiene	Inadequate hand hygiene as a risk factor (OR = 5.32, 95% CI [1.07, 26.37]).[69]
	APACHE II scores	APACHE II scores as a risk factor (OR = 2.41, 95% CI [1.33, 4.37]).[69]
Incidence of sepsis	Interleukin-8 gene polymorphism	The results show, no significant association was found by allele contrast, homozygote comparison, heterozygote comparison, recessive genetic model, or dominant genetic model.[8]
Incidence of sepsis	IL-6 572C/*G* polymorphism	The OR was statistically different between the sepsis patient group and the normal healthy people group in the co-dominant homozygous model GG versus CC (OR = 2.41, 95 % CI [1.80, 3.23], I2 = 0 %, P < 0.0001), recessive model GG versus CC+GC (OR = 1.82, 95 % CI [1.46, 2.27], I2 = 26 %, P < 0.0001), and allele

		model G versus C (OR = 1.33, 95 % CI [1.06, 1.65], I2 = 63 %, P = 0.01), indicating that GG genotype and G allele are risk factors for sepsis.[70]
Incidence of BSI	Duration of catheterisation (≥ 5d)	At least 5 days of catheterisation is a risk factor OR = 2.07, 95%CI = 1.41–3.030.[71]
	Duration of catheterisation (≥ 7d)	At least 7 days of catheterisation is a risk factor (OR = 3.62, 95%CI = 2.65–4.97).[71]
	Duration of catheterisation (≥ 14d)	At least 14 days of catheterisation is a risk factor (OR = 4.85, 95%CI = 3.35–7.01.[71]
	Total parenteral nutrition	Total parental nutrition is a risk factor (OR = 2.27,95%CI = 1.56–3.29).[71]
	Use of multiple-lumen catheters	Use of multiple-lumen catheters is a risk factor (OR = 3.41, 95%CI = 2.27–5.11).[71]
	Times of tube indwelling	Times of tube indwelling is a risk factor (OR = 3.50, 95%CI = 2.93–4.17).[71]
	Length of ICU stay	A higher ICU stay is a risk factor (OR = 4.05, 95%CI = 2.41–6.80).[71]
	The position of indwelling	The position of indwelling is a risk factor (OR = 2.41, 95%CI = 2.03–2.85).[71]
Incidence of sepsis	Decreased serum iron levels	Serum iron levels have negative association with susceptibility to sepsis (OR = 0.81; 95% CI = 0.72-0.91; p=0.0004).[72]
	Increased transferrin saturation	Increased transferrin saturation has an association with susceptibility to sepsis.[72]
	Decreased total iron-binding capacity	Decreased total iron-binding capacity has an association with susceptibility to sepsis.[72]
Incidence of sepsis-induced thrombocytopenia	Elevated lactate	In multivariable models, an elevated lactate (pooled OR = 1.22 per mmol L−1, 95 % CI 1.18–1.25; P < 0.00001) retained independent predictive value for SIT.[73]
	Lower white blood cell count	In multivariable models, a lower WBC count (pooled OR = 0.97 per 109 L−1, 95 % CI 0.96–0.98; P < 0.00001) retained independent predictive value for SIT.[73]
Incidence of acute respiratory distress syndrome (ARDs) in sepsis patients	Chronic pulmonary disease	Chronic obstructive pulmonary disease was significantly associated with an increased risk of ARDS (OR: 1.43, 95% confidence interval (95% CI): 1.02–2.01).[74]
Incidence of cardiovascular events in sepsis patients	Age ≤ 45	Age ≤ 45 years is a risk factor (HR: 2.51; 95% CI: 1.95-3.23).[74]
	Male sex	Male sex is a risk factor (HR: 1.28; 95% CI: 1.20-1.37)
	Diabetes	Diabetes mellitus is a risk factor (HR 1.52, 95% CI 1.36-1.70).[74]
	Hypertension	Hypertension is a risk factor (HR: 1.41, 95% CI 1.25-1.59), COPD (HR: 1.20, 95% CI: 1.11-1.30).[74]
	Chronic kidney disease	Chronic kidney disease is a risk factor (HR: 1.22, 95% CI: 1.14-1.31).[74]
	Coronary heart failure	Coronary heart failure is a risk factor (hr: 1.28, 95% ci: 1.18-1.38).[74]
	Coronary artery disease	Coronary artery disease is a risk factor (HR: 1.38, 95% CI: 1.31-1.47).[74]

	Cardiovascular accidents	Cardiovascular accident is a risk factor (HR: 1.34, 95% CI: 1.30-1.39).[74]
	Hyperlipidaemia	Hyperlipidaemia is a risk factor (HR: 1.60, 95% CI: 1.50-1.69).[74]

Risk factors for mortality from sepsis or bloodstream infections

Comorbidities identified as risk factors for mortality from sepsis or bloodstream infections (BSI) included diabetes mellitus and cancer, each reported in two reviews, as well as chronic kidney disease (Table 9Table 8.7). Severe mental illness was reported to have a protective effect, as was obesity, whereas being underweight was identified as a risk factor. Among the reported risk factors, the need for mechanical ventilation was associated with the highest odds of mortality (OR = 22).

*Table 9.8 Studies investigating risk factors for **mortality** from sepsis and bloodstream infections, and their reportable outcomes. Abbreviations: BSI = bloodstream infections*

Outcome tested	Risk factor	Reportable outcomes
Sepsis mortality	Diabetes	Meta-analysis of 23 studies showed that diabetes mellitus did slightly increase sepsis overall mortality (RR, 1.12; 95% CI 1.00–1.25; I^2 96.1%; p = 0.000).[75]
Sepsis mortality	Cancer	The present analysis revealed a mortality rate in the ICU (53%), at 28 days (59%), in-hospital (50%), and at 90 days (61%); the mortality rate increases to 69% at 180 days. These findings contrast with the mortality observed in the general population reported in a systematic review and meta-analysis, where mortality at 30 and 90 days was 34.7% and 38.5%, respectively. At 90 and 180 days, these rates were 38.5% and 34.7% respectively.[76]
Mortality in *Stenotrophomonas maltophilia* bacteraemia infection	Neutropenia	Neutropenia is a risk factor (OR = 2.12, p < .001, I2 = 29).[77]
	ICU admission	ICU admission is a risk factor (OR = 3.00, p < .001, I2 = 63%).[77]
	Mechanical ventilation	Mechanical ventilation is a risk factor (OR = 2.63, p = .001, I2 = 58%).[77]
	Indwelling central venous catheter	Indwelling central venous catheter is a risk factor (OR = 2.66, p < .001, I2 = 0%).[77]
	Chronic kidney disease	Chronic kidney disease is a risk factor (OR = 1.65, p = .03, I2 = 26%).[77]
	Inappropriate antibiotic therapy	Inappropriate antibiotic therapy is a risk factor (OR = 2.18, p = .02, I2 = 66%).[77]
	Prior antibiotic use	Prior antibiotic use is a risk factor (OR = 2.82, p = .005, I2 = 0%).[77]
Mortality in sepsis	Vitamin D levels	Vitamin D levels in sepsis patients were consistently lower than in the control group. MD = –4.17 (95% CI, –7.87 to –0.47) ng/mL. Vitamin D deficiency is a potential risk factor for sepsis.[78]
	VDR FokI genotype	The relationship between *VDR* FokI genotype and sepsis risk was not statistically significant (p>0.05),

		although several individual studies showed a positive correlation.[78]
Mortality of BSI	Definitive risk factors for mortality included age, any comorbidity score, place of infection acquisition, acute disease severity, source of infection and methicillin susceptibility. Potential risk factors included specific comorbidities, as well as two variables unique to *Staphylococcus aureus* bacteraemia: intravenous (IV) drug use and ID consult that were protective factors for mortality.[79]	
Mortality of BSI	Male sex	Male sex was a risk factor for ICU-BSI in COVID-19 patients (OR = 1.28, 95% CI: 1.10–1.50, P = 0.006).[80]
	High SAPS II score	High SAPS II score was a risk factor for ICU-BSI in COVID-19 patients (WMD = 6.43, 95% CI: 0.23–12.63, P = 0.042).[80]
	Diabetes	Diabetes was a risk factor for ICU-BSI in COVID-19 patients (OR = 1.34, 95% CI: 1.04–1.73, P = 0.022)[80]
	Tracheal intubation	Tracheal intubation was a risk factor for ICU-BSI in COVID-19 patients (OR = 8.68, 95% CI: 4.68–16.08, P < 0.001).[80]
	Mechanical ventilation	The use of mechanical ventilation was a risk factor for ICU-BSI in COVID-19 patients (OR = 22.00, 95% CI: 3.77-128.328, P < 0.001).[80]
	ECMO	ECMO was a risk factor for ICU-BSI in COVID-19 patients (OR = 2.70, 95% CI: 1.17–6.26, P = 0.020).[80]
	Central venous cannulation	Central venous cannulation was a risk factor for ICU-BSI in COVID-19 patients (OR = 9.33, 95% CI: 3.06–28.43, P < 0.001).[80]
	Prolonged ICU stay	Prolonged ICU stay was a risk factor for ICU-BSI in COVID-19 patients (WMD = 10.37, 95% CI: 9.29–11.44, P < 0.001).[80]
	Methylprednisolone use	Methylprednisolone use was a risk factor for ICU-BSI in COVID-19 patients (OR = 2.24, 95% CI: 1.24–4.04, P = 0.008).[80]
	The combination of methylprednisolone and Tocilizumab	The combination of methylprednisolone and Tocilizumab was a risk factor for ICU-BSI in COVID-19 patients (OR = 4.54, 95% CI: 1.09–18.88, P = 0.037).[80]
Mortality of S. aureus BSI	Female sex	Female patients with gram-negative BSI did not have increased risk of mortality relative to male patients (pooled OR, 0.98 [95% CI, 0.81-1.17]).[81]
Mortality of sepsis	Severe mental illness (protective)	SMI patients had a lower case-fatality rate associated with sepsis and septic shock than their non-SMI counterparts (OR 0.61, 95% CI [0.58–0.65], PI 95% CI [0.49–0.77], I2 = 91%).[82]
Mortality of BSI	Multidrug-resistant organism	MDRO BSIs were consistently associated with a higher mortality rate irrespective of MDRO or transplant type. For individual MDROs, MRSA- and VRE-associated mortality were most frequently reported, with a median crude mortality of 36.1% (IQR 19.3%–56.3%) and 37.2% (IQR 30.9%–42.5%), respectively.[83]
Mortality of sepsis	Obesity (protective)	The mortality rate (OR=0.88; 95% CI: 0.81-0.95; I2=0.00%; P=0.000) was lower in patients with obesity.[84]
Mortality of sepsis	Underweight	In-hospital mortality (OR, 1.28), 28-day mortality (OR, 1.54) and 1-year mortality (OR, 1.78) of underweight

		patients were significantly higher than those of normal weight patients.[85]
Mortality of sepsis	Cancer	The pooled ICU, hospital and 30-day mortality across the studies included in the meta-analysis was 44% (95% CI 38%–50%), 54% (95% CI 49%–60%) and 49% (95% CI 44%–55%) respectively.[86]

Discussion

Sepsis is a complex life-threatening condition resulting from a dysregulated host response to infection, with outcomes influenced by patient factors (such as age, sex, genetic susceptibility), comorbidities, infection type, and healthcare settings. The findings from the included reviews highlight how prognostic indicators, clinical scoring systems, and risk stratification approaches can inform prognosis, enhance risk stratification, support personalised clinical decision-making, and ultimately improve patient outcomes.

Clinical and healthcare system factors

Hospital-acquired sepsis carries higher mortality, and longer ICU stays than community-acquired sepsis, emphasising the critical role of infection prevention policies (such as hand hygiene, catheter care protocols). Catheter-related factors, including placement site, duration, type, and number of catheterisations, were consistently associated with bloodstream infections. Clinical interventions such as mechanical ventilation, ECMO, and tracheal intubation were strongly associated with both incidence and mortality of sepsis, highlighting high-risk procedures in ICU settings.

Technological and predictive innovations

Machine learning (ML) and AI algorithms demonstrate superior specificity and overall predictive performance compared to traditional scoring systems such as SOFA, APACHE II, and SAPS II. Models including XGBoost, random forest, and logistic regression effectively predicted sepsis-associated acute kidney injury, mortality, and progression of critical illness. However, sensitivity remained variable, and data limitations in early-stage sepsis highlight the need for further refinement and external validation. Ethical concerns regarding fairness and potential bias must also be considered when integrating AI into clinical workflows.

Clinical scoring systems remain valuable, particularly for immediate bedside assessment. High APACHE II and SAPS II scores were strongly associated with sepsis incidence, severity, and mortality. Integration of ML/AI models with these scores may optimise risk stratification and guide timely interventions.

Biomarkers and laboratory parameters

Biomarkers provide critical insights into sepsis risk and prognosis. Elevated lactate, procalcitonin, C-reactive protein, hypoalbuminemia, and abnormal iron parameters (low serum iron, high transferrin saturation) were associated with increased susceptibility and worse outcomes. Microcirculatory measurements (for example, sublingual microcirculation) also predicted severity and mortality, offering a functional assessment of perfusion and tissue oxygenation.

Cardiac and haemodynamic parameters

Echocardiographic assessments, such as left ventricular global longitudinal strain (GLS) and left ventricular outflow tract velocity time integral (LVOT VTI), are strong predictors of mortality and fluid responsiveness. Hyperdynamic left ventricular function, LV systolic/diastolic dysfunction, and right ventricular dysfunction were consistently associated with higher mortality. Point-of-care echocardiography improved management of septic shock, demonstrating the potential of rapid bedside diagnostics.

Predisposing and patient-level factors

Age, sex, comorbidities (diabetes, cancer, chronic kidney disease, COPD, hypertension), infections, and genetic factors (IL-6 572C/G polymorphism) influence both susceptibility to sepsis and outcomes. Protective factors such as obesity and severe mental illness suggest complex interactions between host factors and disease progression. Nutritional status and vitamin D deficiency were also associated with worse outcomes, underscoring the multifactorial nature of risk.

Implications and Recommendations

In clinical practice, sepsis management should adopt combined predictive strategies that integrate machine learning and AI algorithms with established clinical scores such as SOFA, APACHE II, and SAPS II, alongside biomarkers including lactate, procalcitonin, and albumin, as well as echocardiographic parameters. This multi-modal approach enables comprehensive risk stratification and individualised patient care. Optimising ICU and hospital workflows is critical to minimising catheter-associated infections and mitigating procedural risks related to mechanical ventilation and ECMO. Furthermore, routine microcirculatory and haemodynamic monitoring should be integrated into care protocols to guide tailored fluid management and haemodynamic support.

From a policy and health system perspective, infection prevention should remain a priority, emphasising hand hygiene, catheter care, and antimicrobial stewardship to reduce the burden of hospital-acquired sepsis. Healthcare systems should support the implementation of validated AI and machine learning predictive tools, ensuring clear guidelines regarding data privacy, fairness, and clinical accountability. Efforts should also focus on promoting equitable access to advanced monitoring technologies, diagnostic imaging, and laboratory assays across diverse healthcare settings.

In terms of research and innovation, prospective studies are needed to evaluate integrated, multi-modal approaches that combine biomarkers, clinical scores, ML/AI tools, and echocardiography to improve early detection and patient outcomes. Standardising biomarker thresholds, clinical scoring cut-offs, and machine learning model validation metrics will enhance reproducibility and clinical applicability. Additionally, investigating genetic and molecular determinants of susceptibility and disease progression will support targeted prevention strategies and the development of personalised care pathways.

Conclusion

Sepsis remains a complex, multifactorial syndrome with outcomes shaped by host characteristics, environmental conditions, and healthcare system factors. Predictive tools, including ML/AI algorithms, clinical scoring systems, biomarkers, and echocardiography,

provide complementary insights for early detection and prognostication. A multi-modal, integrated approach that combines these tools with evidence-based clinical interventions has the potential to reduce mortality, improve patient outcomes, and optimise ICU resource utilisation. Future research should place stronger emphasis on well-designed prospective studies, alongside standardisation of biomarkers, scoring systems, and model evaluation methods, to support robust validation and facilitate equitable translation of these approaches into routine clinical practice.

Other information

Support

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Competing interests

The authors report no competing interests to declare.

Availability of data, code and other materials

With the agreement of our stakeholders, the data gathered while undertaking this horizon scan may be requested under reasonable circumstances.

Appendix A

Date of Search 041225

Sepsis + ADJ4 Prognosis

Database(s): **Embase** 1974 to 2025 December 02
Search Strategy:

#	Searches	Results
1	(Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)	722966
2	(prognos* or outcome prediction* or predicted outcome or prognostic factor* or prognosis or prognostic indicator* or prognostic marker* or outcome predictor* or mortality predictor* or risk stratification or clinical prediction or predictive factor* or predictive marker* or prognostic model or prediction model or severity assessment or clinical outcome* or mortality or in-hospital mortality or 30-day mortality or treatment outcome* or SOFA score or qSOFA or APACHE II or SAPS II or early warning score*).ti,ab. or prognosis/	3749969
3	((Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis	41553

	factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)) adj4 ((prognos* or outcome prediction* or predicted outcome or prognostic factor* or prognosis or prognostic indicator* or prognostic marker* or outcome predictor* or mortality predictor* or risk stratification or clinical prediction or predictive factor* or predictive marker* or prognostic model or prediction model or severity assessment or clinical outcome* or mortality or in-hospital mortality or 30-day mortality or treatment outcome* or SOFA score or qSOFA or APACHE II or SAPS II or early warning score*).ti,ab. or prognosis/)	
4	limit 3 to yr="2024 - 2025"	6536
5	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1328764
6	animal experiment/ not (human experiment/ or human/)	2810605
7	5 or 6	2897598
8	4 not 7	6200
9	(systematic review or meta-analysis).pt.	0
10	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	808530
11	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	542793
12	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	24665
13	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	69409
14	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	67227
15	(handsearch* or hand search*).ti,ab,kf.	14895
16	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	57774
17	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	25788
18	(meta regression* or metaregression*).ti,ab,kf.	24243

19	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).ti,ab,kf.	706318
20	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,kf.	567341
21	(cochrane or (health adj2 technology assessment) or evidence report).ti,ab,kf.	240087
22	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	35540
23	(outcomes research or relative effectiveness).ti,ab,kf.	19017
24	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	9257
25	(meta-analysis or systematic review).ti,ab,kf.	641716
26	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	496
27	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	270
28	umbrella review*.ti,ab,kf.	3422
29	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	39
30	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	23
31	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	32
32	or/9-31	1254601
33	8 and 32	464

Sepsis + ADJ4 Predisposing factors

Database(s): **Embase** 1974 to 2025 December 02
Search Strategy:

#	Searches	Results
1	(Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis	722966

	factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)	
2	(predisposing Factor* or factors predispos* or prone or inclined or susceptible or tendencies or propensities or inclinations or risk factor* or susceptibility or host susceptibility or predisposition or vulnerability or patient characteristics or comorbidity or underlying condition* or chronic disease* or immunosuppression or immune dysfunction or prior infection or prior hospitalization or healthcare exposure).ti,ab. or disease predisposition/	2855320
3	((Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)) adj4 ((predisposing Factor* or factors predispos* or prone or inclined or susceptible or tendencies or propensities or inclinations or risk factor* or susceptibility or host susceptibility or predisposition or vulnerability or patient characteristics or comorbidity or underlying condition* or chronic disease* or immunosuppression or immune dysfunction or prior infection or prior hospitalization or healthcare exposure).ti,ab. or disease predisposition/)	20304
4	limit 3 to yr="2024 - 2025"	2429
5	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1328764
6	animal experiment/ not (human experiment/ or human/)	2810605
7	5 or 6	2897598
8	4 not 7	2293

9	(systematic review or meta-analysis).pt.	0
10	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	808530
11	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	542793
12	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	24665
13	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	69409
14	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	67227
15	(handsearch* or hand search*).ti,ab,kf.	14895
16	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	57774
17	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	25788
18	(meta regression* or metaregression*).ti,ab,kf.	24243
19	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).ti,ab,kf.	706318
20	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,kf.	567341
21	(cochrane or (health adj2 technology assessment) or evidence report).ti,ab,kf.	240087
22	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	35540
23	(outcomes research or relative effectiveness).ti,ab,kf.	19017
24	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	9257
25	(meta-analysis or systematic review).ti,ab,kf.	641716
26	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	496
27	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	270
28	umbrella review*.ti,ab,kf.	3422
29	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	39
30	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	23

31	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	32
32	or/9-31	1254601
33	8 and 32	125

Sepsis + ADJ 4 Deterioration monitoring

Database(s): **Embase** 1974 to 2025 December 02
Search Strategy:

#	Searches	Results
1	(Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)	722966
2	((deterioration adj2 (monitor* or assess* or surveillance or observ* or clinical or physiological or patient)) or (organ dysfunction or organ failure or hemodynamic instability or respiratory failure or acute kidney injury or lactate elevation or hypotension or deterioration monitoring or early warning or clinical monitoring or continuous monitoring or vital signs monitoring or hemodynamic monitoring or biomarker monitoring or risk stratification or early warning scores or NEWS2 or qSOFA or SOFA score or SIRS criteria or deterioration prediction models or machine learning prediction or prognostic models)).ti,ab.	527900
3	((Septicaemia* or Septicemia* or pyemia* or Pyaemia* or Bloodstream infection* or Acute deterioration or Septic shock* or Septicaemic shock or Septicemic shock or Endotoxic shock* or Systemic Inflammatory Response Syndrome or SIRS or Bacteraemia or Bacteremia or (inflammatory adj2 mediators) or Gram?positive bacterial infection or Gram-positive bacterial	26482

	infection or Gram-negative bacterial infection or Gram?negative bacterial infection or Fungal infection or Viral infection or Blood Poisoning* or Toxic Shock* or pyohemia* or Serious Bacterial Infection* or SBIs or sepsis syndrome* or abdominal sepsis or focal sepsis or intraabdominal sepsis or generalized infection or systemic infection or systemic infectious disease or "infection in blood stream" or poisoning blood or TNF-alpha or tumo?r necrosis factor-alpha or calprotectin or (sepsis adj2 scoring system) or Sequential Organ Failure Assessment).ti,ab. or (*sepsis/ or *pyemia/ or *bloodstream infection/ or *septic shock/ or *endotoxic shock/ or *systemic inflammatory response syndrome/ or *bacteremia/ or *Gram positive infection/ or *Gram negative infection/ or *toxic shock syndrome/ or *tumor necrosis factor/ or *calgranulin/)) adj4 ((deterioration adj2 (monitor* or assess* or surveillance or observ* or clinical or physiological or patient)) or (organ dysfunction or organ failure or hemodynamic instability or respiratory failure or acute kidney injury or lactate elevation or hypotension or deterioration monitoring or early warning or clinical monitoring or continuous monitoring or vital signs monitoring or hemodynamic monitoring or biomarker monitoring or risk stratification or early warning scores or NEWS2 or qSOFA or SOFA score or SIRS criteria or deterioration prediction models or machine learning prediction or prognostic models)).ti,ab.	
4	limit 3 to yr="2024 - 2025"	4532
5	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1328764
6	animal experiment/ not (human experiment/ or human/)	2810605
7	5 or 6	2897598
8	4 not 7	4334
9	(systematic review or meta-analysis).pt.	0
10	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	808530
11	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	542793
12	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	24665
13	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	69409
14	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	67227

15	(handsearch* or hand search*).ti,ab,kf.	14895
16	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	57774
17	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	25788
18	(meta regression* or metaregression*).ti,ab,kf.	24243
19	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).ti,ab,kf.	706318
20	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,kf.	567341
21	(cochrane or (health adj2 technology assessment) or evidence report).ti,ab,kf.	240087
22	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	35540
23	(outcomes research or relative effectiveness).ti,ab,kf.	19017
24	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	9257
25	(meta-analysis or systematic review).ti,ab,kf.	641716
26	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	496
27	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	270
28	umbrella review*.ti,ab,kf.	3422
29	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	39
30	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	23
31	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	32
32	or/9-31	1254601
33	8 and 32	205

Appendix B

Reviews not meeting DARE criteria

Acinetobacter baumannii Bloodstream Infections in Hematopoietic Stem Cell Transplant Recipients: A Worldwide Systematic Review	https://doi.org/10.6002/ect.2024.0234
Which neurogenic bladder patients are at higher risk of sepsis after percutaneous nephrolithotomy?	https://doi.org/10.1007/s00345-025-05836-6
Vitamin B12 And Septic Shock Mortality: A Systematic Review And Meta-Analysis	https://doi.org/10.1016/j.chest.2024.06.1588
Neonatal Mortality Due to Early-Onset Sepsis in Eastern Europe: A Review of Current Monitoring Protocols During Pregnancy and Maternal Demographics in Eastern Europe, with an Emphasis on Romania-Comparison with Data Extracted from a Secondary Center in Southern Romania	https://doi.org/10.3390/children12030354
Mortality and genetic diversity of antibiotic-resistant bacteria associated with bloodstream infections: a systemic review and genomic analysis	https://doi.org/10.1186/s12879-024-10274-7
Mood and Psychotic Disorders as Prognostic Factors for Sepsis and Septic Shock Mortality: A Meta-Analysis	https://doi.org/10.1164/ajrccm.2025.211.Abstracts.A5580
A meta-analysis of whole blood transcriptome reveals genes associated with increased neutrophil activity and T cell suppression in sepsis	https://doi.org/10.1186/s43042-025-00640-8
Machine learning models for predicting mortality in sepsis: a systematic review	https://doi.org/10.3389/fmed.2022.964667
Inflammatory protein signatures of sepsis risk and mortality: a mendelian randomization study	https://doi.org/10.1097/shk.0000000000002599

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