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Review of trigger tools to support the early identification of sepsis in healthcare settings

The George Institute for Global Health, Sydney, Australia, prepared this report for the Australian Commission on Safety and Quality in Health Care.

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Preface

The Australian Commission on Safety and Quality in Health Care (the Commission) has commenced a program of work to improve early recognition, treatment and outcomes for patients with sepsis in Australia.

In consultation with internal and external stakeholders, the Commission has identified a series of actions that will be implemented over 2020–22. The program of work to improve outcomes in patients with sepsis in Australia includes:

- Performing an [epidemiological analysis](#) of national inpatient sepsis data
- Conducting a retrospective medical record review of sepsis patient clinical documentation to examine aspects of sepsis recognition, management and clinical coding
- Conducting a literature review of trigger tools that promote the early detection of sepsis symptoms (**this report**)
- Developing materials relevant to Standard 3 and Standard 8 of the National Safety and Quality Health Service (NSQHS) Standards (2nd edition) to ensure health service organisations demonstrate the use of evidence-based practice in the early detection, treatment and monitoring of sepsis
- Revising the [Antimicrobial Stewardship Clinical Care Standard](#) to strengthen Quality Statement 1 with regard to the role that prompt treatment with intravenous antibiotics in patients with suspected severe infection
- Developing a dedicated Sepsis Clinical Care Standard
- Partnering with the Australian Government, states and territories and the George Institute for Global Health to lead a multi-modal public awareness campaign
- Scoping the need to establish a coordinated approach for improving sepsis services, to address the high rates of disease recurrence and associated morbidity and disability and publish a [report](#).

Aim

This systematic review was commissioned to investigate trigger tools that promote the early detection of sepsis symptoms, including the use of lactate testing in patients experiencing rapid clinical deterioration or suspected of having infection.

Review questions

This integrative systematic review sought to address the following:

1. Identify tools and triggers used for the early identification of sepsis
2. Determine the relevant parameters and what, if any, additional measures should be considered for minimum requirements for clinical monitoring
3. Describe and evaluate the evidence according to a validated level of evidence classification and critical appraisal quality assessment tools
4. Describe and evaluate the evidence within prehospital, emergency departments (ED) and acute care settings for neonatal, paediatric, maternal and adult patient cohorts
5. Determine whether serum lactate (sLA), point of care lactate (pLA), or a surrogate measure, improves the performance of selected triggers and so should be added to minimum monitoring requirements and any existing tool(s).

Results

The main findings from this systematic review include:

- Sufficient evidence to support use of the quick Sequential Organ Failure Assessment (qSOFA) scoring system with the addition of rapid lactate measurement (LqSOFA).
- The National Early Warning Score (NEWS) or Modified Early Warning (MEWS) scoring systems offer slightly improved sensitivity to identify deteriorating patients, but may not offer any advantage over LqSOFA (with which they have not been directly compared).
- Further research is required to identify the best tools for use in neonatal and maternal populations.
- An automated alert system embedded within electronic health records (EHR) is likely to be a viable alternative to identify patients deteriorating from sepsis in the acute care setting in the near future.

Conclusion

This systematic review found evidence to support the use of the LqSOFA scoring system as a triage tool for patients presenting to the ED and within acute care hospitals. The NEWS or MEWS scoring systems offer slightly improved sensitivity to identify deteriorating patients, however may not offer any advantage over LqSOFA with which they have not been directly compared.

Recommendations and next steps for the Commission

Based on wide consultation and the findings described in this systematic review, the following recommendations are proposed:

- The Commission considers developing advice for the states and territories regarding routine lactate measurement in patients with clinical deterioration or suspected sepsis.
- The Commission consults with the states and territories, associated peak bodies and professional colleges on:
 - the feasibility of implementing LqSOFA (using rapid lactate measurement) as a sepsis screening tool in emergency departments and acute care settings for adults
 - identifying clinically appropriate sepsis detection tools for neonatal and maternal populations.
- The Commission develops resources to support health service organisations to incorporate sepsis alerts and clinical decision support tools into their EHRs and clinical information systems nationally.
- The Commission collaborates with health service organisations to promote the use of sepsis alerts and clinical decision support tools into EHRs and clinical information systems which include:
 - clinically appropriate threshold values for neonates, young children, pregnant and post-partum women, and other high-risk populations
 - recognition and response systems which support the early identification of sepsis.



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Review of trigger tools to support the early identification of sepsis in healthcare settings.

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Disclaimer:

This review was produced using systematic review methodology in response to specific questions from the commissioning agency.

The information presented provides a comprehensive review of the literature relating to the topic area at the time of production of the report.

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Abbreviations

Abbreviation	Full Name
AUROC	Area Under the Receiver Operating Characteristic curve
BES	Best Evidence Synthesis
BE	Base Excess
BP	Blood pressure
BSL	Blood sugar level
BTF	Between the flags
CARS	Compensatory Anti-inflammatory Response syndrome
CASP	Critical Appraisal Skills Program
CRP	C-reactive protein
DBP	Diastolic Blood Pressure
DOR	Diagnostic Odds Ratio
ED	Emergency department
EHR	Electronic health record
EMIP	Early Maternal Infection Prompts
ESI	Emergency Severity Index
ETCO ₂	End Tidal Carbon Dioxide
EWA	Early Warning Algorithm
GCS	Glasgow Coma Scale
GBD	Global Burden of Disease
HEWS	Hamilton Early Warning Score
HCO ₃	Bicarbonate
HR	Heart Rate
ICU	Intensive Care Unit
LoS	Length of Stay
LqSOFA	Blood Lactate + Quick sequential organ failure assessment
LR	Likelihood ratio
MBIS	Mecklenburg Bacterial Infection Scale
MEDS	Mortality in ER Sepsis
MEWS	Modified Early Warning Score
MLA	Machine Learning Algorithms
NEWS	National Early Warning Score
NHMRC	National Health and Medical Research Council
NLCR	Neutrophil-Lymphocyte Count Ratio
NPV	Negative Predictive Value
NST	Nurse Screening tool
PCT	Procalcitonin
PHANTASi	Prehospital ANTibiotics Against Sepsis
PITSTOP	Paramedic Initiated Treatment of Sepsis Targeting Out-of-hospital Patients
pLA	Point of care lactate test
POC	Point of Care
POC lactate	Point of Care Lactate
PPV	Positive Predictive Value
PreSAT	Prehospital Sepsis Assessment Tool
PRESEP	Prehospital Early Sepsis Detection

Cont'd.

Abbreviation	Full Name
PRESS Score	Prehospital Severe Sepsis score
Pts	Points
QCRT	Capillary refill time
qSOFA	Quick sequential organ failure assessment
qSOFA-65	Quick Sequential Organ Function Assessment-65
RCT	Randomised Controlled Trial
RETTS	Rapid Emergency Triage and Treatment System
RoS	Reactive Oxygen Species
RR	Respiratory Rate
SaO ₂	Oxygen Saturation
SBP	Systolic Blood pressure
sBPA	Sepsis Best Practice Alert
SEAT	Sepsis Early Alert Tool
SIRS	Systemic Inflammatory Response Syndrome
SJSA	St Johns Sepsis Agent
sLA	Serum lactate
Sn	Sensitivity
SOFA	Sequential Organ Failure Assessment
SOS	Sepsis Obstetric Calculator
Sp	Specificity
Spot	Sepsis Prediction and Optimisation of Therapy
SpO ₂	Peripheral capillary oxygen saturation
SSA	Sepsis Sniffer Algorithm
SSC	Surviving Sepsis Campaign
SSS	Sepsis Severity Score
tCFI	Triage concern for infection
WBC	White blood cell
WHO	World Health Organisation

Executive summary

Background

Sepsis is a time-critical medical emergency that arises when the body's response to an infection damages its own tissues and organs leading to organ failure. If not recognised promptly and treated sepsis results in avoidable death and disability. The best estimate of the burden of sepsis is that there were 49 million sepsis cases and 11 million deaths globally in 2017, with 55,000 of those cases and 8,700 deaths occurring in Australia.¹ In May 2017, the World Health Organisation (WHO) declared sepsis as a global health priority, and in response, the Australian Sepsis Network (ASN) produced the *Stopping Sepsis National Action Plan*.²

Recognising that early detection, appropriate antibiotics and supportive therapy are currently the only interventions that unequivocally reduce death and disability from sepsis, the plan recommended improved detection and recognition of sepsis as a leading priority. Currently the most effective way to identify patients who have sepsis in Australian healthcare settings is not clear. Therefore, a comprehensive review was conducted of the existing evidence, relevant to the Australian Healthcare System, to evaluate potential triggers and tools to assist in the early detection of sepsis.

Objective

The primary objective of this review was to identify the best screening and clinical assessment tools and alerts to detect patients with sepsis. The review was conducted within the broader context of early recognition of patient deterioration in prehospital, emergency department (ED) and acute care hospital settings for neonatal, paediatric, maternal and adult patients. The primary focus was on tools with the best supporting evidence in respect of diagnostic accuracy and the potential for use within routine clinical practice across a variety of healthcare settings.

Review questions

This integrative systematic review sought to address the following:

1. Identify tools and triggers used for the early identification of sepsis
2. Determine the relevant parameters and what, if any, additional measures should be considered for minimum requirements for clinical monitoring
3. Describe and evaluate the evidence according to a validated level of evidence classification and critical appraisal quality assessment tools
4. Describe and evaluate the evidence within prehospital, ED and acute care settings for neonatal, paediatric, maternal and adult patient cohorts
5. Determine whether serum lactate (sLA), point of care lactate (pLA), or a surrogate measure, improves the performance of selected triggers and so should be added to minimum monitoring requirements and any existing tool(s).

Methods

The systematic review was conducted using methods aligned with the Preferred Reporting Items for Systematic reviews and Meta-analyses of Diagnostic test accuracy studies, and in accordance with a pre-specified protocol registered at PROSPERO (CRD42020186151).

Multiple electronic databases were searched to identify studies (systematic reviews, randomised controlled trials or cohort studies) in adult, paediatric, neonatal and maternal populations. Studies conducted in pre-hospital, ED and hospital inpatient settings, where clinical tools or diagnostic tests were used to identify patients with suspected sepsis or trigger changes to the clinical management were included in the review. Subject matter experts reviewed the search strategy and were asked to identify relevant grey literature.

The eligibility of studies for inclusion was assessed independently by two researchers. Quality of the included studies was assessed using validated tools for each study design. Data were extracted with standardised data collection instruments. Heterogeneity of studies prevented quantitative analysis. Results were summarised according to the included population and clinical setting.

Results

The search identified 4137 unique studies of which 124 studies met the inclusion criteria. There were 109 cohort studies, adjudicated as being of low risk of bias with minimal concerns regarding applicability, and 15 systematic reviews adjudicated as having a moderate risk of bias with some concerns regarding applicability.

Key findings:

1. Tools and triggers used for the early identification of sepsis:

- 1.1. Systemic Inflammatory Response Syndrome (SIRS) has higher sensitivity than quick Sequential Organ Failure Assessment (qSOFA) but similar when lactate is added to qSOFA (LqSOFA). However, in some studies SIRS has unacceptable specificity.
- 1.2. Aggregate scoring systems such as National Early Warning Score (NEWS) or Modified Early Warning Score (MEWS) may have a slight advantage over LqSOFA but are more complex and have not been directly compared
- 1.3. Biomarkers are useful confirmatory diagnostic tests for sepsis, particularly in neonates, but are not early clinical triggers for suspected sepsis
- 1.4. Electronic Health Record (EHR) alerts and machine learned algorithms (MLA) offer sensitive early detection tools, but are not yet ready for system-wide implementation.

2. Tools and triggers specific to healthcare settings and patient populations:

- 2.1. No single sepsis screening tool can be applied uniformly to neonatal, paediatric, maternal and adult populations, or system-wide across prehospital, emergency and acute care settings
- 2.2. Prehospital setting - the use of a screening tool improves sepsis detection but there are insufficient data to recommend any one tool

- 2.3. Emergency Department - LqSOFA is a feasible and sensitive tool for sepsis screening in all patients presenting with suspected infection and non-specific symptoms at triage
 - 2.4. Acute care - aggregate scoring systems, such as NEWS or MEWS, were slightly more sensitive, but more complex, than single or multiple parameter system
 - 2.5. Limited evidence is available for sepsis screening tools in neonatal and maternal populations.
- 3. Lactate:**
- 3.1. The measurement of lactate improves the sensitivity of scoring systems
 - 3.2. High specificity of pLA in the prehospital setting may trigger pre-notification of a critically unwell patient to ED but requires further research
 - 3.3. In ED, at a lactate cut off of 2 mmol/L or greater, pLA was observed to perform moderately well as a marker of sepsis and demonstrated a consistently high correlation with sLA concentrations in both adult and paediatric populations
 - 3.4. Base deficit may be a useful surrogate when lactate measurement is not available.
- 4. Minimum monitoring requirements:**
- 4.1. Sepsis trigger tools relevant to this review use similar vital sign parameters including respiratory and heart rate, systolic blood pressure, temperature, conscious level and oxygen saturation, which are consistent with the minimum monitoring requirements in the draft National Consensus Statement: Essential elements for recognising and responding to acute physiological deterioration (3rd ed) (NCS)
 - 4.2. In Australia, tools commonly used for sepsis screening and pathways have routinely added measurement of serum Lactate as an additional parameter
 - 4.3. The three components of qSOFA align closely to the yellow zone criteria in the NSW Between the Flags (BTF), Queensland Adult Deterioration Detection System (Q- ADDS) and ACSQHC Adult Deterioration Detection System (ADDS) chart.

Conclusion

This systematic review found evidence to support the use of the LqSOFA scoring system as a triage tool for patients presenting to the ED and within acute care hospitals. The NEWS or MEWS scoring systems offer slightly improved sensitivity to identify deteriorating patients, however may not offer any advantage over LqSOFA with which they have not been directly compared.

Further research is required to identify the best tools for use in neonatal and maternal populations. An automated alert system embedded within the electronic health record is likely to be a viable alternative to identify patients deteriorating from sepsis in the acute care setting in the near future.

Recommendations

Based on wide consultation and the findings described in the systematic review, the following recommendations are proposed:

- The Commission considers developing advice for the states and territories regarding routine lactate measurement in patients with clinical deterioration or suspected sepsis.
- The Commission consults with the states and territories, associated peak bodies and professional colleges on:
 - the feasibility of implementing LqSOFA (using rapid lactate measurement) as a sepsis screening tool in emergency departments and acute care settings for adults
 - identifying clinically appropriate sepsis detection tools for neonatal and maternal populations.
- The Commission develops resources to support health service organisations to incorporate sepsis alerts and clinical decision support tools into their EHRs and clinical information systems nationally.
- The Commission collaborates with health service organisations to promote the use of sepsis alerts and clinical decision support tools into EHRs and clinical information systems which include:
 - clinically appropriate threshold values for neonates, young children, pregnant and post-partum women, and other high-risk populations
 - recognition and response systems which support the early identification of sepsis.

Introduction

The George Institute for Global Health (TGI) Australian Sepsis Network (ASN) was engaged by the Australian Commission on Quality and Safety in Health Care (the Commission) to undertake a systematic integrated literature review to identify trigger tools that support the early identification of sepsis in settings where health care is delivered. The review aims to support the development of strategies to improve the early identification of sepsis, detect physiological deterioration and expedite clinical interventions to reduce the disease burden.

Purpose

This document outlines the study aims and questions, methodology, quality appraisal of the strength of evidence, results and recommendations in regard to trigger tools for sepsis.

Background

Sepsis is a time-critical medical emergency that arises when the body's response to an infection damages its own tissues and organs leading to failure of multiple organs, and death if not recognised and not treated promptly. The best estimate of the burden of sepsis (from the Global Burden of Disease) reported that there were 49 million sepsis cases and 11 million deaths globally in 2017¹, with 55,000 of those cases and 8,700 deaths occurring in Australia.³ This is higher than previous estimates of the burden of sepsis which were limited to those treated in intensive care units (ICU), and which put the number of cases and deaths at 18,000 and 5,000 respectively.³

In May 2017, the World Health Organisation (WHO) recognised sepsis as a global health priority⁴, and in response, the ASN convened National Sepsis Summit in 2017 produced the *Stopping Sepsis National Action Plan*. Recognising that early recognition and appropriate antibiotic and supportive therapy are currently the only interventions that reduce death and disability from sepsis, the plan recommended improved detection and recognition of sepsis as a leading priority.²

The Surviving Sepsis Campaign recommends that systems have a performance improvement program for sepsis, which includes sepsis screening.⁵ Earlier recognition through the use of triggers and screening mechanisms is associated with earlier treatment.⁵ Notably, the use of sepsis triggers for screening has been associated with decreased mortality.⁶ Early recognition in non-acute and pre-hospital settings is also being linked to faster treatment and improving outcomes.⁷ In hospital, sepsis patients have predominantly been cared for in ICUs. However increasingly, sepsis patients are being cared for in hospital wards which has been associated with clinical deterioration requiring rapid response and resuscitation.^{8,9}

Currently the most effective sepsis trigger tools for Australian healthcare settings is not clear. The burden of sepsis on individuals and health systems warrants further research through a comprehensive review of emerging evidence on potential triggers to assist in the early recognition of sepsis.

Scope and objective

For the purpose of this review, 'trigger tools' were defined as including screening and clinical assessment tools and alerts for detecting clinical risk and deterioration in patients with an infection and/or confirmed sepsis. The review was conducted from the perspective of trigger tools within the broader context of early recognition of patient deterioration in prehospital, ED and acute care hospital settings for neonate, paediatric, maternal and adult populations.

The primary focus was on tools with supporting evidence, efficacy and the potential for routine clinical use across a variety of healthcare settings. Evidence on patient outcomes, change in health service utilisation following implementation of the identified tools, and implementation enablers and barriers were investigated. Minimum requirements for monitoring set out in the National Consensus Statement: Essential elements for recognising and responding to acute physiological deterioration (3rd edition) (Draft and Unpublished) were also considered.¹⁰

Methods

The review comprised three stages:

1. A standalone scoping evaluation of available sepsis trigger review studies
2. A systematic review of primary empirical studies of sepsis triggers
3. An evaluation of congruence of the selected triggers and clinical practice.

The Australian Sepsis Network subject matter expert reference group were consulted to ensure the review was comprehensive and relevant to their respective healthcare settings.

A key methodological assumption is that heterogeneity, within and between patient populations, may confound the causal and inferential relationships in outcome studies thereby limiting generalisability of findings to the broader patient population.¹¹ To address this issue, sepsis recognition triggers need to be clinically relevant, evidence-based, clearly defined, case-mix adjusted and universally applicable.^{12,13} These requirements underpin the need for a systematic integrative review of a diverse range of research designs and methods.^{14,15}

Research questions

In Australia, various physiological deterioration trigger tools are already in use. This review sought to address the following:

1. Identify tools and triggers used for the early identification of sepsis
2. Determine the relevant parameters and what, if any, additional measures should be considered for minimum requirements for clinical monitoring
3. Describe and evaluate the evidence according to a validated level of evidence classification and critical appraisal quality assessment tools
4. Describe and evaluate the evidence within prehospital, ED and acute care settings for neonatal, paediatric, maternal and adult patient cohorts
5. Determine whether sLA, pLA or a surrogate measure, improves the

performance of selected triggers and so should be added to minimum monitoring requirements and any existing tool(s).

Study protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement.¹⁶ The study protocol was registered and approved on the international prospective register of systematic reviews PROSPERO before the start of the study (reference number CRD42020186151).

Search strategy and study selection

Search terms and concepts included sepsis and septic shock; triggers, alerts and screening; early warning, recognition, diagnosis and identification; clinical emergency response systems; and study type. The full search strategy, which was developed with input from subject matter experts (Appendix 1) and is presented in Appendix 2. Databases interrogated included MEDLINE, CINAHL, EMBASE, Scopus and Cochrane Database of Systematic Reviews. Grey literature was sourced from the World Health Organisation, Global Sepsis Alliance, regional and national sepsis agencies, Australian Government Department of Health and Ageing, Agency for Healthcare Research and Quality, National Health Service UK and other authoritative sources.

All studies were independently examined for inclusion by two reviewers and reasons for excluding articles were recorded. Reference lists of identified articles were checked for additional papers. Disagreements between the independent reviewers were resolved either by discussion or referred to a third independent reviewer. This process was followed for all title-abstract and full text screening.¹⁷

Study inclusions

To align with the first definition of sepsis published in 1992¹⁸, all relevant published literature from 1991 to 2020 were included according to the following criteria:

- Study type: systematic reviews, meta-analyses, randomised controlled trials, cohort studies with controls, and diagnostic accuracy
- Setting: prehospital, ED, and acute hospital in-patient including maternity
- Populations: adult, paediatric, neonate or maternal
- Intervention/test: Trigger tools to identify patients with or at risk of sepsis including triggers, tools and readily available blood tests
- Outcomes: diagnostic accuracy, process of care measures including time to diagnosis and antibiotic treatment, mortality, clinical deterioration, unplanned ICU admission, and hospital or ICU length of stay.

Studies were excluded if judged not applicable to the Australian healthcare setting and where the publication was is not available in English.

Data collection and extraction

All studies identified by the search were downloaded to an Endnote 9.0 database. After exclusion of duplicate records, the remaining studies retained for abstract screening were exported into Covidence to facilitate independent reviews.¹

The following data were extracted from each study:

- Author, year and country
- Sepsis trigger and/or tool investigated
- Aim of the investigation pertaining to diagnostic accuracy and the association with clinical process measures and patient outcomes
- Study design
- Health care setting, population and sample
- Sepsis definition and reference standards applied to each study
- Diagnostic accuracy data, extracted where available i.e.
 - Cut-off point or threshold against which diagnostic accuracy was tested, for example, diagnostic accuracy at an sLA level of 2.0 mmol/L
 - Diagnostic sensitivity and specificity, likelihood ratio's, Area Under the Receiver Operating Characteristic (AUROC) and diagnostic ratios.

To determine the optimum trigger tools, sensitivity, specificity, reliability, ease of use, generalisability and impact on process measures and clinical outcomes were analysed. Data accuracy was cross checked by two reviewers. Data definitions and quality appraisal explanatory notes are provided in Appendix 3.

Methodological quality appraisal and evidence rating

The following study appraisal tools for the Joanna Briggs Institute (JBI), relevant to the study type, were used to evaluate methodological quality and level of supporting evidence:

- Systematic reviews – JBI Checklist for Systematic Reviews²
- Randomised controlled trials – JBI Checklist for Randomised Control Trials³
- Cohort observational studies – JBI Checklist for Cohort Studies⁴
- Diagnostic accuracy studies – JBI Checklist for Diagnostic Accuracy Studies⁵

Review Manager (RevMan 5.4)⁶ was used to create the methodological quality summary and to graph risk of bias and applicability concerns for each study type (cohort-diagnostic accuracy studies, cohort–process measure and patient outcome studies, and systematic reviews along

¹ Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org ² The Joanna Briggs Institute Critical Appraisal Tools for use in Systematic Reviews (https://joannabriggs.org/sites/default/files/2020-08/Checklist_for_Systematic_Reviews_and_Research_Syntheses.pdf)

³ The Joanna Briggs Institute Critical Appraisal Tools – Checklist for Randomised Trials (https://joannabriggs.org/sites/default/files/2020-08/Checklist_for_RCTs.pdf)

⁴ The Joanna Briggs Institute Critical Appraisal Tools – Checklist for Cohort Studies (https://joannabriggs.org/sites/default/files/2020-08/Checklist_for_Cohort_Studies.pdf)

⁵ The Joanna Briggs Institute Critical Appraisal Tools – Checklist for Diagnostic Test Accuracy Studies (https://joannabriggs.org/sites/default/files/2020-08/Checklist_for_Diagnostic_Test_Accuracy_Studies.pdf)

⁶ Review Manager Web (RevMan Web). The Cochrane Collaboration, 2019. Available at revman.cochrane.org

with individual tools and biomarkers). The level of evidence available for each trigger tool was then rated and presented using the “Best-Evidence Synthesis” (BES) method,^{19,20} rating the available evidence at five levels; no evidence, conflicting, limited, moderate or strong evidence (Table 1) as per Agency for Healthcare Research and Quality (AHRQ) criteria²¹, and similar to a previous systematic review.²²

Table 1 Best evidence synthesis levels

Level of evidence	Criteria for inclusion in BES
Strong	Generally consistent findings in >2 high quality cohort studies
Moderate	Generally consistent findings in: a) 1 high quality cohort study and >2 high quality case control studies b) >3 high quality case control studies
Limited	Generally consistent findings in: a) Single cohort study b) 1 or 2 case control studies c) >2 cross-sectional studies
Limited	Inconsistent findings in <75% of the trials
No evidence	No studies could be found

Source: AHRQ²¹

Data analysis

Studies of each tool and trigger, which reported at least one diagnostic accuracy parameter, process measure or patient outcome were included. Results are presented by population and healthcare setting. The sample size was calculated by adding sample size of all included studies. In the case of systematic reviews, sample size from relevant studies was used for calculation and if the same study was included both in a systematic review and as a result of the current review, it was included only once. Due to heterogeneity across the studies in terms of study populations, study design, reference standards and analytical techniques, identified during the scoping stage of the review, pooling of individual studies for a comprehensive meta-analysis and performance point estimate was not possible.

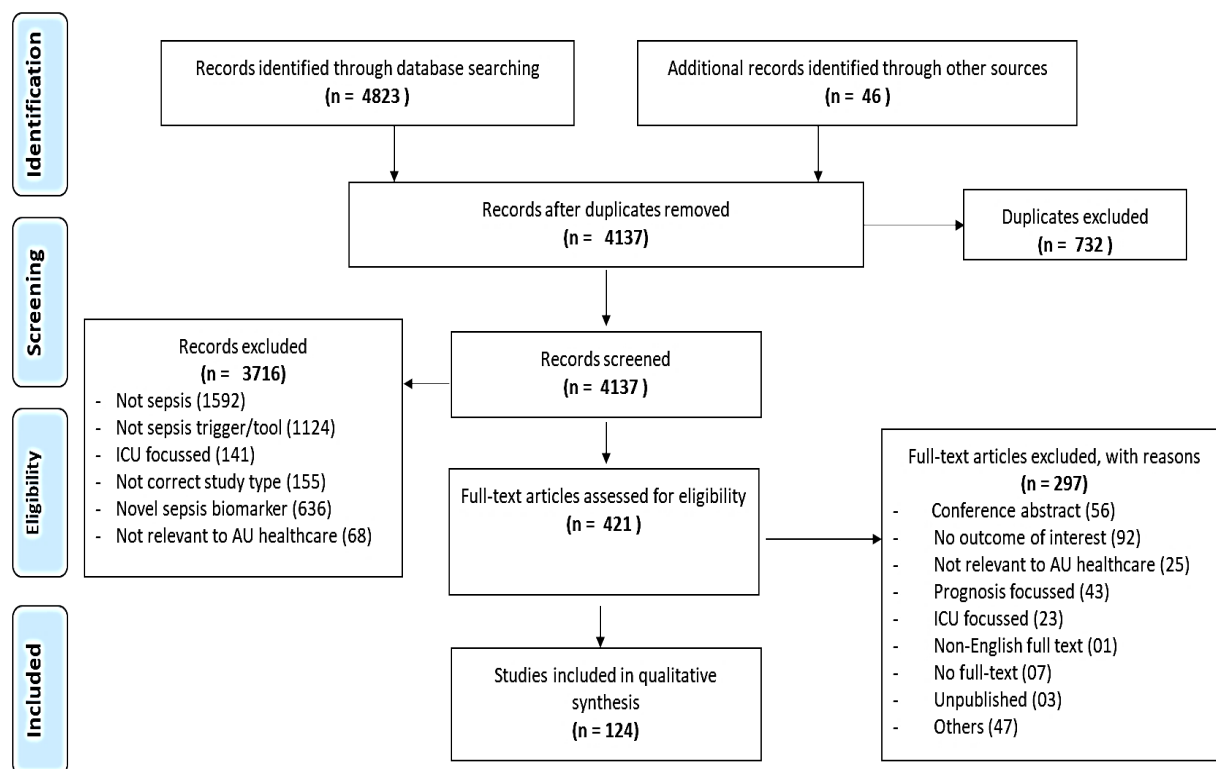
Descriptive analysis was performed on individual studies for each tool with confidence intervals and significance reported where available. Sepsis biomarker studies across multiple cut-off thresholds and studies involving Electronic Health Record (EHR) Machine Learning Algorithms (MLA) were summarised by generating pooled means, ranges, medians and interquartile range (IQR) (where possible) for diagnostic accuracy parameters. The limited number of process measures and patient outcomes reported were evaluated individually.

Optimal sepsis trigger tools ideally possess both high diagnostic sensitivity and specificity, which will be reflected in a strong AUROC.²³ As the focus of this review was on the early identification of sepsis, high sensitivity was considered of prime interest to reduce the risk of missing cases. Lower specificity, meaning a higher rate of false positives, is an accepted feature of clinical early warning systems.

Results

The stepwise systematic review, study screening and assessment procedure applied to the publications resulting from the search strategy is presented in a PRISMA flow diagram (Figure 1).²⁴

Figure 1 PRISMA flow chart of included studies*



* See supplementary information (1) for a web accessibility version of this figure

Study characteristics

Study characteristics for each of the 124 empirical studies included in this review is provided in Appendix 4 and summarised in Table 2. Program evaluation reports on sepsis trigger tools, sourced from the available grey literature, are summarised in Appendix 5.

Studies were conducted across 22 countries, including Northern Europe and the United Kingdom, United States and Canada, and high-income countries in Asia with seven studies conducted in Australia. Study types included 48 prospective and 61 retrospective cohort designs and 15 systematic reviews.

Diagnostic accuracy was the most common investigation (42%) followed by studies combining diagnostic accuracy with process measures and patient outcomes (39%), with the remaining 19% of studies solely investigating process measures and outcomes. Process measures included time to test result/diagnosis, time to antibiotics or treatment, and ease of use. Patient outcome measures were sepsis diagnosis, LoS, ICU admission and mortality in hospital and after discharge.

Table 2 Study characteristics summary

		No. studies	%
Geographic setting	Northern Europe	22	18
	UK	10	8
	USA	66	53
	Canada	5	4
	Asia (high income)	14	11
	Australia	7	6
Study type	Prospective cohort	48	39
	Retrospective cohort	61	49
	Systematic review	15	12
Study outcome	Diagnostic Accuracy	95	48
	Process – time to antibiotics	23	12
	Process – time to treatment	4	2
	Process – ease of use	1	1
	Process – cost	3	2
	Patient centred – length of stay	27	14
	Patient centred – ICU admission	14	7
	Patient centred - mortality	47	24
Sepsis definitions	ICD coding	17	13
	SIRS-based	70	51
	Sepsis 3 (SOFA-based)	38	28
	Other, undefined	11	8
Healthcare setting	Pre-hospital	22	18
	ED	55	44
	Acute care	40	32
	ED and acute care	7	6
Patient population	Adult	102	82
	Paediatric	10	8
	Neonate	6	5
	Maternal	2	2
	All	4	3
Tools assessed	SIRS	9	6
	qSOFA	17	12
	LqSOFA	2	1
	MEWS	4	3
	NEWS	4	3
	Robson	4	3
	Mod Robson	3	2
	BAS 90-30-90	3	2
Triggers assessed	Biomarkers - PCT, CRP, NLCR	40	27
	Lactate – sLA and pLA	20	14
	Others	6	4
EHR	Sepsis alerts and algorithms	35	28

Overall methodological quality of all studies, presented in Appendix 6, indicates low risk of bias and minimal applicability concerns in the cohort studies of diagnostic accuracy, process measures and patient outcomes, but a moderate risk of bias and moderate applicability concerns in the systematic reviews. The broad timeframe of the review from 1991 to 2020, over which time sepsis definitions have been revised and refined, was reflected in the use of early consensus definitions, SIRS and Sepsis 3 (SOFA) definitions applied in the studies, with a small proportion of studies not specifying a sepsis definition.

Studies were conducted across all healthcare settings of interest with a small proportion of prehospital studies including ED as an end point, and similarly a small proportion of combined ED and acute care studies that included ICU as an end point. In these cases, studies were allocated to the preceding health care setting based on the assumption that was where the initial screening, suspicion, onset or diagnosis of sepsis had occurred. The majority of studies across all settings involved solely adults, including three maternal studies. The remainder investigated neonates, paediatrics and combined adults and paediatrics, with a small proportion of studies including all patient cohorts.

Primary interventions included the:

- Systemic Inflammatory Response Syndrome (SIRS) criteria
- quick Sepsis Related Organ Failure Assessment (qSOFA) score
- Lactate plus qSOFA (LqSOFA)
- Modified Early Warning Scoring (MEWS)
- National Early Warning Score (NEWS)
- Robson screening tool
- Modified Robson screening tool
- BAS 90-30-90

Not included for full analysis were a small number of single local protocol and guideline studies with limited available evidence that investigated the:

- Sepsis Severity Score (SSS)
- St. John's Sepsis Agent (SJSA) screening tool
- Sepsis Prediction and Optimisation of Therapy (SPoT) screening tool
- triage Concern for Infection (tCFI) criterion
- Sepsis Obstetric Score (SOS)
- Sequential Organ Failure Assessment (SOFA) score
- Three 100's screening tool
- Prehospital Early Detection Score (PRESEP)
- Mecklenburg Bacterial Infection Scale (MBIS)
- Rapid Emergency Triage and Treatment System (RETTTS)
- Prehospital Severe Sepsis (PRESS) screening tool
- Emergency Severity Index (ESI)
- Mortality in Emergency Department Sepsis (MEDS) score
- Paramedic Initiated Treatment of Sepsis Targeting Out-of-hospital Patients
- Prehospital Antibiotics Against Sepsis Trial (PHANTASi)
- Early Maternal Infection Prompts (EMIP).

Emerging interest in EHR sepsis alert and machine learning algorithm (MLA) clinical decision support applications was evident, representing 25% of all investigations in this review. Triggers primarily investigated were biomarkers Procalcitonin (PCT), C-reactive protein (CRP) and Neutrophil-Lymphocyte Count Ratio (NLCR) and lactate with particular attention on the evaluation of pLA accuracy compared to sLA. See Appendix 7 for further details on components of the sepsis tools and triggers.

Tools and triggers for early identification of sepsis

The literature search strategy identified both individual parameter score criteria and aggregated parameter score tools and triggers for methodological quality assessment and detailed analysis.

Individual parameter score criteria

- Systemic Inflammatory Response Syndrome (SIRS) which requires two or more of the following parameters for diagnosis:
 - Temperature $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$
 - Heart Rate (HR) > 90 beats per minute (bpm)
 - Respiratory Rate (RR) > 20 breaths per min (bpm) or PaCO₂ < 32 mmHg
 - White Blood Cell Count (WBC) $> 12,000$ or $< 4,000 \times 10^9$ or $> 10\%$ bands.²⁵
- quick Sequential Organ Failure Assessment (qSOFA) score which is a bedside prompt that may identify patients outside the intensive care unit (ICU) with suspected infection who are at greater risk of sepsis and an adverse outcome.²⁶ Presence of two or more of the following criteria indicates a positive qSOFA score:
 - RR ≥ 22 bpm
 - Systolic Blood Pressure (SBP) ≤ 100 mmHg
 - Glasgow Coma Scale (GCS) score < 15 .²⁶
- qSOFA with the addition of serum lactate (LqSOFA) with a concentration equal to or greater than 2 mmol/L as a qualifying parameter to improve the performance of qSOFA alone in identifying patients with suspected sepsis at risk of adverse outcomes.²⁷
- Robson screening tool is used to identify sepsis in the pre-hospital setting where a patient has a history suggestive of a new infection and if two of the following criteria are met ²⁸:
 - RR > 20 bpm
 - HR > 90 bpm
 - Acutely altered mental status (cognition)
 - Temperature $> 38.3\text{C}^{\circ}$ or $< 36.0\text{C}^{\circ}$
 - Glucose Blood Serum Level (BSL) < 6.6 mmol/L.
- Modified Robson prehospital screening tool has the additional parameter SaO₂%
- BAS 90-30-90 is a prehospital tool recommended for use in Swedish Emergency Medical services (EMS) guidelines.²⁹ Parameters measured are:
 - RR > 30 bpm
 - SaO₂% < 90
 - SBP < 90 mmHg
- Biomarkers PCT, CRP and NLCR
- Lactate for which higher concentrations associated with an increased risk of adverse patient outcomes, not specific to only sepsis. Its use as a sepsis screening parameter, either individually or in combination with other sepsis

screening tools, is the subject of ongoing investigation and discussion with the Sepsis 3 Taskforce having recommended adding a lactate concentration ≥ 2 mmol/L as an adjunct to qSOFA.²⁷

- EHR sepsis clinical decision support tools using data for real-time alerts or incorporated into MLA's to automate and hasten the identification of sepsis.

Parameter aggregate scores

Two aggregate scoring tools were identified. The Modified Early Warning System (MEWS) is designed to identify deteriorating patients and is based on the principle that clinical deterioration can be seen through subtle changes in a number of parameters as well as large changes within a single variable. The scale is calibrated to different populations and sometimes expanded to include additional parameters. While a score of five or more has been shown to be associated with a higher likelihood of admission to ICU or death, this threshold can be modified to accommodate different patient populations or clinical settings.³⁰

The National Early Warning Score (NEWS) was developed to standardise the approach to detection of clinical deterioration in acutely ill patients in the United Kingdom. The physiological parameters of the NEWS score were derived from existing early warning systems. Previous studies have identified NEWS as high-performance, easily calculable and useful for both ED and inpatient settings.³¹ Table 3 describes the parameters and scores for MEWS and NEWS.

Table 3 MEWS and NEWS aggregated parameter scores

Tools	Parameter							
	Pts ¹	RR min	SpO2 %	HR min	BP mmH	Temp C°	GCS	Additional
MEWS ²	3				SBP ≤ 70			
	2	≤ 8		≤ 40	SBP 71-80	≤ 35	$\leq 14, \leq 9$	Urine <0.5 ml/kg/hr
	1			41-50	SBP 81-100	35.1-36		
	0	9-14		51-100	SBP 101-199	36.1-38		
	1	15-20		101-110		38.1-38.5		
	2	21-29		111-129	SBP ≥ 200	≥ 38.6	≤ 6	
	3	>29		> 129				
NEWS ³	3	≤ 8	≤ 91	≤ 40	SBP ≤ 90	≤ 35		
	2		92-93		SBP 91-100			O2 supplement
	1		94-95	41-50	SBP 101-110	35.1-36		
	0		≥ 96	51-90	SBP 111-219	36.1-38		
	1			91-110		38.1-39	< 15	
	2			111-130		≥ 39.1		
3			≥ 131	SBP ≥ 220				

1. Points score per parameter 2. MEWS score > 5 associated with ICU admission or death 3. NEWS score > 5 associated with ICU admission or death³²

Biomarkers

Three biomarkers were identified, in addition to lactate, to determine their utility in relation to sepsis diagnoses:

- Procalcitonin (PCT) – a widely reported useful biochemical marker to differentiate sepsis from other non-infectious causes of systemic inflammation. However, recent evidence has yielded conflicting results^{33,34}, as reflected by the weak recommendation in the 2016 Surviving Sepsis Campaign (SSC).⁵ Rapid measurement of PCT is not currently available in many Australian hospitals.
- C-reactive protein (CRP) – an acute-phase protein released after the onset of infection but also in response all types of non-infectious inflammation.^{35,36}
- Neutrophil-Lymphocyte Count Ratio (NLCR) – increased with sepsis but also in many other conditions and not extensively investigated as a sepsis screening tool.^{37,38}

The diagnostic performance of PCT, CRP and NLCR and methodological quality appraisal of the associated studies are presented in Appendix 8. Interval ranges associated with the potential for sepsis in the published literature, were used to stratify each biomarker and allocate the relevant studies. Overall there was a low level of bias and minimal applicability concerns. The supporting evidence for all three biomarkers in ED and acute care settings in all cohorts, other than maternal patients, was reliable.

Biomarker sample timing, cut-off values and the relation to blood culture results for the diagnosis of sepsis varied significantly across the studies assessed.³⁹ Therefore the mean cut-off value for each biomarker interval was calculated as the reference against which diagnostic accuracy was assessed. PCT demonstrated the best sensitivity (80%), specificity (72%) and overall performance (AUROC 0.833) of the three biomarkers. However, in clinical practice PCT, CRP and NLCR have not been routinely used for the early recognition of sepsis, but rather as confirmatory diagnostic tests for discriminating infection related inflammation and non-infection inflammation, to track the progress of infections and non-infectious inflammatory states, and to guide duration of antibiotic treatment.³⁹⁻⁴¹ As the focus of this review was on trigger tools that can alert clinicians early to suspected sepsis, these confirmatory biomarker tests were not considered further in this review.

Evidence for sepsis screening tools

The scope of studies, supporting evidence, and level of evidence are summarised in Table 4 with the methodological quality assessment presented in Appendix 9. A total of seven studies (six adult and one maternal involving 21,543 patients) across both prehospital and emergency and acute healthcare settings (three retrospective and three prospective) which compared SIRS and qSOFA were identified.

In these studies, SIRS showed low to moderate sensitivity but was consistently more sensitive than qSOFA and other tools and therefore most relevant to early sepsis identification. In the only maternal study conducted in the acute care setting, SIRS showed high sensitivity and was more sensitive than qSOFA and MEWS, a maternal specific sepsis tool, despite SIRS not being validated in a maternal population. Overall the level and quality of evidence were high with low

risk of bias and minimal applicability concerns.

Table 4 Screening tools, strength of evidence and methodological quality summary

	Author, year	Comparator	Study design	Setting	Pop ⁿ	N	Evidence (level)	Evidence (quality)
SIRS	Askim et al., 2017	qSOFA	Prospective	ED	Adult	1535		
	Bauer et al., 2019	qSOFA, MEW	Retrospective	Acute	Maternal	410		
	Dorsett et al., 2017	qSOFA ± Modified Robson	Retrospective	Prehospital	Adult	152		
	Nieves et al., 2019	qSOFA, NEWS, Triage scr. ESI	Prospective	ED	Adult	2523		
	Prasad et al., 2020	SOFA, qSOFA	Retrospective	ED	Adult	16612		
	Lane et al, 2020	qSOFA, MEWS, NEWS, BAS, Robson	Prospective	Prehospital	Adult	131745	Strong	High
	Haydar et al, 2017	SIRS	Retrospective	ED	Adult	200		
	Rodriguez et al, 2018	qSOFA, Lactate	Retrospective	ED	Adult	3743		
	Sloane et al., 2018	qSOFA, 100-100-100	Prospective	Prehospital	Adult	236		
	Usman et al, 2019	qSOFA, NEWS	Retrospective	ED	Adult	115,734		
	Yasufumi et al., 2019	qSOFA, Q-CRT	Retrospective	ED	Adult	75		
qSOFA	Lane et al, 2020	SIRS, MEWS, NEWS, BAS, Robson	Prospective	Prehospital	Adult	131745		
	Shu et al 2019	Clinical diagnosis	Retrospective	Prehospital	Adult	2292		
	Silcock et al 2019	NEWS –	Retrospective	Prehospital	Adult	1713		
	Sloane et al., 2018	SIRS, 100-100-100	Retrospective	Prehospital	Adult	236		
	Dorsett et al., 2017	qSOFA + Modified Robson	Retrospective	Prehospital/ED	Adult	152		
	Nieves et al., 2019	NEWS, Triage scr. ESI	Prospective	ED	Adult	2523	Strong	High
	Yasufumi et al., 2019	qSOFA+ Q-CRT	Retrospective	ED	Adult	75		
	Filbin et al, 2018	sPOT, tCFI	Retrospective	ED	Adult	19670		
	Rodriguez et al, 2018	SIRS, Lactate	Retrospective	ED	Adult	3743		
	Haydar et al, 2017	SIRS	Retrospective	ED	Adult	200		
	Bauer et al., 2019	MEW, SIRS	Retrospective	Acute	Maternal	410		
Usman et al, 2019	SIRS, NEWS	Retrospective	ED	Adult	115,734			
LqSOFA	Baumann et al, 2019	qSOFA, Lactate	Retrospective	Acute	Adult	3743		
	Shetty et al, 2017	SOFA, qSOFA	Retrospective	ED	Adult	12555	Limited	High
MEWS	Geier et al, 2013	ESI, MEDS	Prospective	ED	Adult	151		
	Bayer et al, 2015	BAS, Mod. Robson	Retrospective	Prehospital	Adult	375	Moderate	Medium
NEWS	Lane et al, 2020	SIRS, MEWS, qSOFA, BAS, Robson	Prospective	Prehospital	Adult	131745		
	Silcock et al, 2019	qSOFA	Retrospective	Prehospital	Adult	1713	Strong	High
	Nieves et al., 2019	qSOFA, Triage scr., ESI	Prospective	ED	Adult	2523		
	Usman et al, 2019	SIRS	Retrospective	ED	Adult	115,734		
Robson	Wallgren et al, 2016	Clinical judgment	Retrospective	Prehospital	Adult	577		
	Wallgren et al, 2014	BAS –	Retrospective	Prehospital	Adult	353	Limited	Low
Modified Robson	Dorsett et al., 2017	qSOFA + Modified Robson	Retrospective	Prehospital	Adult	152		
	Bayer et al, 2015	BAS, MEWS	Retrospective	Prehospital	Adult	375		
	Smyth et al, 2016*	CIS, PRESS, PRESEP, Robson Tool, BAS 90-30-90, MEWS	Systematic review	Prehospital	Adult	49/147,320	Limited	Low

BAS	Wallgren et al, 2014	Robson tool	Retrospective	Prehospital	Adult	353		
	Bayer et al, 2015	Modified Robson tool, MEWS	Retrospective	Prehospital	Adult	375	Limited	Medium

Overall, for SIRS, qSOFA and NEWS the level of evidence was strong and study methodological quality high. Similarly, methodological quality was high for LqSOFA, but the level of available evidence was limited. Of the remaining tools included in this review, MEWS was found to have a moderate level of supporting evidence and medium quality, while the level of evidence for the Robson, Modified Robson and BAS screening tools was limited and study methodology of low to medium quality.

Evidence for screening tools by setting and cohort

Results are presented according to the prehospital setting and combined emergency and acute health care setting to discriminate the settings in which the tools were applied and where the subsequent supporting body evidence was available.

Prehospital

A total of nine studies relating to SIRS, qSOFA, Robson, Modified Robson and BAS 90-30-90 tools were identified consisting of two prospective, six retrospective and one systematic review study of sepsis tools in prehospital settings (Appendix 10). The most assessed tool was qSOFA with five studies (one prospective and four retrospective involving 136,138 patients) followed by three studies for SIRS (one prospective and two retrospective involving 132,133 patients).

Only a small number of studies investigated tools specifically developed for prehospital setting. Three retrospective studies (one systematic review and two retrospective involving 576 patients, were identified for the modified Robson tool followed by two studies each for NEWS (one each prospective and retrospective involving 133,458 patients), BAS 90-30-90 (two retrospective involving 728 patients) and Robson (two retrospective involving 930 patients). Only one study was identified for MEWS (retrospective involving 375 patients). All studies were in the adult population with no studies identified in maternal, paediatric and neonatal cohorts.

All identified studies for qSOFA and SIRS used a cut-off of more than or equal to two for their respective score and a low sensitivity for identifying sepsis was found for both qSOFA (7.0 to 42.9%) and SIRS (10.0 to 45.0%) in the prehospital setting. Amongst tools specially developed for the prehospital setting, the Robson screening and BAS 90-30-90 demonstrated consistently high sensitivity for the identification of sepsis with sensitivities of 63 to 75% and 62 to 70% respectively in each of the 2 studies assessed. While the sensitivity of modified Robson screening tool ranged from a high sensitivity of 95%, the highest reported of any sepsis tool, in one study down to 30-46.5% in the other two studies.

The predictive ability of NEWS for sepsis identification was denoted by C-stats (0.76), an alternate measure of diagnostic accuracy and was higher than qSOFA, SIRS, BAS, Robson tool. In addition, NEWS showed high performance with an AUROC 0.7-0.8 in the

prediction of adverse outcomes. The only MEWS study reported a high sensitivity of 74% for identifying sepsis. Few studies reported impact of qSOFA, NEWS, Robson tool or modified Robson tool on patient outcomes, with no patient outcomes reported for either for SIRS or BAS 90-30-90.

Ease of implementation and use was not explored comprehensively for any tools with some commentary noted on the ease of implementation of qSOFA as it comprises of only vital signs unlike SIRS, which also includes WBC measurement and Robson screening tool which requires BSL to be measured. As such, given both BAS 90-30-90 and qSOFA don't require any laboratory parameters, they are likely to be slightly easier to implement and use by clinicians.

Emergency and acute care

Five sepsis tools were assessed in a total of 12 studies (two prospective and 10 retrospective) in ED or the acute care (Appendix 11). Both SIRS and qSOFA were the two most commonly assessed tools with eight studies each (two prospective and six retrospective involving 140,832 patients and one prospective and seven retrospective involving 142,507 patients, respectively) followed by two studies each for LqSOFA (both retrospective involving 16,298 patients) and NEWS (one each prospective and retrospective involving 118,257 patients) and one prospective study for MEWS involving 151 patients. All identified studies were in the adult population with one investigation in the maternal cohort.

Studies of SIRS criteria at a cut-off equal or greater than two criteria demonstrated high sensitivity (56.4 to 81.0%) and moderate to high specificity (40.0 to 86.4%), while qSOFA at the same cut-off demonstrated low sensitivity (15.4 to 67.4%) to identify sepsis but with high specificity (86.2 to 100%). In one study, the sensitivity of qSOFA for the identification of sepsis and adverse outcomes was higher at a cut-off of equal to or greater than 1 than a cut-off of greater than or equal to two.

The addition of lactate to qSOFA improved its ability to identify the risk of adverse outcomes but its impact on sensitivity for sepsis identification was not assessed. When qSOFA was used in combination with Quantitative Capillary Refill Time (Q-CRT) its sensitivity for sepsis identification increased from 67% to 83%.

The highest sensitivity for sepsis diagnosis was observed for the NEWS at the cut-off equal or greater than four (71.8 to 88.1%) along with high specificity (84.8 to 90.2%). NEWS also demonstrated high sensitivity (92.9%) and good predictive ability for prediction of sepsis-related mortality and ICU admission.

Overall level and evidence of quality was strong and high, respectively for qSOFA, SIRS and NEWS and limited-moderate and low-medium for LqSOFA and MEWS. Ease of qSOFA implementation, which is comprised of vital signs only, was assessed. This feature was not explored in relation to other sepsis trigger tools.

Lactate

Lactate is a non-specific marker of illness severity in acutely ill patients and has proven value in predicting outcomes following sepsis.⁴² The evidence pertaining to lactate as a trigger for detecting sepsis is presented in Appendix 12. Table 5 provides a summary of the studies

identified with the methodological quality appraisal presented in Appendix 13. Overall the level of evidence was strong and quality medium to high with low risk of bias and negligible applicability concerns.

Table 5 Lactate level of evidence and study methodological quality summary

Mode	Author, year	Study Lactate	Study Design	Setting	Population	N	Level of Evidence ¹	Quality
sLA	Shetty, 2018	1, 2, 3, 4	Retrospective	ED	Adult	12349	Strong	High
	Ljungstrom, 2017	3	Prospective	ED	Adult	1572		
	Berkman, 2009	4	Prospective	ED	Adult	1419		
	Visveswari, 2019	1.55	Prospective	Acute	Adult	126		
	Hunter, 2013	1.7	Prospective	Acute	Adult	201		
	Baumann, 2019	2	Retrospective	Acute	Adult	2584		
	Rodriguez, 2019	2	Retrospective	Acute	Adult	3743		
	Baumann, 2019	4	Retrospective	Acute	Adult	2584		
	Rodriguez 2019	4	Retrospective	Acute	Adult	3743		
	Ismail 2015	2.4	Prospective	Acute	Adult	26		
Reed, 2013	2.04	Retrospective	ED	Paediatric	283			
pLA	Morris (13), 2014	ns	Prospective	Prehospital	Adult	59	Strong	Medium
	Swan, 2018	2	Retrospective	Prehospital	Adult	155		
	Boland, 2016	4	Prospective	Prehospital	Adult	112		
	Morris (10), 2015	ns	Prospective	ED	Adult	160		
	Morris (14) 2014	ns	Retrospective	ED	Adult	865		
	Morris (15), 2014	ns	Retrospective	ED	Adult	1430		
	Morris (16), 2010	ns	Retrospective	ED	Adult	210		
	Morris (17), 2007	ns	Prospective	ED	Adult	92		
	Karon, 2017	1.3	Prospective	ED	Adult	501		
	Contenti, 2014	2	Retrospective	ED	Adult	103		
	Singer(a), 2014	2	Prospective	ED	Adult	160		
	Singer (b), 2014	2	Retrospective	ED	Adult	258		
	Goyal, 2010	2.15	Prospective	ED	Adult	238		
	Singer, 2014	4	Retrospective	ED	Adult	258		
	Gaieski, 2013	4	Prospective	ED	Adult	24		
	Morris (12), 2011	ns	Prospective	ns	Paediatric	247		

1. AHRQ²¹

Thirty-five studies of sLA and pLA tests were initially identified but on further assessment 16 were excluded due to no specific result reported on the diagnostic accuracy of lactate, process measures or patient outcomes as these studies investigated screening tools in which lactate was one of several components. The remaining 19 studies included 10 prospective, 8 retrospective cohort studies, and one systematic review that included results from seven individual studies (four prospective and three retrospective) relevant to this review.

Subsequently, the results of 25 individual lactate tests, each with specific cut off thresholds, were reviewed. Eleven sLA test results were reported from four ED studies, consisting of three adult cohorts and one paediatric cohort (sample range 286 to 12349), and seven acute care studies involving adults (sample range 26 to 3,743). Results of 16 pLA tests were also reported from three adult prehospital studies (sample range 59 to 155), 12 adult studies in ED (sample

range 24 to 1430) and one paediatric study (sample 247) with no setting specified. No maternal or neonate lactate studies were identified.

Lactate cut-off thresholds below 2.0 mmol/L or equal to and above 2.0 mmol/L were used to group results based on the significant association between exceeding the threshold of 2.0 mmol/L and the diagnosis of sepsis and subsequent organ dysfunction as previously reported.^{27,43} Stratification of results by pLA and sLA, lactate cut-off level, setting and cohort provided only a small number of studies for analysis in each group preventing calculation of median results therefore individual results, means, ranges, odds ratio's and 95% confidence intervals are presented where available.

Lactate point of care test results at pLA \geq 2.0 mmol/L in adults in the prehospital setting was found to over-estimate the sLA (mean pLA 3.0 [IQR = 2.0] vs. sLA 1.95 [IQR =1.7]; $t(267) = -3.67$; $p < 0.001$). However, in the prehospital setting a high pLA specificity (91%) warrants its use in triggering pre-notification to ED of critically unwell patients, despite its low sensitivity (19%).

In the ED, a pLA $<$ 2.0 mmol/L was deemed to have limited utility to predict sepsis due to low sensitivity (55.1%) and specificity (62.7%), AUROC of 0.63 and DOR 1.44; $p = 0.05$. At a lactate of \geq 2.0 mmol/L, in both adults and paediatrics in ED, pLA sensitivity ranged widely from a low of 7.0% to a high of 81%, with specificity ranging from 42 to 98%, and a mean AUROC of 0.646 further suggesting moderate performance overall.⁴⁴ This was observed despite consistently high and statistically significant correlations between pLA and sLA ranging from $r = 0.90$ to 0.99 reported in four ED studies.

Some improvement in ED and acute care process measures were reported with statistically significant reductions in time to test result or diagnosis (mean reduction 79 min [6 to 151 min]; $p < 0.05$). Diagnosis within one hour was more likely (pLA OR 4.6; $p < 0.05$) and antibiotics to be administered (pLA 25.1% vs sLA 15.0%; $p = 0.007$). Similarly, in comparison with sLA at a level of \geq 2 mmol/L, the use of pLA was associated with reduction in hospital mortality (pLA 6% vs sLA 19%; $p = 0.02$). Mortality risk was reduced using pLA (OR 0.60; $p = 0.001$) and (OR 0.71; $p = 0.006$) as was hospital length of stay (pLA 5.8 vs. 7.5 days sLA; $p = 0.05$), though lactate cut off levels were not specified in regard to the length of stay studies.

Eleven sLA studies (lactate cut off \geq 2.0 mmol/L) investigated diagnostic accuracy primarily in adults within ED and acute care settings, with one paediatric study. Limited investigation was available on any association with process measures and patient outcomes, and again no maternal or neonate studies were identified. Three studies involved an sLA cut-off less than 2.0 mmol/L with one adult acute care study reporting a sensitivity of 67.2%, specificity 47% and AUROC 0.577, and another similar study finding low performance in predicting mortality (AUROC 0.61). However, one large Australian study conducted in ED, found even a low sLA of 1 mmol/L was associated with higher mortality risk (OR 2.93; 95%CI 2.08-4.13). Overall, most evidence was related to studies of sLA cut-off \geq 2 mmol/L with seven diagnostic accuracy studies permitting assessment of the median sensitivity 61.5% (IQR = 54), specificity 71.6% (IQR = 27) and AUROC 0.73 (IQR = 0.17), which suggested moderate performance.

Surrogate lactate measures

A study of the relationship between $sLA \geq 2\text{mmol/L}$ and a range of vital signs in paediatric ED demonstrated a small positive correlation with heart rate ($r = 0.35$; $p=0.0001$), respiratory rate ($r = 0.30$; $p=0.0001$) and WBC ($r = 0.21$; $p=0.004$); a small negative correlation with HC03 ($r = 0.35$; $p=0.001$) and no significant correlation with temperature or $\text{SpO}_2\%$ suggesting these parameters are not a strong predictor of sLA.

However, one large adult study conducted in ED, which examined the correlation between anion gap and $sLA > 4\text{ mmol/L}$, found a moderate correlation ($r = 0.40$; $p<0.001$), which may suggest anion gap as a potential surrogate measure for sLA, warranting further prospective studies.

Parameters for the early identification of sepsis

The National Consensus Statement: Essential elements for recognising and responding to acute physiological deterioration (3rd ed) (NCS)¹⁰ lists minimum requirements for monitoring physiological parameters and emphasises the importance of determining the reason for acute physiological deterioration. Particular consideration was given to congruence between the evidence identified in this review for vital sign parameters and the minimum requirements for patient monitoring plans for early detection of physiological deterioration as specified in the NCS.

The broad scope of available evidence identified, across a range of health care settings and population cohorts, enabled congruence with current clinical best practice and recommended standards for monitoring to ensure early detection of deterioration to be assessed. A matrix was created of sepsis trigger tool parameters, plus additional triggers, and those currently collected in system-wide patient observation charts and sepsis specific pathways (Table 6). These parameters were then assessed for congruence with those recommended minimum monitoring requirements in the NCS, and to identify any additional parameters that would improve the utility of the minimum monitoring requirements.

On comparison, the minimum monitoring requirements proposed in the NCS demonstrated strong congruence with the parameters in the sepsis screening tools, the sample of early warning observation charts currently in use⁴⁵⁻⁴⁷, and with the sample of validated sepsis screening and management pathways currently in use system-wide in New South Wales. Based on the available evidence for sepsis screening tools and high congruence with current best practice supports no additional vital sign parameters are required for the proposed minimum monitoring requirements.

However, the evidence pertaining to sepsis identification tools and current best practice sepsis pathways in use in Australia and the United Kingdom (Appendix 14) does support the addition of lactate to the minimum monitoring requirements as an adjunct to sepsis screening when a specified threshold is breached. Point of care testing in emergency and acute care is supported by the evidence for diagnostic accuracy, qualitative evaluation of system-wide application and the ease of use.⁴⁸⁻⁵⁰ Though in the prehospital setting, the evidence for point of care testing is weak with concerns around diagnostic accuracy.⁵¹

Sepsis Pathway Paediatric ¹³			Late sign	Rash	Periph. perf ⁷	sLA	Low urine	Parent concern
Sepsis Pathway Newborn ⁸	Nasal flare		Late sign	Rash	Periph. perf ⁷		GIT	Bulge Fontanelle

1.3rd NCS; 2. New confusion or behaviour change; 3. sLA = serum Lactate; 4. AVPU = Alert, Verbal, Pain, Unresponsive; 5. ACSQHC General Observation Chart (Adult); 6. NSW Between the Flags - General Observation Chart (Adult); 7. Poor peripheral perfusion; 8. NSW CEC Sepsis Pathway ; 9. BE = Base Excess; 10. Temperature may fluctuate in sepsis; 11. Modified Early Obstetric Warning System; 12. Australian Capital Territory; 13. QEC – Queensland Children’s Hospital

The minimum requirements for patient monitoring plans for early detection of clinical deterioration, as currently stated in the draft NCS¹⁰, propose RR, SaO₂%, HR, BP, temperature, level of consciousness and cognition. Improving the precision of these parameters by specifying significant thresholds would enhance the sensitivity of the proposed parameters, foster alignment with existing sepsis screening pathways and patient observation best practice (Appendix 15) and facilitate a shift towards system-wide standardisation, where suitable, across emergency and acute care settings, and adjusted for newborn, paediatric and maternal cohorts. The benefits of this approach has recently been demonstrated by the program evaluation of the Safer Care Victoria ‘Think sepsis. Act fast.’ scaling collaboration’ project⁵², which achieved sustainable system-wide change resulting in significant improvements in patient outcomes.

EHR – Early Warning Algorithms and Machine Learning

Table 7 summarises the evidence assessed for the use and effectiveness of EHR-MLA screening tools with the overall level of evidence considered to be strong in the adult population with low risk of bias and applicability concerns, while in paediatric population evidence level was medium with low risk of bias and applicability concerns (Appendix 16).

Table 7 Summary of evidence for EHR-based sepsis trigger tools

	Studies N (Pooled sample size)	Diagnostic accuracy – median (range)			Other outcomes	Evidence	
		Sn%	Sp%	Others		Level	Quality
ADULT							
ED	08 (1,055,217)	79.5 (74-80.1)	93.1 (76.2-.95.3)	AUROC Sepsis 0.86-0.92 Severe sepsis 0.87 Septic shock 0.99 PPV% 4.9-5.8 NPV% 99.9 C-stats 0.82-0.88	28-d Mortality: 17.7% (pre) to 15.2% (post) 90d mortality: 24% (pre) vs 22.8% (post) LOS: 7 (pre) vs 6 (post)	Strong	High
Acute inpatients	15 (3,083,983)	67 (17-100)	82 (69-98)	AUROC 0.89-0.97 PPV% 10- 50.3 NPV% 90.7-100 +LR: 5.26-13.0 -LR: 0.06-0.29	Mortality: 9-47% (pre) to 4.2-27% (post) Tm to Ab: 3.9 hour	Strong	High
Mixed	04 (4,262,372)	80 (36.2-84)	75 (18.1-99.6)	AUROC 0.83-0.97 PPV% 40.7-53.8 NPV% 76.5-1-100 DOR 3.15-14.79		Moderate	High
PAEDIATRIC							
ED	03 (206,618)	86.2 (81-92.1)	89 (83.4-99.1)	PPV% 2.5-25.4 NPV% 99.9-100 AUROC 0.88		Moderate	High
ED/Acute inpatients	02 (32,252)	72-75 (73.5)	91.8-94 (92.9)	DOR 64.44		Moderate	High

ADULT/PAED/NEON							
ED	02 (7625)	17-99 (58)	21-99 (60)	PPV% 50.23 (44.7-55.7)		Moderate	High
				NPV% 97.5 (95-100)			
ED/Acute inpatients	01 (21183)				Mortality OR: 0.76 LOS => 7d OR: 0.93 Timely Abs OR: 1.71	Low	High

* p=0.14; **p=0.01; ***p=0.001; #p=0.26

A total of 35 studies (eight prospective, 23 retrospective and four systematic reviews; sample size 8,669,250) were identified in which various EHR-based tools were assessed for sepsis diagnosis and/or prediction of sepsis-related adverse outcomes, and of these, seven studies used EHR algorithms.

Most studies involved adults (total 27; 15 in acute care with pooled sample size of 3,083,983; and eight in ED with pooled sample size of 1,055,217 and four in combined settings with pooled sample size of 4,262,372). Five paediatric studies were conducted (three in ED with pooled sample size of 206,618 and two in combined settings with pooled sample size of 32,252) and three studies were conducted in mixed adult and paediatric populations (two in ED with pooled sample size of 7625 and 01 in combined settings with sample size of 21,183). There were no studies identified in maternal populations.

Overall, acute care was the most common setting with 15 studies followed by 13 in ED and seven in combined with no study in prehospital setting. A moderate to high median sensitivity (58-86.2%) and median specificity (60-93.1%) was noted for the range of EHR-based tools across various healthcare settings and populations. However, there was wide variation across the studies. The overall quality of evidence was high in all patient populations with a strong level of evidence in adults and low-moderate in paediatric and neonatal population.

Discussion

Sepsis is life threatening organ dysfunction due to a dysregulated host response to infection. The diagnosis of sepsis remains a clinical one as there are no definitive diagnostic tests. There is no specific pharmacological treatment for sepsis and reducing the burden of disease from sepsis requires early recognition, appropriate antimicrobial therapy and supportive care. Delays in recognition of sepsis and in starting appropriate treatment are recognised causes of preventable death and disability around the world, including in Australia. Instituting appropriate screening and track and trigger systems to improve recognition and reduced time to treatment reduces preventable death and disability.

Sepsis occurs in people of all ages but with two age-related peaks, one in the very young (neonates and young infants) and again in the elderly. People with other underlying diseases including cancer, diabetes, cardiovascular, renal and respiratory disease are at increased risk of sepsis and of adverse outcomes as a result of sepsis. Socially disadvantaged groups, including Aboriginal and Torres Strait Islander peoples are also at increased risk. It also affects patients in all healthcare settings including those presenting to primary and secondary care and patients already being treated in hospital for other conditions. Screening and track and trigger systems are needed for all at risk populations and in all healthcare settings.

The presence of infection is a prerequisite for the diagnosis of sepsis. A confirmed diagnosis of

infection relies on isolation of the infecting microorganism or evidence of the presence of a specific antigen or antibody response. A detailed discussion of the diagnosis of infection is outside the scope of this review but the following points are relevant. The diagnosis of infection may be obvious, such as when a patient presents to an emergency department with classic signs and radiological evidence of community acquired pneumonia, or the classic rash of meningococemia.

In other cases, and populations, the presentation may be non-specific and subtle, notably in young infants and in the elderly. Screening and track and trigger systems are based on physiological and laboratory abnormalities occurring in response to infection but must be combined with appropriate prompts and health care worker education to ensure that sepsis is considered as a potential cause of these abnormalities.

Features of track and trigger tools and systems

The physiological abnormalities accompanying sepsis are consistently observed in the cardiovascular system (systemic arterial pressure and heart rate), respiratory system (respiratory rate and oxygenation), neurological system (confusion, agitation, or reduced level of consciousness), renal function (manifesting as no urine output) and altered body temperature (fever or hypothermia). Laboratory abnormalities accompanying sepsis may be evident in relation to all organ systems. Those most commonly recognised include changes in white blood cell count (Increase in neutrophil count and lymphopenia and the presence of immature neutrophils in peripheral blood), urea and creatinine, platelets and coagulopathy, liver function tests, and measures related to acid base status including serum lactate and base deficit. Specific biomarkers used to monitor infection or inflammation include C reactive protein, procalcitonin and the neutrophil to lymphocyte ratio.

Track and trigger tools may include any combination of physiological and laboratory abnormalities. A positive score or alert may rely on abnormality in a single parameter (for example medical emergency team calling criteria), multiple parameters (for example the quick sequential organ failure assessment score; qSOFA) or exceeding a threshold score in a multi parameter aggregate scoring system, for example, NEWS.

The performance of track and trigger tools can be assessed by their ability to accurately identify sepsis, most commonly reported through assessment of sensitivity, specificity and AUROC under the receiver operator characteristic curve, but also by their ability to improve healthcare delivery (for example, time to resuscitation or administration of antibiotics) and to improve patient outcomes through measurable reductions in morbidity and mortality.

Given the harm that results from delayed diagnosis and treatment of sepsis, track and trigger systems should have high sensitivity (low rate of false negatives) even if this is at the cost of lower than ideal specificity (higher false positive rate). Blood tests incorporated in to track and trigger systems should be available through point-of-care testing to avoid the obligatory delay in awaiting results from a central laboratory.

Single parameter systems

The review identified no single parameter screening or trigger systems for sepsis.

Multiple parameter systems

There are a number of multi-parameter screening and trigger systems for sepsis in common use, most notably systems based around the SIRS criteria and qSOFA. The number of variables included in multi-parameter systems varies between three and six and are those related to the cardiovascular, respiratory and neurological system plus temperature and, for SIRS, the WBC count. Although the cut off or threshold values for individual parameters vary slightly between systems, they are generally very similar and are just above or below the normal physiologic range for a healthy adult. The addition of serum lactate measurement to the physiological variables has been investigated in a number of studies and generally improves the performance of the system.

Aggregate scoring systems

Aggregate scoring systems include these SOFA, NEWS and MEWS and variations for different populations such as paediatrics (PEWS) and Modified Early Obstetric Warning System (MEOWS). The SOFA score forms part of the diagnostic criteria Sepsis 3 that requires central laboratory investigations making it unsuited as a screening or track and trigger system.

In the UK, a standardised national early warning score (NEWS) used, while MEWS and its variants are used in many locations in different countries. Aggregate scoring systems can provide multiple threshold levels at which increasing levels of urgency are indicated but at the cost of increased complexity.

Performance of screening and track and trigger tools and systems

The SIRS criteria have been used to screen and identify sepsis since 1992.⁵³ In the 1992 definition the presence of infection and SIRS, when two of the criteria were met, was called sepsis and when organ dysfunction was present, it indicated severe sepsis. This definition has been superseded and there is general acceptance that organ dysfunction must be present to indicate sepsis.

In 2016, due to concerns about the low specificity of SIRS the Sepsis-3 Task Force introduced a definition based on SOFA but recognising that components of the SOFA score were not commonly available outside of intensive care units recommended qSOFA for sepsis screening.²⁶ The qSOFA score is a readily available bedside tool without laboratory tests however, while it has higher specificity than SIRS, it has lower sensitivity which may limit its use as a bedside screening tool.

The addition of increased serum lactate to qSOFA produces the LqSOFA score which can be readily available in all healthcare setting and has similar sensitivity to the SIRS criteria. The Sepsis-3 task force emphasised that neither qSOFA nor SOFA is intended to be a stand-alone definition of sepsis and failure to meet two or more qSOFA or SOFA criteria should not lead to deferral of investigation or treatment of infection or to a delay in any other aspect of care deemed necessary by the treating practitioners.⁵⁴

Multi-parameter aggregate scoring systems such as MEWS, Early Warning Scoring System (EWSS), and NEWS, were developed to screen patients at high risk of deterioration. In direct comparisons with SIRS and qSOFA they show slightly improved performance at the cost of

increased complexity and depending on the cut off value used. They have not been compared directly with LqSOFA.

Different healthcare settings

The early detection of sepsis is important in all health care settings. As 80% of sepsis arises in the community, with the remaining 20% arising de novo within the hospital system, the first point of contact with health care workers in primary care, ambulance services or emergency departments is a critical setting for the early detection of sepsis.

This review found no compelling evidence for the use of specific scores or triggers in different health care settings. Additionally, workforce mobility between different health care settings makes it desirable that the same or a similar system is used across the health care system. A notable exception to this principle is patients being treated in intensive care units where additional detailed physiologic and laboratory data are available. Given the ready availability of the variables of the qSOFA score and ability to add point of care lactate to increase sensitivity to match that of other scores, the LqSOFA score is recommended for use across the healthcare system.

Different populations

Maternal Sepsis

The results of this systematic review highlighted a major gap in the evidence that pertains to screening for sepsis in pregnancy. Only three studies were identified from ED and acute care settings including a:

1. A small retrospective audit (n= 73) to evaluate Early Maternal Infection Prompts (EMIP), a suite of four bedside clinical criteria used to identify maternal infection before sepsis develops which concluded EMIP was an effective tool but highlighted the gap in prospective large-scale maternal research.⁵⁵
2. A retrospective study (n=82:328) that compared SIRS >2, qSOFA >1 and MEWS >1 scores, with conflicting results indicating that MEWS performed best overall but SIRS was more sensitive, benefiting early sepsis screening but lacking robust evidence specific to the maternal cohort.⁵⁶
3. A prospective assessment of the Sepsis Obstetrics Score (SOS) to predict organ dysfunction in pregnant and post-partum women with suspected sepsis which focused primarily on prognoses as opposed to early screening for sepsis.⁵⁷

Subject matter experts engaged for this review advised that pregnancy presents a unique physiological milieu, which results in unique responses to disease processes, including sepsis. Yet it can be difficult to diagnose sepsis in pregnancy because physiological changes of pregnancy can mimic the signs of sepsis.⁵⁶ Recognising these alterations and modifying diagnostics and interventions is essential to optimal care of unwell pregnant women.

Much of the current literature excludes, or does not consider, the unique physiological responses of pregnancy, and guidance on management of sepsis in obstetrics care is often derived from research on non-pregnant adults. Moreover, the pathogens causing sepsis in

pregnant women can differ from those in other populations, both due to the immunologic alterations associated with pregnancy, and the anatomical specifics of gestation, labour and birth that increase the likelihood of upper genital tract infections with commensal organisms from the gut. Ultimately, observational studies and interventional clinical trials are needed to assess the implementation of specific triggers and tools for the identification and management of sepsis in this unique population.

Numerous measures can be used to screen for sepsis but consideration needs to be given to the altered physiology of pregnancy.⁵⁸ The Society of Obstetric Medicine Australia and New Zealand (SOMANZ) Guidelines⁵⁸, for the Investigation and Management of Sepsis in Pregnancy, recommend that maternal populations be:

- Screened for sepsis using the obstetrically modified qSOFA (omqSOFA) score based on a respiratory rate ≥ 25 min, mental status (any non-alert state) and systolic blood pressure < 90 mmHg; and
- Assessed for any evidence of end organ dysfunction by reviewing for signs such as oliguria or by using omSOFA (increase > 2) with particular attention to hypotension despite fluid resuscitation and the presence of an elevated serum lactate⁵⁸

The qSOFA score is derived from retrospective data validated in a heterogeneous population, with an average age of 61 years, of which half were male and its extrapolation to pregnant and postpartum women should be undertaken with caution as woman's gravid state will significantly impact several of the variables in qSOFA.⁵⁸ The omqSOFA score is derived from SOFA and is considered an effective sepsis screening tool in maternal populations.⁵⁴

Despite these strategies maternal sepsis remains a preventable cause of direct maternal death and a key barrier to the evolution of maternal sepsis screening and interventions is lack of consensus on the definition of maternal sepsis. Standardising the criteria for maternal sepsis optimises clinical audit and research to facilitate evidence-based evaluation of different clinical parameters and biomarkers in the early recognition of maternal infection and sepsis.⁵⁹

Neonates, infants and young children

Neonates, infants and young children have a higher incidence of infection and sepsis than other age groups with the exception of the very elderly. Approximately 500 children are treated for sepsis in Australian paediatric intensive care units each year and around 50 children die of sepsis. Infants and young children suffer repeated episodes of viral infections as they have little or no prior exposure or immunity. Preschool and school-age children also mix closely with each other, often with direct physical contact, leading to infection outbreaks in preschool and school facilities.

Normal ranges for vital signs change significantly as children age meaning that no single abnormal threshold is appropriate for all children; thresholds have to be age adjusted. The identification of sepsis is further complicated in the very young by the non-specific nature of the early symptoms. This review identified 16 eligible studies conducted in paediatric or neonatal populations. However, other than EHR tools, no sepsis screening tool specific to paediatrics and neonates was identified in any setting, though one study each for sLA and pLA reported an associated reduction in mortality and LOS.

In Australia, systemwide sepsis pathways specific to paediatrics and neonates have been implemented in several states^{9,10} with components and parameters that align closely with the NCS minimum monitoring requirements and LqSOFA (see Table 6 and Appendices 14 and 15). These pathways reflect current best practice in Australia and align with international best practice for sepsis screening and clinical escalation of care, such as the tools provided by the UK Sepsis Trust¹¹ based on guidance provided by the National Institute for Health Care Excellence.⁶⁰ In the absence of evidence to support the adoption of an alternative sepsis trigger tool in paediatric and neonatal populations, the existing sepsis pathways should be considered for national implementation following standardisation, where possible, of the parameters measured and age specific thresholds.

Lactate

Lactate is a normal product of metabolism and a non-specific marker of acute illness when the serum concentration is increased. On its own, it does not indicate either infection or sepsis.

Serum lactate concentration is typically above the normal range in patients with severe sepsis or septic shock and is an independent predictor of mortality in patients with infections.⁶¹ The degree by which lactate concentration is increased is a marker of severity early in the course of sepsis. Persisting hyperlactatemia is associated with an increased risk of death and lactate concentration may be monitored to assess response to treatment.

The advent of point-of-care lactate testing has made it feasible to include lactate in screening and trigger systems for sepsis. Including lactate improves the sensitivity of qSOFA in the Emergency Department and improves the predicted value of SIRS.

Evidence for the use of lactate as an individual trigger for the early identification of sepsis in the prehospital setting is weak with pLA being the only feasible mode. High specificity in this setting helps to identify critically unwell patients and should prompt urgent transfer to a higher level of care.

Evidence for its use in ED and acute care to indicate more severe severity of illness is moderately strong with good diagnostic accuracy and associated with improved process measures and outcomes when used with a clinical screening tool based on SIRS or qSOFA e.g. LqSOFA. The NSW CEC sepsis pathways reflect this approach and has been validated in Australian ED and acute care settings for newborn, paediatric, maternal and adult cohorts.

Evidence supports the use of lactate in ED and acute care settings as a standard component when assessing clinical deterioration. Its use would increase the sensitivity of other scoring systems, it is easy to use and is applicable across the healthcare system.

Evidence for the use of surrogates for lactate measurement is limited to small studies of base excess and anion gap; both require a blood sample similar to lactate and offer no benefit over measurement and monitoring of lactate.

⁹ <http://www.cec.health.nsw.gov.au/keep-patients-safe/Deteriorating-patient-program/Sepsis/sepsis-tools>

¹⁰ <https://www.childrens.health.qld.gov.au/guideline-sepsis-recognition-and-emergency-management-in-children/>

¹¹ <https://sepsistrust.org/wp-content/uploads/2018/06/Inpatient-u5-NICE-Final-1107-2.pdf>

Observation and response charts

State based observation and response charts currently in use have thresholds for a response to respiratory rate, systolic blood pressure and neurological status (see Table 6). These thresholds are closely aligned or identical to the thresholds in the qSOFA score, for example, those in use NSW¹² and QLD¹³ (see Appendices 14 and 15). As a result, these charts can readily be adapted to indicate a positive qSOFA score.

As infection is a prerequisite for the occurrence of sepsis, rapid diagnosis and treatment depends on health care workers considering infection as a potential cause for any patient deterioration. The review does not support the addition of any new parameters to the routine observation of in-patients but where infection is considered a possible or likely cause of deterioration, adding a (rapid or point of care) lactate measurement to improve the sensitivity of systems designed to detect sepsis is recommended.

EHR-based machine learning algorithms (EHR-MLA)

Sepsis triggers have traditionally relied on assessment and observation by clinical staff although automated sepsis alerts, or triggers, aided by technology embedded in electronic health records (EHR) may also be an effective screening mechanism.^{62,63} In recent years research has evaluated various EHR-based automated tools for the early diagnosis of sepsis. This has primarily been driven by widespread implementation of EHRs particularly in resource-rich countries. Previous evaluations of sepsis specific trigger tools have found that electronic tools can recognise abnormal parameter values and activate an alert in real time.⁶⁴ However, the accuracy of the tools assessed has been found to be inconsistent⁶⁵, while paper-based, nurse-led screening tools have been found to be more sensitive and to be associated with improved process of care measures.⁶⁶

In the current review, about a quarter of all eligible studies evaluated EHR-based tools with studies across all healthcare settings except prehospital and all patient populations except maternal. Amongst various EHR tools, eight studies assessed SIRS-based tools and reported sensitivity ranging between 21.6-98.6%. Algorithm based clinical decision support systems were assessed in seven studies with reported sensitivity between 26-84%. In addition, the use of EHR tools improved patient outcomes such as mortality and LoS as well as other process measures such as time to administration of antibiotics, time to intravenous fluids and lactate measurement.

Generally, EHR-based tools performed better than clinical tools such SIRS and qSOFA. In a retrospective study of EHR data, although the sensitivity of EHR-MLA was comparable to manual sepsis tools e.g., SIRS, SOFA and qSOFA, EHR-MLA showed particular utility in improving sepsis detection up to 48 hours prior to clinical sepsis detection.⁶⁷ A recent systematic review reported significant reduction in both hospital and ICU length of stay but no reduction in mortality or time to antibiotics.⁶⁸

¹² <http://cec.health.nsw.gov.au/keep-patients-safe/Deteriorating-patient-program/between-the-flags/observation-charts>

¹³ <http://staging.clinicalexcellence.qld.gov.au/sites/default/files/docs/resources/qadds-summary-of-findings.pdf>

A high degree of variation was noted in the sensitivity of various EHR tools due to heterogeneity of included studies which is in line with previous similar reviews.^{65,68,69} Moreover, most studies were single centre which limits their external validity. Therefore, caution should be exercised in interpreting these results due to variability in the EHRs of different countries or between hospitals within the same country, and differences in the algorithms, triggers and sepsis definitions used in these tools. EHR-based tools show promise for use in the early detection of sepsis but more research across multiple centres and various healthcare settings is needed to evaluate their utility within Australian healthcare system.

Conclusion

This systematic review found evidence to support the use of the LqSOFA scoring system as a triage tool for patients presenting to the ED and within acute care hospitals. The NEWS or MEWS scoring systems within the current system offer slightly improved sensitivity to identify deteriorating patients but may not offer any advantage over LqSOFA with which they have not been directly compared.

Further research is required to identify the best tools for use in neonatal and maternal populations. An automated alert system embedded within the electronic health record is likely to be a viable alternative to identify patients deteriorating from sepsis in the acute care setting in the near future.

Strengths and limitations

This systematic review has a number of strengths. It was conducted in accordance with current methodological guidelines and in alignment with a pre-published protocol. The search strategy was comprehensive and informed in collaboration with a panel of subject matter experts. The use of pre-specified data collection tools facilitated consistent data collection.

There were also some weaknesses. The biggest issue was the scope of the review. The inclusion of multiple sub-populations (neonatal, paediatric, maternal and general adult populations), multiple settings (pre-hospital, Emergency Departments and acute hospital inpatients) and with multiple outcomes (diagnostic utility and process measures) necessarily introduces heterogeneity that precludes detailed quantitative assessments of specific tests and tools. As noted, a paucity of literature within certain populations, notably maternal and neonatal populations, limited the conclusions that could be drawn. There was a lack of high-quality randomised trials, with cluster randomised designs or stepped wedge designs that could inform system-based recommendations to improve clinical outcomes and processes of care.

Key findings

1. Tools and triggers used for the early identification of sepsis:
 - 1.1. Systemic Inflammatory Response Syndrome (SIRS) has higher sensitivity than quick Sequential Organ Failure Assessment (qSOFA) but similar when lactate is added to qSOFA (LqSOFA). However, in some studies SIRS has unacceptable specificity.
 - 1.2. Aggregate scoring systems such as National Early Warning Score (NEWS) or Modified Early Warning Score (MEWS) may have a slight advantage over LqSOFA but are more complex and have not been directly compared
 - 1.3. Biomarkers are useful confirmatory diagnostic tests for sepsis, particularly in neonates, but are not early clinical triggers for suspected sepsis
 - 1.4. Electronic Health Record (EHR) alerts and machine learned algorithms (MLA) offer sensitive early detection tools but are not yet at a stage for systemwide implementation.
2. Tools and triggers specific to healthcare settings and patient populations:
 - 2.1. No single sepsis screening tool can be applied uniformly to neonatal, paediatric, maternal and adult populations, or system-wide across prehospital, emergency and acute care settings
 - 2.2. Prehospital setting - the use of a screening tool improves sepsis detection but there are insufficient data to recommend any one tool
 - 2.3. Emergency Department - LqSOFA is a feasible and sensitive tool for sepsis screening in all patients presenting with suspected infection and non-specific symptoms at triage
 - 2.4. Acute care - aggregate scoring systems, such as NEWS or MEWS, were slightly more sensitive, but more complex, than single or multiple parameter system
 - 2.5. Limited evidence is available for sepsis screening tools in neonatal and maternal populations.
3. Lactate:
 - 3.1. The measurement of lactate improves the sensitivity of scoring systems
 - 3.2. High specificity of pLA in the prehospital setting may trigger prenotification of a critically unwell patient to ED but requires further research
 - 3.3. In ED, at a lactate cut off of 2 mmol/L or greater, pLA was observed to perform moderately well as a marker of sepsis and demonstrated a consistently high correlation with sLA concentrations in both adult and paediatric populations
 - 3.4. Base deficit may be a useful surrogate when lactate measurement is not available.
4. Minimum monitoring requirements:
 - 4.1. Sepsis trigger tools relevant to this review use similar vital sign parameters including respiratory and heart rate, systolic blood pressure, temperature, conscious level and oxygen saturation, which are consistent with the minimum monitoring requirements in the draft National Consensus Statement: Essential elements for recognising and responding to acute physiological deterioration (3rd ed) (NCS)
 - 4.2. In Australia, tools commonly used for sepsis screening and pathways have routinely added measurement of serum Lactate as an additional parameter
 - 4.3. The three components of qSOFA align closely to the yellow zone criteria in the

NSW Between the Flags (BTF), Queensland Adult Deterioration Detection System (Q- ADDS) and ACSQHC Adult Deterioration Detection System (ADDS) chart.

Recommendations

Based on wide consultation and the findings described in this systematic review, the following recommendations are proposed:

- The Commission considers developing advice for the states and territories regarding routine lactate measurement in patients with clinical deterioration or suspected sepsis.
- The Commission consults with the states and territories, associated peak bodies and professional colleges on:
 - the feasibility of implementing LqSOFA (using rapid lactate measurement) as a sepsis screening tool in emergency departments and acute care settings for adults
 - identifying clinically appropriate sepsis detection tools for neonatal and maternal populations.
- The Commission develops resources to support health service organisations to incorporate sepsis alerts and clinical decision support tools into their EHRs and clinical information systems nationally.
- The Commission collaborates with health service organisations to promote the use of sepsis alerts and clinical decision support tools into EHRs and clinical information systems which include:
 - clinically appropriate threshold values for neonates, young children, pregnant and post-partum women, and other high-risk populations
 - recognition and response systems which support the early identification of sepsis.

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Appendix 1 Sepsis subject matter experts

Professor Bala Venkatesh	Director of Intensive Care, Wesley Hospital, Professor of Intensive Care University of QLD, Chair, Queensland State-wide Sepsis Steering Committee,
A/Professor Paula Lister	Director Paediatric Critical Care, Sunshine Coast Hospital and Health Service Griffith University, University of Queensland
A/Professor Luregn Schlapbach	Paediatric Intensive Care Staff Senior Staff Specialist Paediatric Intensive Care Unit - Queensland Children's Hospital, ANZICS Paediatric Study Group, Chair, State-wide Paediatric Sepsis Clinical Advisory Group Paediatric Sepsis Clinical Nurse Consultant
Ms Amanda Harley	Clinical Director – Patient Experience and System Performance Division
Dr Amith Shetty	Ministry of Health NSW
Ms Mary Fullick	Senior Improvement Lead, Adult Patient Safety Team. Clinical Excellence Commission, Sydney, New South Wales, Australia.
Mr Paul Hunstead	Improvement advisor (Paediatric)- Clinical Excellence Commission
Professor Adrienne Gordon	Discipline of Obstetrics, Gynaecology and Neonatology, Faculty of Medicine and Health, University of Sydney, Senior Staff Specialist Neonatologist, RPA Newborn Care, Sydney Local Health District
Dr Robert Guaran	Executive Clinical Advisor, Neonatology, NSW Perinatal Services Network
Professor Imogen Mitchell	Dean, ANU Medical School & Senior ICU Specialist, Canberra Hospital
Dr Anne Mitchell	Paediatrician – University of Canberra Hospital
Professor Karin Thursky	Associate Director of Health Services Research and Implementation Sciences Implementation Stream Lead National Centre for Infections in Cancer Peter MacCallum Cancer Centre. Director NHMRC National Centre for Antimicrobial Stewardship University of Melbourne
Professor Daryl Jones	Senior Specialist ICU Austin Health, Monash University and University of Melbourne
Dr Elliott Long	Paediatric Emergency Physician
Dr Sean Beggs	Paediatrician – The Royal Hobart Hospital
Dr Juan-Ascencio Lane	Staff Specialist, Emergency Medicine, Staff Specialist, Diving & Hyperbaric Medicine, Royal Hobart Hospital Senior Lecturer, University of Tasmania
Dr Celia Cooper	Infectious Diseases Department, Adelaide Women's and Children's Hospital
Dr Subodh Ganu	Paediatric ICU, Women's and Children's Hospital Adelaide
Dr Stephen Macdonald	Senior Lecturer in Emergency Medicine, University of Western Australia Emergency Physician, Royal Perth Hospital Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research Emergency Department
Mr Scott Stokes	Paediatric Nurse Practitioner (Acute Care) - WA Country Health Service (Kimberley) Broome Hospital
Dr Sandra Brownlea	Royal Darwin Hospital, NT Health
Dr Josh Francis	Paediatrician & Paediatric Infectious Diseases Specialist Department of Paediatrics, Royal Darwin Hospital
Dr Sam Mooney	Maternity (RANZCOG)

Appendix 2 Database search strategy and terms

MEDLINE (Ovid SP)

- 1 exp clinical decision support system/ or ((automat* or electronic) adj5 (monitoring or detect* or evaluat* or diagnos* or tool* or decision*)).mp. or (early adj3 (monitoring or detect* or treat* or recogn* or initiat* or therap* or diagnos*)).ti,kw. or ((predefined or predefined) adj3 criteria).kw. or (system* adj5 (paper or computer or monitoring or recogn* or detect* or automated)).kw. or alert*.kw. or surveillance.kw. or screening.kw. or screening.ti. or early diagnosis.kw. or early diagnosis.ti. or early recognition.kw. or early recognition.ti. or early identification.kw. or early identification.ti. or early detection.kw. or early detection.ti. or (medical record or electronic medical record or electronic health record or EHR).ti,kw. or (machine learning or artificial neural network or bayesian learning or classification algorithm or deep learning or learning algorithm or supervised machine learning or unsupervised machine learning or artificial intelligence).ti,kw. or (lactate or lactic acid or biomarker*).ti. or (lactate or lactic acid or biomarker*).kw. or (Emergency Service, Hospital or Hospital Rapid Response Team or Emergency Medical Services).ti,kw or Clinical emergency response system*.mp.
- 2 exp sepsis/di or sepsis.ti or Shock, Septic/di or (septic* or sepsis or septic?emia or Systemic Inflammatory Response Syndrome or SIRS or py?emia).ti. or (septic* or sepsis or septic?emia or Systemic Inflammatory Response Syndrome or SIRS or py?emia).kw. or urosepsis/di or bloodstream infection/di or Bacteraemia/di or Fungemia/ or Parasitemia/di or Viremia/di or newborn sepsis/di or neonatal sepsis/di or maternal sepsis/di or Systemic Inflammatory Response Syndrome/di
- 3 (randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. or Epidemiologic studies/ or Exp case control studies/ or Exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy\$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or "Sensitivity and Specificity"/ or sensitivity.tw. or specificity.tw. or ((pre-test or pretest) adj probability).tw. or post-test probability.tw. or predictive value\$.tw. or likelihood ratio\$.tw.
- 4 1 and 2 and 3
- 5 (4 AND humans/) OR (4 NOT animals/)
- 6 limit 5 to (yr="1991 - 2020" and english)

EMBASE (Ovid SP)

- 1 exp clinical decision support system/ or ((automat* or electronic) adj5 (monitoring or detect* or evaluat* or diagnos* or tool* or decision*)).mp. or (early adj3 (monitoring or detect* or treat* or recogn* or initiat* or therap* or diagnos*)).ti,kw. or ((predefined or predefined) adj3 criteria).kw. or (system* adj5 (paper or computer

- or monitoring or recogn* or detect* or automated)).kw. or alert*.kw. or surveillance.kw. or screening.kw. or screening.ti. or early diagnosis.kw. or early diagnosis.ti. or early recognition.kw. or early recognition.ti. or early identification.kw. or early identification.ti. or early detection.kw. or early detection.ti. or (medical record or electronic medical record or electronic health record or EHR).ti,kw. or (machine learning or artificial neural network or bayesian learning or classification algorithm or deep learning or learning algorithm or supervised machine learning or unsupervised machine learning or artificial intelligence).ti,kw. or (lactate or lactic acid or biomarker*).ti. or (lactate or lactic acid or biomarker*).kw. or (Emergency Service, Hospital or Hospital Rapid Response Team or Emergency Medical Services).ti,kw or Clinical emergency response system*.mp.
- 2 exp sepsis/di or sepsis.ti or Shock, Septic/di or (septic* or sepsis or septic?emia or Systemic Inflammatory Response Syndrome or SIRS or py?emia).ti. or (septic* or sepsis or septic?emia or Systemic Inflammatory Response Syndrome or SIRS or py?emia).kw. or urosepsis/di or bloodstream infection/di or Bacteraemia/di or Fungemia/ or Parasitemia/di or Viremia/di or newborn sepsis/di or neonatal sepsis/di or maternal sepsis/di or Systemic Inflammatory Response Syndrome/di
- 3 (Clinical trial or Randomized controlled trial).pt. or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomi?ed controlled trial\$.pt. or Rct.pt. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.ab. or (allocated adj2 random).ab. or Single blind\$.ab. or Double blind\$.ab. or ((treble or triple) adj blind\$).ab. or Placebo\$.ab. or Prospective study.pt. or Clinical study.pt. or Case control study.pt. or Longitudinal study.pt. or Retrospective study/ or Prospective study.pt. or Cohort analysis.pt. or (Cohort adj (study or studies)).pt. or (Case control adj (study or studies)).pt. or (follow up adj (study or studies)).pt. or (observational adj (study or studies)).pt. or (epidemiologic\$ adj (study or studies)).pt. or (cross sectional adj (study or studies)).pt. or Meta Analysis.pt. or ((meta adj analy\$) or metanalysis\$).pt. or (systematic adj (review\$1 or overview\$1)).pt. or cochrane.pt. or "SENSITIVITY AND SPECIFICITY"/ or sensitivity.kw. or specificity.kw. or ((pre-test or pretest) adj probability).kw. or post-test probability.kw. or predictive value\$.kw. or likelihood ratio\$.kw. or Diagnostic Accuracy.kw.
- 4 1 and 2 and 3
- 5 (4 AND human/) OR (4 NOT animals/)
- 6 limit 5 to ('English' and yr = "1991 – 2020")

Scopus

((KEY (*sepsis*) OR KEY ("*septic shock*") OR TITLE (*sepsis*) OR TITLE ("*septic shock*") OR KEY ("*Systemic inflammatory response syndrome*") OR KEY ("*severe sepsis*") OR TITLE ("*severe sepsis*") OR TITLE ("*Systemic inflammatory response syndrome*")) AND (TITLE-ABS-KEY ("*early detection*" OR "*early recognition*" OR "*early diagnosis*" OR "*early identification*" OR *screen* OR "*Electronic Health Record*" OR "*Electronic Medical Records*" OR "*Machine Learning*" OR *lactate* OR *biomarker* OR "*Emergency Service, Hospital*" OR "*Hospital Rapid Response Team*" OR "*Emergency Medical Services*")) AND NOT INDEX (*Medline*) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-

TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000) OR LIMIT-TO (PUBYEAR , 1999) OR LIMIT-TO (PUBYEAR , 1998) OR LIMIT-TO (PUBYEAR , 1997) OR LIMIT-TO (PUBYEAR , 1996) OR LIMIT-TO (PUBYEAR , 1995) OR LIMIT-TO (PUBYEAR , 1994) OR LIMIT-TO (PUBYEAR , 1993) OR LIMIT-TO (PUBYEAR , 1992) OR LIMIT-TO (PUBYEAR , 1991) AND (LIMIT-TO (EXACTKEYWORD , "Human")

CINAHL

1 (MH "Shock, Septic/DI") OR (MH "Neonatal Sepsis/DI") OR (MH "Sepsis/DI") OR (MH "Bacteremia/DI") OR (MH "Systemic Inflammatory Response Syndrome/DI") OR (MH "Fungemia/DI") OR "sepsis or septic or severe sepsis or septic shock"

AND

2 (MH "Neural Networks (Computer)") OR (MH "Machine Learning") OR (MM "Deep Learning") OR (MH "Artificial Intelligence") OR "machine learning or artificial intelligence or deep learning or neural network" OR (MH "Early Diagnosis") OR (MH "Early Intervention") OR "early detection or early diagnosis or early identification" OR (MH "Electronic Health Records") OR (MH "Patient Record Systems") OR (MH "Medical Records") OR " ehr or emr or electronic health record or electronic medical record" OR (MH "Decision Support Systems, Clinical") OR (MH "Decision Making, Computer Assisted") OR (MH "Diagnosis, Computer Assisted") OR (MH "Computer Systems") OR ""clinical decision support systems" or "computerized provider order entry" or "diagnosis, computer assisted" or "computer-assisted" or "expert systems"" OR (MH "Biological Markers") OR "biomarkers or biological markers or biomarker or biological marker" OR "lactate" OR "lactic acid" OR (MH "Emergency Service, Hospital") OR (MH "Hospital Rapid Response Team") OR (MH "Emergency Medical Services") OR (MH "Clinical emergency response system")

AND

3 ((Clinical trial or Randomized controlled trial).pt. or Randomization/ or Single blind procedure/ or Double blind procedure/ or Crossover procedure/ or Placebo/ or Randomized controlled trial\$.pt. or Rct.pt. or Random allocation.tw. or Randomly allocated.tw. or Allocated randomly.ab. or (allocated adj2 random).ab. or Single blind\$.ab. or Double blind\$.ab. or ((treble or triple) adj blind\$.ab. or Placebo\$.ab. or Prospective study.pt. or Clinical study.pt. or Case control study.pt. or Longitudinal study.pt. or Retrospective study/ or Prospective study.pt. or Cohort analysis.pt. or (Cohort adj (study or studies)).pt. or (Case control adj (study or studies)).pt. or (follow up adj (study or studies)).pt. or (observational adj (study or studies)).pt. or (epidemiologic\$ adj (study or studies)).pt. or (cross sectional adj (study or studies)).pt. or Meta Analysis.pt. or ((meta adj analy\$) or metanalysis\$.pt. or (systematic adj (review\$1 or overview\$1)).pt. or cochrane.pt. or "SENSITIVITY AND SPECIFICITY"/ or sensitivity.kw. or specificity.kw. or ((pre-test or pretest) adj probability).kw. or post-test probability.kw. or predictive value\$.kw. or likelihood ratio\$.kw. or Diagnostic Accuracy.kw.)

Limiters: Date Published: 19910101-20201231;
English Language; Exclude Pre-CINAHL;
Exclude MEDLINE records;
Human;
Language: English

Cochrane

#1 "sepsis" OR "septic shock" OR "Systemic Inflammatory Response Syndrome" in Record Title

AND

#2 "early diagnosis" or "early detection" or "Machine learning" or "algorithm" or "tool" or "early identification" or "clinical decision support system" or "biomarker" or "lactic acid" or "Emergency Service, Hospital" OR "Hospital Rapid Response Team" or "Emergency Medical Services" or "Clinical emergency response system" in Record Title OR "early diagnosis" or "early detection" or "Machine learning" or "algorithm" or "tool" or "early identification" or "clinical decision support system" or "biomarker" or "lactic acid" or "Emergency Service, Hospital" OR "Hospital Rapid Response Team" or "Emergency Medical Services" or "Clinical emergency response system" in Keyword

#3 "review" in Publication Type

#4 #1 or #2 and #3

#5 publication date Between Jan 1991 and Apr 2020

(Word variations have been searched)

Appendix 3 Data dictionary and quality appraisal metrics

Term	Definition*
Sepsis definition	<ul style="list-style-type: none"> Choose between Sepsis-1, Sepsis-2 (SIRS) or SEPSIS-3
Reference/Standard Comparator	<ul style="list-style-type: none"> The intervention which was used as control or comparator. For example, in case of pre & post cohort studies, mention 'pre-cohort'
Sepsis Trigger	<ul style="list-style-type: none"> A physiological variable or marker which aids helps clinicians with early recognition of sepsis and clinical decision-making for sepsis management
Sepsis Tool	<ul style="list-style-type: none"> A tool is any instrument which uses a combination of elements of patient history, physical signs and readily available investigations to aid clinicians with early recognition of sepsis and clinical decision-making for sepsis management
Biomarker	<ul style="list-style-type: none"> A measurable indicator that is objectively measured and evaluated as an indicator of sepsis
Setting	<ul style="list-style-type: none"> Settings of interest include facilities where health care is delivered
Cohort	<ul style="list-style-type: none"> Population of interest i.e. neonate, paediatric, maternal and adult
Sensitivity%	<ul style="list-style-type: none"> Diagnostic sensitivity is a measure of the proportion of actual positives that are correctly identified as positive. That is, it is a measure of the ability of the tool or biomarker to identify a particular disease condition. Risk false positives vs missing – more important for early detection
Specificity%	<ul style="list-style-type: none"> Diagnostic specificity measures the proportion of negatives that are correctly identified and is a measure of the tool or biomarker to exclude a particular disease. Confirmatory after sensitive screening has picked up
PPV%	<ul style="list-style-type: none"> proportion of patients with positive test result in total of subjects with positive result - True Positive (TP)/[True Positive (TP)+ False Positive (FP)].
NPV%	<ul style="list-style-type: none"> Proportion of subjects without the disease with a negative test result in total of subjects with negative test results - (True Negative (TN)/ [True Negative (TN)+ False Negative (FN)].
Positive likelihood ratio	<ul style="list-style-type: none"> Likelihood of the positive test result in subjects with the disease compared to those without the disease. $LR+ = \text{sensitivity} / (1-\text{specificity})$
Negative likelihood ratio	<ul style="list-style-type: none"> Ratio of the probability that a negative result will occur in subjects with the disease to the probability that the same result will occur in subjects without the disease. $LR- = (1-\text{sensitivity}) / \text{specificity}$
Area Under the Receiver Operating Characteristic (AUROC) curve.	<ul style="list-style-type: none"> A global measure of diagnostic accuracy and is used for general assessment and for comparison of two or more diagnostic tests.
Diagnostic odds ratio (DOR)	<ul style="list-style-type: none"> Ratio of the odds of positivity in subjects with disease relative to the odds in subjects without disease. $DOR = (TP/FN)/(FP/TN)$
Time to test/diagnosis	<ul style="list-style-type: none"> Time to sepsis diagnosis since trigger of a sepsis tool
Time to antibiotics	<ul style="list-style-type: none"> Time to start antibiotics since trigger of a sepsis tool
Mortality	<ul style="list-style-type: none"> Patient centred outcome – in hospital or at 30 or 90 days post discharge
LoS	<ul style="list-style-type: none"> Length of stay (days) in hospital and/or ICU
ICU admission	<ul style="list-style-type: none"> % patients with an unplanned admission to ICU

* Study Protocol: TGI Sepsis Triggers Review v1.0 09062020

Methodological quality critical appraisal tool definitions

Cohort studies Critical Appraisal Tool⁷⁰

- 1. Were the two groups similar and recruited from the same population?**

Check the paper carefully for descriptions of participants to determine if patients within and across groups have similar characteristics in relation to exposure (e.g. risk factor under investigation). The two groups selected for comparison should be as similar as possible in all characteristics except for their exposure status, relevant to the study in question. The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants.
 - 2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?**

A high-quality study at the level of cohort design should mention or describe how the exposures were measured. The exposure measures should be clearly defined and described in detail. This will enable reviewers to assess whether or not the participants received the exposure of interest.
 - 3. Was the exposure measured in a valid and reliable way?**

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed. Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and interobserver reliability.
 - 4. Were confounding factors identified?**

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups, and it influences the direction of the study results. A high-quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioural, attitudinal or lifestyle factors may impact on the results.
 - 5. Were strategies to deal with confounding factors stated?**

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of regression statistical methods such as logistic regression are usually employed to deal with confounding factors/variables of interest.
 - 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?**

The participants should be free of the outcomes of interest at the start of the study. Refer to the 'methods' section in the paper for this information, which is usually found in descriptions of participant/sample recruitment, definitions of variables, and/or inclusion/exclusion criteria.
 - 7. Were the outcomes measured in a valid and reliable way?**

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or underreporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity. Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?
 - 8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?**

The appropriate length of time for follow up will vary with the nature and characteristics of the population of interest and/or the intervention, disease or exposure. To estimate an appropriate duration of follow up, read across multiple papers and take note of the range for duration of follow up. The opinions of experts in clinical practice or clinical research may also assist in determining an appropriate duration of follow up. For example, a longer timeframe may be needed to examine the association between occupational exposure to asbestos and the risk of lung cancer. It is important, particularly in cohort studies that follow up is long enough to enable the outcomes. However, it should be remembered that the research question and outcomes being examined would probably dictate the follow up time.
 - 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?**

It is important in a cohort study that a greater percentage of people are followed up. As a general guideline, at least 80% of patients should be followed up. Generally, a dropout rate of 5% or less is considered insignificant. A rate of 20% or greater is considered to significantly impact on the validity of the study. However, in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected. A decision on whether to include or exclude a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether dropout rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be
-

regarded as an indicator of a well conducted study. Look for clear and justifiable description of why people were left out, excluded, dropped out etc. If there is no clear description or a statement in this regard, this will be a 'No'.

10. Were strategies to address incomplete follow up utilized?

Some people may withdraw due to change in employment or some may die; however, it is important that their outcomes are assessed. Selection bias may occur as a result of incomplete follow up. Therefore, participants with unequal follow up periods must be considered in the analysis, which should be adjusted to allow for differences in length of follow up periods. This is usually done by calculating rates which use person-years at risk, i.e. considering time in the denominator.

11. Was appropriate statistical analysis used?

12. As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used.

The methods section of cohort studies should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured. For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

Diagnostic Test Accuracy Studies Critical Appraisal Tool^{71,72}

Patient selection:

- a. Was a consecutive or random sample of patients enrolled? Studies should state or describe their method of enrolment. If it is claimed that a random sample was chosen the method of randomization should be stated (and appropriate). It is acceptable if studies do not say 'consecutive' but instead describe consecutive enrolment; i.e. 'all patients from till were included'.
 - b. Was a case control design avoided? Case control studies are described in detail in the reviewer's manual. In essence, if a study design involves recruiting participants who are already known by other means to have the diagnosis of interest and investigating whether the test of interest correctly identifies them as such, the answer is 'No'.
 - c. Did the study avoid inappropriate exclusions? If patients are excluded for reasons that would likely influence the conduct, interpretation or results of the test, this may bias the results. Examples include excluding patients on which the test is difficult to conduct, excluding patients with borderline results, excluding patients with clear clinical indicators of the diagnosis of interest. Index test
 - d. Were the index test results interpreted without knowledge of the results of the reference standard? The results of the index test should be interpreted by someone who is blind to the results of the reference test. The reference test may not have been conducted at the point that the index test is carried out, if so the answer to this question will be 'Yes'. If the person who interprets the index test also interpreted the reference test then it is assumed that this question will be answered 'No' unless there are other factors in play (for instance, the interpretation of the © Joanna Briggs Institute 2017 Critical Appraisal Checklist for Diagnostic Test Accuracy Studies 5 results may be separate from their collection, in which case the interpreter may be blinded to patient identity and past reference test results).
 - e. If a threshold was used, was it pre-specified? Diagnostic thresholds may be chosen based on what gives the optimum accuracy from the data, or they may be pre-specified. When no diagnostic threshold is applied (i.e. the results of a test is based on the observation of a specific characteristic which is either there or not) this question will be answered NA.
 - f. Is the reference standard likely to correctly classify the target condition? The reference test should be the gold standard for the diagnosis of the condition of interest. Additionally, the reporting of the study should describe its conduct in sufficient detail that the reviewers can be confident that it has been correctly and competently implemented.
 - g. Were the reference standard results interpreted without knowledge of the results of the index test? The points made for criteria 4 apply equally here. The results of the reference test should be interpreted by someone who is blind to the results of the index test. The index test may not have been conducted at the point that the reference test is carried out, if so the answer to this question will be 'Yes'. If the person who interprets the reference test also interpreted the index test then it is assumed that this question will be answered 'No' unless there are other factors in play (for instance, the interpretation of the results may be separate from their collection, in which case the interpreter may be blinded to patient identity and past index test results).
 - h. Was there an appropriate interval between index test and reference standard? The index test and the reference test should be carried out close enough together that the status of the patient could not have meaningfully changed. The maximum acceptable time will vary based on characteristics of the population and condition of interest.
 - i. Did all patients receive the same reference standard? The reference standard by which patients are classed as having or not having the condition of interest should be the same for all patients. If the results of the index test influence how or whether the reference test is used (i.e. where an apparent false negative may be detected the study design may call for a 'double check') this may result in biased estimates of sensitivity and specificity. Additionally, in some studies two parallel reference tests may be used (on different patients) and the results then pooled. In either case the results should be 'No'.
 - j. Were all patients included in the analysis? Losses to follow up should be explained and their cause and frequency should be considered in whether they are likely to have had an effect on the results (Subjectivity may exist in this context, overall low tolerance should be applied in deciding to answer 'No' to this question, but a single withdrawal from a large cohort should not
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necessarily force a negative response). However, if a patient's results being difficult to interpret causes their data to be excluded from the analysis this will exaggerate the estimate of DTA, and this question should definitely be answered 'No'.

JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses⁷³

When conducting an umbrella review using the JBI method, the critical appraisal instrument for Systematic Reviews should be used.

- a. The primary and secondary reviewer should discuss each item in the appraisal instrument for each study included in their review. In particular, discussions should focus on what is considered acceptable to the aims of the review in terms of the specific study characteristics. When appraising systematic reviews this discussion may include issues such as what represents an adequate search strategy or appropriate methods of synthesis. The reviewers should be clear on what constitutes acceptable levels of information to allocate a positive appraisal compared with a negative, or response of "unclear". This discussion should ideally take place before the reviewers independently conduct the appraisal.
 - b. Within umbrella reviews, quantitative or qualitative systematic reviews may be incorporated, as well as meta-analyses of existing research. There are 11 questions to guide the appraisal of systematic reviews or meta-analyses. Each question should be answered as "yes", "no", or "unclear". Not applicable "NA" is also provided as an option and may be appropriate in rare instances. 1. Is the review question clearly and explicitly stated? The review question is an essential step in the systematic review process. A well-articulated question defines the scope of the review and aids in the development of the search strategy to locate the relevant evidence. An explicitly stated question, formulated around its PICO (Population, Intervention, Comparator, Outcome) elements aids both the review team in the conduct of the review and the reader in determining if the review has achieved its objectives. Ideally the review question should be articulated in a published protocol; however, this will not always be the case with many reviews that are located.
 - c. Were the inclusion criteria appropriate for the review question? The inclusion criteria should be identifiable from and match the review question. The necessary elements of the PICO should be explicit and clearly defined. The inclusion criteria should be detailed, and the included reviews should clearly be eligible when matched against the stated inclusion criteria. Appraisers of meta-analyses will find that inclusion criteria may include criteria around the ability to conduct statistical analyses which would not be the norm for a systematic review. The types of included studies should be relevant to the review question, for example, an umbrella review aiming to summarize a range of effective non-pharmacological interventions for aggressive behaviours amongst elderly patients with dementia will limit itself to including systematic reviews and meta-analyses that synthesize quantitative studies assessing the various interventions; qualitative or economic reviews would not be included.
 - d. Was the search strategy appropriate? A systematic review should provide evidence of the search strategy that has been used to locate the evidence. This may be found in the methods section of the review report in some cases, or as an appendix that may be provided as supplementary information to the review publication. A systematic review should present a clear search strategy that addresses each of the identifiable PICO components of the review question. Some reviews may also provide a description of the approach to searching and how the terms that were ultimately used were derived, though due to limits on word counts in journals this may be more the norm in online only publications. There should be evidence of logical and relevant keywords and terms and also evidence that Subject Headings and Indexing terms have been used in the conduct of the search. Limits on the search should also be considered and their potential impact; for example, if a date limit was used, was this appropriate and/or justified? If only English language studies were included, will such a language bias have an impact on the review? The response to these considerations will depend, in part, on the review question.
 - e. Were the sources and resources used to search for studies adequate? A systematic review should attempt to identify "all" the available evidence and as such there should be evidence of a comprehensive search strategy. Multiple electronic databases should be searched including major bibliographic citation databases such as MEDLINE and CINAHL. Ideally, other databases that are relevant to the review question should also be searched, for example, a systematic review with a question about a physical therapy intervention should also look to search the PEDro database, whilst a review focusing on an educational intervention should also search the ERIC. Reviews of effectiveness should aim to search trial registries. A comprehensive search is the ideal way to minimize publication bias, as a result, a well conducted systematic review should also attempt to search for grey literature, or "unpublished" studies; this may involve searching websites relevant to the review question, or thesis repositories.
 - f. Were the criteria for appraising studies appropriate? The systematic review should present a clear statement that critical appraisal was conducted and provide the details of the items that were used to assess the included studies. This may be presented in the methods of the review, as an appendix of supplementary information, or as a reference to a source that can be located. The tools or instruments used should be appropriate for the review question asked and the type of research conducted. For example, a systematic review of effectiveness should present a tool or instrument that addresses aspects of validity for experimental studies and randomized controlled trials such as randomization and blinding – if the review includes observational research to answer the same question a different tool would be more appropriate. Similarly, a review assessing diagnostic test accuracy may refer to the recognized QUADAS1 tool.
 - g. Was critical appraisal conducted by two or more reviewers independently? Critical appraisal or some similar assessment of the quality of the literature included in a systematic review is essential. A key characteristic to minimize bias or systematic error in the conduct of a systematic review is to have the critical appraisal of the included studies completed independently and in duplicate by members of the review team. The systematic review should present a clear statement that critical appraisal was
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conducted by at least two reviewers working independently from each other and conferring where necessary to reach decision regarding study quality and eligibility on the basis of quality.

- h.** Were there methods to minimize errors in data extraction? Efforts made by review authors during data extraction can also minimize bias or systematic errors in the conduct of a systematic review. Strategies to minimize bias may include conducting all data extraction in duplicate and independently, using specific tools or instruments to guide data extraction and some evidence of piloting or training around their use.
 - i.** Were the methods used to combine studies appropriate? A synthesis of the evidence is a key feature of a systematic review. The synthesis that is presented should be appropriate for the review question and the stated type of systematic review and evidence it refers to. If a meta-analysis has been conducted this needs to be reviewed carefully. Was it appropriate to combine the studies? Have the reviewers assessed heterogeneity statistically and provided some explanation for heterogeneity that may be present? Often, where heterogeneous studies are included in the systematic review, narrative synthesis will be an appropriate method for presenting the results of multiple studies. If a qualitative review, are the methods that have been used to synthesize findings congruent with the stated methodology of the review? Is there adequate descriptive and explanatory information to support the final synthesized findings that have been constructed from the findings sourced from the original research?
 - j.** Was the likelihood of publication bias assessed? As mentioned, a comprehensive search strategy is the best means by which a review author may alleviate the impact of publication bias on the results of the review. Reviews may also present statistical tests such as Egger's test or funnel plots to also assess the potential presence of publication bias and its potential impact on the results of the review. This question will not be applicable to systematic reviews of qualitative evidence.
 - k.** Were recommendations for policy and/or practice supported by the reported data? Whilst the first nine (9) questions specifically look to identify potential bias in the conduct of a systematic review, the final questions are more indicators of review quality rather than validity. Ideally a review should present recommendations for policy and practice. Where these recommendations are made there should be a clear link to the results of the review. Is there evidence that the strength of the findings and the quality of the research been considered in the formulation of review recommendations?
 - l.** Were the specific directives for new research appropriate? The systematic review process is recognized for its ability to identify where gaps in the research, or knowledge base, around a particular topic exist. Most systematic review authors will provide some indication, often in the discussion section of the report, of where future research direction should lie. Where evidence is scarce or sample sizes that support overall estimates of effect are small and effect estimates are imprecise, repeating similar research to those identified by the review may be necessary and appropriate. In other instances, the case for new research questions to investigate the topic may be warranted.
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Appendix 4 Study characteristics

TOOLS - Cohort Studies									
Author (year) country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Agarwal et al., 2019 ⁵⁷ , India	SOS	Sepsis diagnosis & severity	Prospective	ED	Maternal	136	SIRS	SIRS > 2 criteria + infection + OD	SOS correlated well with OD in pregnancy-associated sepsis
Amland et al., 2019 ⁷⁴ , US	EHR - EWA	Sepsis diagnosis & severity; ICU admission & LoS; mortality	Retrospective	ED	Adult	6200	SIRS	ICD9-CM codes	Sepsis CDS accelerate diagnostic and therapeutic interventions
Askim et al., 2017 ⁷⁵ , Norway	qSOFA vs SIRS vs RETTS	Sepsis diagnosis; mortality	Prospective	ED	Adult	1535	Sepsis-3, SIRS	SIRS	qSOFA performed poorly for detection of sepsis & for severity prediction
Baez et al., 2016 ⁷⁶ , US	EHR - (PSS + POC Lactate)	Sepsis diagnosis	Retrospective	Prehospital	Adult/Paed/Neon	NS	SIRS based ICD-9 codes	Chart audit	PSP can be clinically complemented with POC lactate
Balamuth et al., 2015 ⁷⁷ , US	EHR - EWA (MLA) vs clinical assessment	Sepsis diagnosis	Retrospective	ED	Paediatric	19524	SIRS > 2 criteria + infection + OD	Clinician assessment	MLA sensitive but less specific; sequential MLA alert plus clinical assessment better detects sepsis
Balamuth et al., 2017 ⁷⁸ , US	EHR - EWA (MLA) vs clinical assessment	Sepsis diagnosis	Prospective	ED	Paediatric	182500	AAP Septic Shock collaborative SIRS	Clinician assessment	ESA demonstrated improved recognition of severe sepsis
Barbara et al., 2018 ⁷⁹ , US	qSOFA (\geq criteria)	Sepsis diagnosis; mortality	Retrospective	Prehospital	Adult	72	SIRS	SIRS > 2 criteria + infection + OD (shock); sepsis vs non-sepsis cohort	Positive qSOFA screens identified sepsis diagnosis in ED
Barton et al., 2019 ⁶⁷ , US	EHR - EWA (MLA) vs SIRS, SOFA, MEWS & and qSOFA	Sepsis diagnosis	Retrospective	ED/Acute/ICU	Adult	113000	Sepsis-3	SIRS, SOFA, MEWS, and qSOFA	MLA predicts sepsis up to 48 hours prior to onset, exceeding existing tools
Bauer et al., 2019 ⁶⁶ , US	SIRS vs qSOFA vs MEWS	Sepsis diagnosis	Retrospective	Acute	Maternal	410	Sepsis-3, SIRS	SIRS >2, qSOFA >1, MEWS >1	MEWS has the best balance of sensitivity & specificity

TOOLS - Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Baumann et al., 2019 ⁸⁰ , US	LqSOFA (Lactate added) vs qSOFA	Sepsis diagnosis; mortality	Retrospective	Acute/ICU	Adult	3743	Sepsis-3	qSOFA \geq 2 & Lactate \geq 4, Chart audit	Combination of qSOFA \geq 1 OR Lactate \geq 2 improves sepsis screening
Bayer et al., 2015 ²⁹ , Germany	PRESEP vs MEWS	Sepsis diagnosis	Prospective	Prehospital/ED	Adult	375	SIRS > 2 criteria + infection	MEWS	PRESEP detects sepsis better than MEWS
Bedoya et al., 2020 ⁸¹ , US	EHR - EWA (MLA) vs SIRS, qSOFA, MEWS	Sepsis diagnosis & time	Retrospective	ED	Adult	83000	SIRS > 2 criteria + infection + OD	SIRS, qSOFA, NEWS	Deep learning model better detected sepsis than other MLA & clinical scores
Borrelli et al., 2019 ⁸² , US	Screening tool RR, HR, SBP, Temp, Mentation, SpO2%, infection EHR - EWA	Time to lactate & antibiotics; ICU & Hospital LoS; mortality	Retrospective	Prehospital	Adult, Paed, Neonate	63	SIRS	SIRS \geq 2 criteria	Improved 3-hour bundle compliance due to improved recognition of sepsis
Brandt et al., 2015 ⁸³ , US	EHR - EWA	Sepsis diagnosis & time	Prospective	Acute	Adult	164	SIRS > 2 criteria + infection + OD	Chart audit; ICD-9 codes	Electronic surveillance was sensitive but not specific
Brown et al., 2016 ⁸⁴ , US	EHR - EWA (MLA routine clinical data)	Sepsis diagnosis	Prospective	ED	Adult	58603	SIRS, ICD-9 codes	Sepsis vs non-sepsis cohort, chart audit	Probabilistic sepsis alert model identified sepsis with high sensitivity & low false positive rate
Chiew et al., 2019 ⁸⁵ , Singapore	EHR - EWA MLA	Sepsis diagnosis; 30- day mortality	Retrospective	ED	Adult	368	SIRS	qSOFA, NEWS and MEWS	Gradient boosting was the best model to prediction of 30-day mortality in suspected sepsis patients
Cruz et al., 2012 ⁸⁶ , US	EHR - EWA (T + variable HR)	Sepsis diagnosis & severity	Prospective	ED	Paediatric	4592	SIRS	Clinical septic shock	Automated sepsis alert using T & HR heart rate led to early identification of sepsis
Danner et al., 2017 ⁸⁷ , US	EHR - EWA (SI)	Sepsis diagnosis	Retrospective	ED	Adult	53313	Sepsis-3	SIRS \geq 2 criteria	Variations in HR:SBP ratio improved accuracy & expediency of sepsis identification
Delahanty et al., 2019 ⁸⁸ , US	EHR - EWA (MLA RoS)	Sepsis diagnosis	Retrospective	Acute	Adult	2759529	Sepsis-3	SIRS, SOFA, qSOFA, MEWS & NEWS	RoS was more timely and discriminant than benchmark sepsis screening tools
Dong et al. 2020 ⁸⁹ , China	EHR - (eSOFA) vs SOFA	Sepsis diagnosis; ICU admission & LoS; mortality	Retrospective	Acute	Adult	1716	Sepsis-3	CDC Adult Sepsis Event's criteria	eSOFA has low sensitivity and high specificity for sepsis diagnosis
Dorsett et al., 2017 ⁹⁰ , US	qSOFA \pm Modified Robson	Sepsis diagnosis	Retrospective	Prehospital/ED	Adult	152	ICD-9 codes	SIRS \geq 2 criteria	Combining qSOFA with other clinical information is better at sepsis detection

TOOLS – Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Eisenberg et al., 2019 ⁹¹ , US	EHR - EWA (SJSA)	Sepsis diagnosis	Retrospective	ED/Acute	Paediatric	22766	SIRS > 2 criteria + infection + OD	Paediatric Sepsis Consensus Definition	ML-AL supports early sepsis detection
Faisal et al., 2018 ⁹² , UK	EHR - EWA (CARS + NEWS)	Sepsis diagnosis & severity	Retrospective	ED	Adult	73851	ICD-10 codes	Comparable ED	Good performance for estimating the risk of sepsis in ED medical admissions
Fesnak et al., 2020 ⁹³ , US	EHR - EWA	Sepsis diagnosis; timeliness to result, antibiotics & treatment;	Retrospective	ED	Paediatric	1107	Sepsis-3	Paediatric Septic Shock Collaborative Trigger Tool	Timeliness was no different in high-risk patients with sepsis when using an electronic sepsis alert
Filbin et al., 2018 ⁹⁴ , US	SPot & tCFI vs qSOFA	Sepsis diagnosis	Retrospective	ED	Adult	19670	ICD9 codes - Angus criteria	At triage vs end of ED stay	SPoT criteria at triage is positive for sepsis earlier
Giannini et al., 2019 ⁹⁵ , US	EHR - EWA (MLA)	Sepsis diagnosis & time; Lactate test time, time to antibiotic, ICU admission; mortality	Retrospective	Acute	Adult	162212	SIRS > 2 criteria + infection + OD	Silent vs alert cohort	ML-AL predicts sepsis, severity & impacts process measures
Geier et al., 2013 ⁹⁶ , Germany	ESI vs MEWS vs MEDS	Sepsis diagnosis; mortality	Prospective	ED	Adult	151	SIRS	ESI, MEWS	MEDS score detects sepsis & critically ill sepsis patients
Goerlich et al., 2014 ⁹⁷ , US	Triage screening tool + St02	Sepsis diagnosis	Prospective	ED	Adult	500	SIRS > 2 criteria + infection	Non-sepsis cohort	HR, RR and T have good potential diagnosis of sepsis
Guerra et al. 2013 ⁹⁸ , US	Sepsis Alert Protocol	Time to antibiotics; hospital LoS; mortality	Prospective	Prehospital	Adult	112	ICD-9 codes, SIRS	Usual care	Prehospital screen with lactate reduced ICU intervention & mortality
Gyang et al., 2015 ⁹⁹ , US	NST	Sepsis diagnosis	Prospective	Acute	Adult	245	SIRS > 2 criteria + infection	ICD9-codes, chart audit	NST can achieve early identification of sepsis
Haydar et al., 2017 ¹⁰⁰ , US	qSOFA vs SIRS	Sepsis diagnosis; timeliness of score	Retrospective	ED	Adult	200	Sepsis 3	SIRS	qSOFA screening is less accurate & takes longer than SIRS

TOOLS – Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Honeyford et al. 2020 ¹⁰¹ , UK	EHR – EWA	Sepsis diagnosis; Time to antibiotics; hospital LoS; mortality	Retrospective	Acute	Adult	21732	SIRS > 2, St John Sepsis Alert; ICD9 codes	Usual care, no alert	Digital sepsis alert reduced time to antibiotics, LoS & mortality
Hunter et al., 2018 ¹⁰² , US	qSOFA + ETC02	Sepsis diagnosis; mortality	Retrospective	Prehospital	Adult	330	SIRS > 2, St John Sepsis Alert; ICD9 codes	qSOFA score ≥ 2	qSOFA score & ETC02 detect sepsis; ETC02 better outcome predictor
Idrees et al. 2016 ¹⁰³ , Australia	SEAT + pathway	Sepsis diagnosis; Time to blood culture & antibiotics;	Retrospective	ED	Adult	100	SIRS	Usual care	SEAT screen is associated with earlier recognition of sepsis
Judd et al., 2014 ¹⁰⁴ , US	EHR - Nurse screening tool	Sepsis diagnosis; Time to antibiotics; ICU & hospital LoS; mortality; cost	Retrospective	ED	Adult	397	SIRS	Usual care, Sepsis DRG's	Early recognition reduced time to intervention, LOS & total cost per case
Kenzaka et al., 2012 ¹⁰⁵ , Japan	SOFA vs vital signs	Sepsis diagnosis; SOFA & vital sign correlation	Prospective	ED	Adult	206	SIRS ≥ 2 criteria	SOFA	Increased RR & SI correlate with severity & can prompt early identification at triage
Kurczewski et al, 2015 ¹⁰⁶ , US	EHR - EWA	Time to lactate, blood culture; antibiotics & IV fluids; ICU admission; hospital LoS; mortality	Retrospective	ED	Adult	60	SIRS > 2 criteria, ICD-9 codes	Usual care	Sepsis alerts decrease time to initial laboratory tests, but outcomes impact is not significant
Lane (c) et al., 2020 ¹⁰⁷ , Canada	EHR - EWA (Diagnostic codes + clinical data)	Sepsis diagnosis	Retrospective	Prehospital/ED	Adult	43297	Sepsis-3	ICD10CA, ≥ 2 SOFA + infection or OD	Combined diagnostic codes and clinical information on OD improves detection of sepsis
Le et al., 2019 ¹⁰⁸ , US	EHR - EWA (MLA) vs PELOD & SIRS	Sepsis diagnosis	Retrospective	ED/Acute	Paediatric	9486	SIRS > 2 criteria + infection + OD	PELOD-2, SIRS	AI-ML provides better detection than PELOD or SIRS
Lee et al. 2020 ¹⁰⁹ , South Korea	qSOFA-65 (age added)	Sepsis diagnosis; ICU admission; 30-day mortality	Retrospective	ED	Adult	2441	Sepsis 3	SIRS & qSOFA	qSOFA-65 was more likely to identify sepsis relative to qSOFA or SIRS
Li et al., 2019 ¹¹⁰ , Australia	EHR - Sepsis Alert, Modified St John Rule	Sepsis diagnosis; ICU admission or mortality	Retrospective	Acute	Adult	36065	Sepsis 3	ICD-10AM	Option 6 (SIRS > 2 criteria) best discrimination for sepsis

TOOLS – Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
MacQueen et al., 2015 ¹¹¹ , US	Screening protocol (vital signs)	Sepsis diagnosis; Hospital LoS	Prospective	Acute	Adult	478	SIRS + infection present	Control group	Highly sensitive method of identifying severe sepsis but not specific
McDonald et al., 2018 ¹¹² , Canada	Sepsis Triage Tool	Time to lactate, blood culture; antibiotics & IV fluids; ICU admission; hospital LoS; mortality	Retrospective	Adult	ED	616	SIRS	Usual care	Triage screening improves timing with nonsignificant outcome improvement
Manaktala et al., 2017 ⁶⁴ , US	EHR - Sepsis Alerts	Sepsis diagnosis; hospital LoS & readmissions; mortality	Retrospective	Acute	Adult	778	SIRS	Chart audit; pre EHR mortality	POC alerts achieved high sensitivity and specificity with decreased mortality and readmissions
Mao et al., 2018 ¹¹³ , US	EHR - EWA (6 vital signs)	Sepsis diagnosis	Retrospective	ED	Adult	774796	Sepsis-3, ICD-9 codes	SIRS > 2 criteria, MEWS, SOFA	InSight (EHR) superior to SIRS, MEWS & SOFA with AUROC of 0.90 using only vital sign inputs
Muratore et al., 2019 ¹¹⁴ , US	EHR - sBPA	Sepsis diagnosis; Lactate done; hospital LoS; mortality	Retrospective	Acute	Adult	10335	Sepsis 3	sBPA in surgical vs nonsurgical	No difference in sBPA or outcomes
Nguyen et al., 2014 ¹¹⁵ , US	EHR - Sepsis Alert	Sepsis diagnosis; hospital admission; mortality	Retrospective	ED	Adult/Paed	1055	SIRS	Non sepsis alert cases; chart audit	Earle detection; false-positives triggered by non-infectious SIRS criteria
Nieves et al., 2019 ¹¹⁶ , Switzerland	qSOFA vs SIRS vs NEWS vs Triage vs ESI	Sepsis diagnosis; ICU admission; hospital & 30-day mortality	Prospective	ED	Adult	2523	Sepsis 3	Chart audit to assign sepsis	qSOFA >2 cut-off had high specificity & low sensitivity; all scores predicted outcomes
Olenick et al., 2017 ¹¹⁷ , US	EHR - SSA vs NST	Sepsis diagnosis & time; workload (time), hospital LoS, cost & mortality	Retrospective	Acute	Adult	68652	SIRS	NST	SSA as an adjunct to NST reduces manual surveillance efforts with similar accuracy
O'Regan et al., 2019 ⁵⁵ , Ireland	EMIP	Sepsis diagnosis	Retrospective	Acute	Maternal	69	Sepsis 3	Usual care	Earlier identification of maternal infection prior to sepsis
Patocka et al., 2014 ¹¹⁸ , Canada	Triage Sepsis Tool	Time to antibiotics	Retrospective	ED	Adult	355	SIRS, infection	Usual care	Decreased the time to antibiotics
Polito et al., 2015 ¹¹⁹ , US	PRESS Score	Sepsis diagnosis & severity; mortality	Retrospective	Prehospital	Adult	555	SIRS > 2 criteria	Modified SIRS, chart audit	Good sensitivity; low specificity

TOOLS – Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Prasad et al., 2020 ¹²⁰ , US	EHR - SIRS vs SOFA vs qSOFA	Time to antibiotics; ICU admission, ICU LoS, mortality	Retrospective	ED	Adult	9087	SIRS (Sepsis 2), Sepsis 3	SIRS, SOFA, qSOFA	EHR systems best likelihood of detecting sepsis is with a combination of SIRS & SOFA elements
Rodriguez et al., 2018 ¹²¹ , US	qSOFA vs SIRS vs Severe Sepsis vs Lactate	Sepsis diagnosis & severity	Retrospective	ED	Adult	3743	Sepsis 3, SIRS	qSOFA >2, SIRS >2, Severe Sepsis; Lactate ≥ 2 or ≥ 4	qSOFA predicted critical illness better than SIRS, Severe Sepsis or lactate levels
Rolnick et al., 2016 ¹²² , US	EHR - Sepsis Alert	Sepsis diagnosis & time	Retrospective	Acute	Adult	175	ICD 9 codes	Clinical review, manual nurse screen	Good sensitivity; Incorporation of physician orders increases specificity
Rosenquist et al., 2020 ¹²³ , Sweden	Triage Sepsis Alert	Time to lactate & antibiotics; hospital LoS; mortality	Prospective	ED	Adult	5321	Sepsis 3	Usual care, clinician chart audit	Improved lactate testing rate & time to antibiotics; no outcome improvements
Rothman et al., 2017 ¹²⁴ , US	EHR - Rothman Index	Sepsis diagnosis	Retrospective	Acute	Adult	258836	ICD 9 codes, Sepsis 3	qSOFA	Good to excellent discriminatory performance
Sawyer et al., 2011 ¹²⁵ , US	EHR - EWA	Sepsis diagnosis; Time to diagnosis, antibiotics & IV fluids; ICU admission; hospital LoS; mortality	Prospective	Acute	Adult	270	SIRS	Usual care	Reduced time to diagnosis & interventions; no impact on outcomes
Shah et al., 2018 ¹²⁶ , US	MEWS	Bundle compliance; time to antibiotics; ICU LoS; mortality	Retrospective	ED	Adult	115	Sepsis 3	Usual care, clinician chart audit	No increased 3hr bundle compliance; improved time to antibiotics; reduced ICU LoS
Shetty et al., 2016 ²⁵ , Australia	EHR - EWA (SIRS)	Sepsis diagnosis & severity	Retrospective	ED	Adult	747	SIRS	SIRS based screening algorithms in USA, Canada, UK, Australia and Ireland	US & Ireland best diagnostic accuracy; Lactate >2 more sensitive >4
Shetty et al., 2017 ²⁷ , Australia	LqSOFA vs qSOFA	Sepsis diagnosis; ICU admission \pm mortality	Retrospective	ED	Adult	12555	Sepsis 3	qSOFA	LqSOFA score performs better than qSOFA alone
Shu et al. 2019 ¹²⁷ , US	qSOFA	Sepsis diagnosis; ICU admission; ICU & hospital LoS; mortality	Retrospective	Prehospital	Adult	2292	Sepsis 3	ED diagnosis of sepsis	Pre-hospital qSOFA is specific but poor sensitivity; no impact on outcomes

TOOLS – Cohort Studies cont'd.

Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Silcock et al., 2019 ¹²⁸ , UK	qSOFA, NEWS	ICU admission; mortality	Retrospective	Prehospital	Adult	1713	Sepsis 3	NEWS vs qSOFA	Elevated qSOFA & NEWS is associated with ICU admission & 30-day mortality
Singer (b) et al., 2014 ¹²⁹ , US	Clinical Screening Tool + POC Lactate	Sepsis diagnosis; ICU admission; mortality	Prospective	ED	Adult	258	SIRS	Combined screening tool and lactate	Combined tool & POC lactate has good specificity but low sensitivity
Sloane et al., 2018 ¹³⁰ , US	SIRS vs. qSOFA vs. 100-100-100	Sepsis diagnosis	Retrospective	Prehospital	Adult	236	SIRS	SIRS, qSOFA, 100-100-100	In elderly 100-100-100 criteria most sensitive; with the quick SOFA most specific
Smyth et al., 2019 ¹³¹ , UK	SEPSIS score > 3 or > 5	Sepsis diagnosis	Retrospective	Prehospital	Adult	22945	Sepsis-3	PreSS, PreSep, Robson tool, qSOFA	SEPSIS score is significantly associated with high risk of severe sepsis
Umscheid et al., 2015 ¹³² , UK	EHR - EWRS	Sepsis diagnosis; time to antibiotics; ICU admission; hospital LoS; mortality	Retrospective	Acute	Adult	4575	ICD-9 codes	Usual care	EWRS improved early intervention, reduced ICU admission; mortality reduction (NS)
Usman et al., 2019 ³¹ , US	NEWS > 4 vs SIRS > 2 vs qSOFA > 2	Sepsis diagnosis; mortality	Retrospective	ED	Adult	115734	Sepsis-3	SIRS, qSOFA	NEWS is more predictive of sepsis than SIRS or qSOFA
Valik et al., 2020 ¹³³ , Sweden	EHR - EWA (SOFA)	Sepsis diagnosis	Retrospective	Acute	Adult	1000	Sepsis 3, ICD-10 codes	Clinical assessment of suspected infection	Automated alerts have good validity compared to clinician assessment
Wallgren et al., 2014 ²⁸ , Sweden	Robson Tool vs. BAS 90-30-90	Sepsis diagnosis	Retrospective	Prehospital	Adult	353	ICD-10 codes	Clinical assessment	Robson tool sensitivity was superior to BAS 90-30-90 and clinical assessment
Wallgren et al., 2016 ¹³⁴ , Sweden	Robson Tool	Sepsis diagnosis; time to antibiotics; mortality	Prospective	ED	Adult	577	ICD-10 codes	Clinical assessment of general deterioration vs sepsis specific	Modified Robson tool had higher sensitivity, but lower specificity compared to clinical judgment
Wang et al., 2015 ¹³⁵ , US	Martin & Angus codes	Sepsis diagnosis	Retrospective	Prehospital	Adult	379	ICD-9 codes	Infection + SIRS _≥ 2 or SOFA > 1	Martin & Angus are both poorly sensitive but highly specific
Wawrose et al., 2016 ¹³⁶ , US	SSS vs. SJSA	Sepsis diagnosis	Prospective	Acute	Adult	348	SIRS	SSS vs SJSA	SSS can detect sepsis more accurately than the SJSA

TRIGGERS – Cohort Studies									
Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) ± process measures ± outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Anand et al., 2015 ¹³⁷ , India	Tr: PCT vs neg BC	Sepsis diagnosis	Prospective	ICU	Adult	208	SIRS > 2 criteria + infection	Culture positive cohort	PCT can differentiate culture-negative sepsis in non-infectious SIRS patients
Berkman et al., 2009 ¹³⁸ , US	Tr: AG > 12 vs Lactate >4	Sepsis diagnosis; AG as a lactate surrogate	Prospective	ED	Adult	1419	SIRS	AG > 12, Lactate >4	AG is a moderately sensitive and specific surrogate for lactate
Boland et al., 2016 ¹³⁹ , US	Tr: Lactate (POC)	Sepsis diagnosis	Prospective	Prehospital	Adult	112	SIRS	Prehospital POCL vs ED Lactate correlation	EMS use of POC lactate did not achieve adequate diagnostic accuracy
Contenti et al., 2015 ¹⁴⁰ , France	Tr: Lactate (POC+Serum)	Sepsis diagnosis & severity; mortality	Prospective	ED	Adult	117	SIRS > 2 criteria + infection + OD	Arterial vs venous vs capillary lactate	Venous was most efficient for early detection of severe sepsis
Freund et al., 2012 ¹⁴¹ , France	Tr: PCT vs Lactate	Sepsis diagnosis & severity	Prospective	ED	Adult	462	SIRS	Serum lactate	PCT best to identify sepsis; Lactate was best to diagnose severe sepsis
Gaieski et al., 2013 ¹⁴² , 2013	Tr: Lactate (POC)	Time to lactate & accuracy	Prospective	ED	Adult	40	SIRS	Serum lactate	POC & serum lactate correlate; reduce test time
Goyal et al., 2010 ¹⁴³ , US	Tr: Lactate (POC)	Time to lactate	Prospective	ED	Adult	149	SIRS	Serum lactate	POC lactate reduces test time
Gupta et al., 2019 ⁴⁰ , India	Tr: PCT	Sepsis diagnosis	Prospective	Acute	Adult	305	Sepsis-3	BC -ve sepsis	PCT identifies sepsis & can reduce dependence on BC
Hicks et al., 2014 ¹⁴⁴ , US	Tr: PCT	Sepsis diagnosis	Prospective	ED	Adult	66	SIRS	Non sepsis control group	Combination of SIRS criteria and PCT is useful for early detection of sepsis
Hollen et al., 2019 ¹⁴⁵ , UK	Tr: PCT	Sepsis diagnosis	Prospective	ED/ICU	Paediatric	29	ABA	≥ 3 of T <36.5 or >38.9, >2h failure to absorb feed, WBC<4.0 or >15, Platelets <100, INR>1.5, CRP >10, BSL >11, HR or RR >2 SDs above age-specific norms	PCT has poor detection of sepsis due to burns triggered SIRS

TRIGGERS – Cohort Studies									
Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) ± process measures ± outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Hunter et al. 2013 ¹⁴⁶ , US	Tr: ETCO2 vs Lactate	Sepsis diagnosis; correlation with lactate; mortality	Prospective	Acute	Adult	201	SIRS > 2 criteria + infection	Lactate	ETCO2 level correlates with lactate & in-hospital mortality
Hunter et al. 2016 ¹⁴⁷ , US	Tr: ETCO2	Sepsis diagnosis; Lactate correlation; mortality	Prospective	Prehospital	Adult/Paed/Neon	330	SIRS > 2 criteria + infection	Protocol non-compliant cohort	Screening with SIRS criteria & ETCO2 improves sepsis prediction
Ismail et al., 2015 ⁵⁰ , UK	Tr: Lactate (POC)	Sepsis diagnosis; time to test; cost	Prospective	Acute	Adult	26	Not specified	ABG analysers (2)	i-STAT POC device is more accurate, timely and efficient (in patients)
Karon et al., 2017 ⁴² , US	Tr: PCT vs Lactate vs NLCR	Sepsis diagnosis	Prospective	ED	Adult	501	Sepsis-1, SIRS	Biomarkers	Lactate best prediction of severe sepsis; other biomarkers have limited prediction
Kuttab et al., 2018 ¹⁴⁸ , US	Tr: Lactate (≥ 4)	Time to antibiotics & IV fluids; ICU & hospital LoS; 30 & 90 day mortality	Retrospective	Acute	Adult	121	ICD-9 codes	Usual care	Adding lactate ≥ 4 mmol/L alert improves recognition & earlier intervention
Lane (b) et al., 2020 ¹⁴⁹ , Canada	Tr: Temp, HR, SBP, RR, PaO2, GCS, age, glucose, ETCO2	Sepsis diagnosis; OD	Retrospective	Prehospital	Adult	131745	Sepsis-3	ICD10CA, ≥ 2 SOFA + infection or OD	Dispatch categories & high temperature identify infection; abnormal GCS, low SBP & abnormal RR detect sepsis
Leante et al. 2012 ¹⁵⁰ , Spain	Tr: Temp gradient >2 C	Sepsis diagnosis	Prospective	Acute/NICU	Neonate	31	SIRS	Central vs peripheral temp. ; CRP ≥ 1.2 mg/dL	Central-peripheral temperature gradient > 2 °C detects late-onset sepsis
Ljungstrom et al., 2017 ¹⁵¹ , Sweden	Tr: PCT vs NLCR vs CRP vs Lactate vs combination	Sepsis diagnosis	Retrospective	ED	Adult	1572	Sepsis 3	SIRS > 2 criteria, OD ≥ 2 rise in SOFA	Biomarker combinations better for detection; NLCR and PCT optimal
Loonen et al., 2014 ³⁵ , Netherlands	Tr: PCT, CRP, NLCR vs BC	Sepsis diagnosis	Retrospective	ED	Adult	125	SIRS > 2 criteria	Positive BC	PCT & NLCR differentiate SIRS patients with and without blood culture proven bacteraemia
Luo et al., 2018 ¹⁵² , China	Tr: PCT/Albumin vs CRP	Sepsis diagnosis	Retrospective	Acute	Adult	140	Sepsis 3	PCT/Albumin 0.44 vs CRP cut off 49	PCT/albumin ratio > 0.44 discriminates for sepsis & is a rapid biomarker at low-cost
Montassier et al., 2012 ¹⁵³ , France	Tr: BE vs lactate	Sepsis diagnosis; BE & lactate correlation	Prospective	ED	Adult	224	SIRS	Lactate > 3 mmol/L vs BE <-4	BE can predict elevated lactate & detect at-risk patients with sepsis earlier

TRIGGERS – Cohort Studies									
Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) ± process measures ± outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Pancer et al., 2011 ¹⁵⁴ , US	Tr: CRP	Sepsis diagnosis	Prospective	Acute	Adult	168	SIRS	CRP (cut off 52 mg/L) vs leucocytosis >12000	CRP can confirm early sepsis; greater efficiency in conjunction with clinical parameters
Perri et al., 2018 ¹⁵⁵ , Italy	Tr: Perfusion index vs CRP & BC	Mean perfusion index	Prospective	Acute	Neonate	80	Not specified	Positive BC	Lower perfusion index correlates with positive BC and high CRP
Ratzinger et al., 2013 ⁴¹ , Austria	Tr: PCT vs CRP	Sepsis diagnosis	Prospective	Acute	Adult	298	SIRS	SIRS > 2 criteria	PCT best predictors of sepsis
Reed et al. 2013 ¹⁵⁶ , US	Tr: Lactate vs Vital signs & Lab results	Sepsis diagnosis; hospital admission & LoS; readmission	Retrospective	ED	Paediatric	283	SIRS	Lactate (mean 2.4) correlation with HR, RR, WBC, Platelets, BUN, HCO ₃ , age	Serum lactate (2.4) correlates vital signs & lab results; predicts hospital admission & increased LOS
Romano et al., 2013 ¹⁵⁷ , Italy	Tr: PCT	Sepsis diagnosis	Prospective	Acute	Adult	140	SIRS	SIRS > 2 criteria	PCT is reliable in frail elderly patients; best cut-off 1.4 ng/ml
Scott et al., 2014 ¹⁵⁸ , US	Tr: Mentation, cold extremities, capillary refill, peripheral pulse	Organ dysfunction; time to antibiotics; ICU admission	Prospective	ED	Paediatric	239	SIRS	Usual care	Altered mentation & peripheral pulse quality were associated with OD with low sensitivity & high specificity
Shetty et al., 2018 ⁴⁹ , Australia	Tr: Lactate thresholds	ICU LoS; mortality	Retrospective	ED	Adult	12349	Sepsis 3	Usual care, lactate cut-off values	Serum lactate of ≥2 mmol/L threshold triggers escalation of care & should be included in sepsis screening algorithms
Singer (a) et al., 2014 ⁴⁸ , US	Tr: Lactate (POC)	Time to lactate, IV fluids & antibiotics; ICU admission & LoS; mortality	Prospective	ED	Adult	160	SIRS ≥ 2 criteria, infection	Serum lactate	POC lactate reduces test & IV fluids time, mortality & ICU admission but not time to antibiotic
Swan et al., 2018 ⁵¹ , Australia	Tr: Lactate (POC)	Sepsis diagnosis	Retrospective	Prehospital	Adult	155	Not specified	Serum lactate	POC lactate prediction was poor & diminished with increasing time between measurements
Tromp et al., 2012 ¹⁵⁹ , Netherlands	Tr: PCT vs PCT+CRP	Sepsis diagnosis	Prospective	ED	Adult	342	SIRS ≥ 2 criteria	Clinical assessment, biomarker correlation	PCT had the best predictive value & does not improve in combination with CRP or clinical signs

TRIGGERS – Cohort Studies									
Author, year country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) ± process measures ± outcomes	Study design (cohort)	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Tsalik et al., 2012 ¹⁶⁰ , US	Tr: PCT vs CRP	Sepsis diagnosis; ICU admission; hospital LoS	Prospective	ED	Adult	336	SIRS ≥ 2 criteria	Clinical assessment, biomarker correlation	PCT & CRP improve diagnostic accuracy but not outcome prediction
Uusitalo-Seppala et al., 2011 ¹⁶¹ , Finland	Tr: PCT vs CRP	Sepsis diagnosis; ICU admission; 28 day mortality	Prospective	ED	Adult	539	SIRS	Clinical assessment	PCT proved superior to CRP in detecting patients with severe sepsis
Visveswari et al., 2019 ¹⁶² , Singapore	Tr: NLCR vs PCT vs CRP vs Lactate vs combined	Sepsis diagnosis	Prospective	ED	Adult	126	SIRS ≥ 2 criteria	SIRS ± infection	NLCR outperforms other markers in diagnosing sepsis.
Yasafumi et al., 2019 ¹⁶³ , Japan	Tr: Capillary refill	Sepsis diagnosis; ease of use	Retrospective	ED	Adult	75	Sepsis 3	qSOFA ≥2, SIRS>2, Lactate	Capillary refill comparable to qSOFA or serum lactate, alternative non-invasive measure

TOOLS – Systematic Reviews

Author (year) country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Alberto et al., 2017 ⁶⁵ , Australia	EHR - EWA (NST)	Sepsis diagnosis; time to lactate, IV fluids & antibiotics; ICU admission & LoS; mortality	Acute	Adult	33514	SIRS > 2 criteria, SSC 2016	Usual care, clinician assessment, chart audit	Nurse screening tool more sensitive, process measures enhanced, inconclusive outcomes
Despins et al., 2017 ¹⁶⁴ , US	EHR - EWA	Sepsis diagnosis	ED	Adult/Paed/Neon	147374	SIRS ≥ 2 criteria	Alternative MLA models	Automated alerts lead to early sepsis treatment
Fleuren et al., 2020 ¹⁷ , Netherlands	EHR - EWA (MLA)	Sepsis diagnosis	ED/Acute/ICU	Adult	4113833	Sepsis3	Alternative MLA models	Machine learning models can accurately predict sepsis
Joshi et al., 2020 ⁶⁸ , UK	EHR - EWA	Time to antibiotic; LoS & mortality	ED/Acute	Adult	8102	SIRS > 2 criteria	Usual care, chart audit	Automated alerts improve sepsis outcomes i.e. LoS.
Lane (a) et al., 2020 ¹⁶⁵ , Canada	Sepsis alert, qSOFA, PITSTOP, qSOFA+ETCO2, PRESS, SEPSIS, BAS 90-30-90, MEWS, PRESEP, MBIS, PSP, PreSAT, PHANTASi, Robson score, SIRS, HEWS, SIRS+ETCO2	Sepsis diagnosis	Prehospital	Adult	131745	Sepsis3	ICD10CA, > 2 SOFA + infection or OD	No strategy had both high sensitivity and specificity; CIP, NEWS and qSOFA best detected sepsis; recommend qSOFA for paramedics
Makam et al., 2015 ¹⁶⁶ , US	EHR - EWA	Sepsis diagnosis; time to lactate, IV fluids & antibiotics; ICU admission & LoS; mortality	ED/Acute/ICU	Adult	35423	SIRS > 2 criteria	Clinician chart review	Sepsis alerts improve processes but not mortality or LoS
Smyth et al., 2016 ¹⁶⁷ , UK	BAS 90-30-90 vs CIS vs MEWS vs Robson	Sepsis diagnosis	Prehospital	Adult	147320	Sepsis3	In-hospital diagnosis	Inconclusive

TRIGGERS – Systematic Reviews

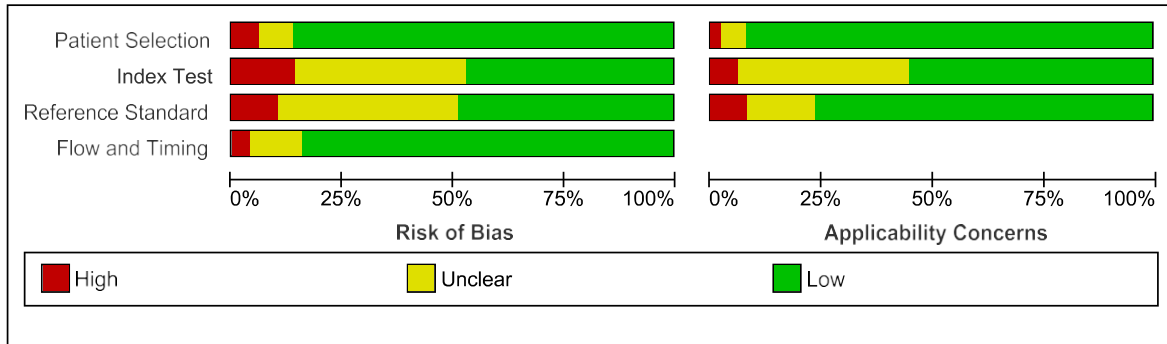
Author (year) country	Tool/Trigger (Tr) (components)	Aim Diagnostic accuracy (sepsis diagnosis) + process measures + outcomes	Setting	Population	N	Sepsis Definition	Reference standard	Interpretation
Ciriello et al., 2013 ²² , UK	Tr: PCT vs CRP	Sepsis diagnosis	ICU	Adult	3969	Sepsis-1	PCT vs CRP	PCT discriminates for sepsis but effectiveness varies according to cut off level
Eschborn et al., 2019 ³⁹ , US	Tr: PCT vs CRP	Sepsis diagnosis	Acute	Neonate	3699	Not specified	PCT vs CRP	PCT & CRP perform better when trended serially & in combination with other clinical & laboratory data
Kondo et al., 2019 ¹⁶⁸ , Japan	Tr: PCT vs Pepsin	Sepsis diagnosis; mortality	ICU	Adult	3012	Sepsis3	PCT vs Pepsin	PCT & Pepsin effective for sepsis diagnosis
Liu et al., 2019 ¹⁶⁹ , China	Tr: CRP	Sepsis diagnosis	Acute	Neonate	1819	Not specified	CRP cut off thresholds	CRP effective for detecting neonatal sepsis
Morris et al., 2017 ¹⁷⁰ , UK	Tr: Lactate (POC)	Time to lactate, & antibiotics; LoS; mortality	Prehospital/ED	Adult/Paed	3063	SIRS \geq 2 criteria	Serum lactate	Lack of evidence supporting POCT Lactate in community settings
Su et al., 2014 ¹⁷¹ , Taiwan	Tr: PCT vs CRP	Sepsis diagnosis	Acute	Neonate	2178	Microbiology	Clinician assessment & micro	PCT most reliable in cord blood
Trippella et al., 2017 ¹⁷² , Italy	Tr: PCT	Sepsis diagnosis	ED	Paediatric	7260	Sepsis3	PCT cut off for bacterial infection	PCT useful in severe infections
Yu et al., 2010 ¹⁷³ , China	Tr: PCT vs CRP	Sepsis diagnosis	Acute/ICU	Neonate	2836	Microbiology	Clinician assessment & micro	PCT more useful than CRP

Appendix 5 Grey literature

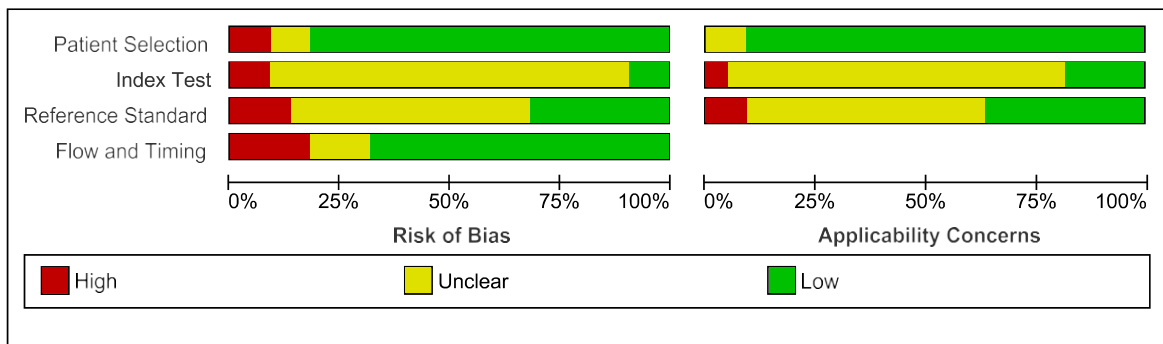
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Appendix 6 Overall study quality

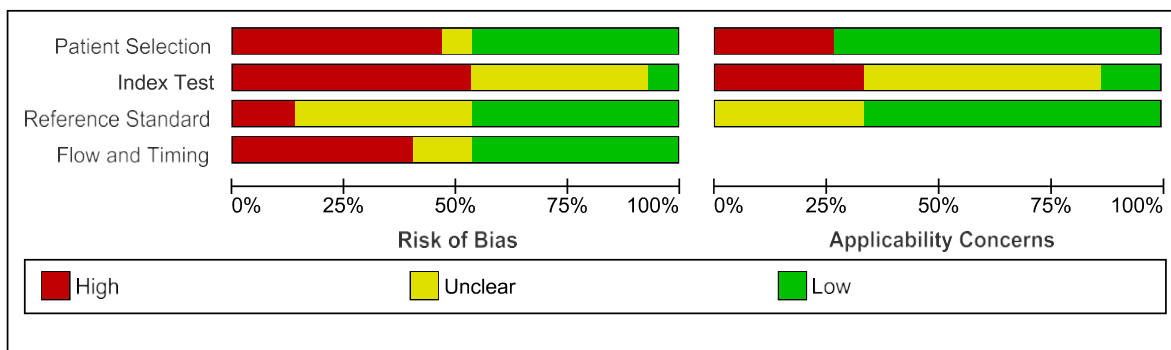
Cohort diagnostic studies (tools) by study and combined summary graph



Cohort process and outcomes studies (tools) by study and combined summary graph



Systematic reviews (tools) by study and combined summary graph



Appendix 7 Description and components of tools and triggers

Code	Definition	Score (suggesting sepsis)	Temp C°	Pulse (min)	SBP mmHg	Resp (min)	SaO2%	GSC	OTHER
100 100 100	Nurse screening tool vital sign combination	> 2	> 37.8	> 100	< 90 (> 40 change)	> 20	< 90	< 15	Suspected infection
BAS 90-30-90	Pre-hospital vital sign combination				< 90	> 30	< 90		
EMIP	Early Maternal Infection Prompts		> 37.5		< 100	> 20	> 100		
ESI	Emergency Severity Index (triage scale)	1 to 5			–	–			
LqSOFA	Lactate + quick Sequential Organ Function Assessment	0 to 3			< 100	> 22		< 15	Lactate
Maternal EWS	Maternal Early Warning Score	1 or 2 or > 2	≥ 37.5 or ≤ 36	> 100 or < 50	> 150 or < 100	21 to 30		< 15	
MBIS	Mecklenburg Bacterial Infection Scale		> 37.8 or < 35	≥ 120	< 100			< 15	Suspected infection
MEDS	Mortality in ED Sepsis score	> 15 (40% mortality)		Shock	Shock	Tachypnoea	Hypoxia	< 15	Terminal illness Age > 65 years Platelets <150x10 ⁹ /L Nursing home resident Lower respiratory infection
MEWS	Modified Early Warning Score (n)	> 5	< 35 (+1) 35-48.4 (0) > 38.5 (+2) –	< 40 (+2) 41-50 (+1) 50-100 (0) > 200 (+2)	< 70 (+3) 71-80 (+2) 81-100 (+1) 101-199 (0) > 200 (+2)	< 9 (+2) 9-14 (0) 15-20 (+1) 21-29 (+2) > 30 (+3)		A (0) V (+1) P (+2) (U)	
MLA	Machine Learned Algorithm		–	–	–	–			
NEWS	National Early Warning Score (n)	> 5	< 35 (+3) < 36 (+2) 31-38 (0) 38.1-39 (+1) > 39.1 (+2)	< 40 (+2) 41-50 (+1) 51-90 (0) 91-110 (+1) 111-130 (+2) > 131 (+3)	< 90 (+3) 91-100 (+2) 101-110 (+1) 111-219 (0) > 220 (+3)	< 8 (+3) 9-11 (+1) 12-20 (0) 21-24 (+2) > 25 (+3)	≤91(+3) 92-93 (+2) 94-95 (+1) ≥96 (0)	A (0) V (+3) P (+3) (U+3)	Supp. 02 (Y/N)
PHANTASi	Prehospital Antibiotics Against Sepsis		> 38 or < 36	> 90		> 20			

Code	Definition	Score (suggesting sepsis)	Temp C°	Pulse (min)	SBP mmHg	Resp (min)	SaO2%	GSC	OTHER
PITSTOP	Paramedic Initiated Treatment of Sepsis Targeting Out-of-Hospital Patients	> 38		< 100					
POC	Point of Care (testing)								
PRESEP	Prehospital Early Sepsis Detection score	> 4	> 38 or < 36	> 90	< 90	> 22	< 92		
PRESS	Prehospital Severe Sepsis score (Prehospital)				<90		< 90	< 15	Age, Dispatch priority, source
qSOFA	quick Sequential Organ Function Assessment						RR >22		
RETTS	Rapid Emergency Triage and Treatment System		>38.5°	>110 or <50			≤95	<15	
Robson	Robson screening tool (Prehospital)		> 38.3 or < 36	> 90		> 20		< 15	BSL > 6.6 mmol/L
SIRS	Systemic Inflammatory Response Syndrome	≥ 2	> 38 or < 36	> 90		> 20			
SJSA	St. John's Sepsis Agent (EHR algorithm)	≥ SIRS			< 90				Supp. O2 (Y/N) Lactate > 2 Total bilirubin ≥2.0 and <10.0 mg/dL Creatinine: Δ↑0.5 mg/dL
SOFA	Sequential Organ Function Assessment				< 70 MAP			13-14 (+1) 10-12 (+2) 6-9 (+3) < 6 (+4)	Vasoactive agents Ventilated/FiO2, PaO2 Platelets Total bilirubin ≥2.0 and <10.0 mg/dL
SOS	Sepsis in Obstetrics Score	≥ 6	> 38.4 or < 36		< 90	Dec-24	< 92		WBC > 16-9 or < 5.7 Lactate < 4
SPoT	Shock Precautions on Triage vital-signs criterion								EHR-MLA algorithm
SSS	Sepsis Screening Score		Temp			RR		< 15	WBC
tCFI	triage Concern-For-Infection								Provisional infection diagnosis
TREWS score	Targeted Real-time Early Warning Score for septic shock (54 characteristics)			Hypotension	HR/SBP	HR	RR		

Appendix 8 Biomarkers

Procalcitonin, CRP and NLCR

	Cut off intervals ^{1,2,3}	No. of studies (sample)	Studies mean cut off	Diagnostic accuracy – mean (range)							Evidence	
				Sn%	Sp%	PPV%	NPV%	LR+	LR-	AUROC		DOR
PCT ng/ml	<0.5	14 (3663)	0.27 (0.004-0.45)	83.70 (63.0-100)	63.90 (37.50-100)	39.60 (26.10-59.70)	88.13 (68.80-93.80)			0.725 (0.652-0.786)	1.01 (n=1)	Strong
	≥0.5 - <2	33 (15251)	0.86 (0.50-1.74)	79.90 (24.0-100)	72.11 (22.0-100)	46.23 (26.30-84.62)	89.45 (81.82-100)	2.42 (1.30-3.90)	0.41 (0.16-0.66)	0.833 (0.620-0.965)	12.52 (3.98-29.44)	
	≥2 - <10	26 (7321)	3.24 (2.0-9.99)	70.97 (15.40-98.6)	77.87 (48.0-100)	60.69 (27.30-97.47)	83.19 (67.50-93.18)	5.15 (1.40-8.90)	0.355 (0.01-0.70)	0.843 (0.682-0.967)	13.70 (4.05-26.50)	
CRP mg/L	< 50	63 (7463)	10.80 (1.0-49.0)	68.75 (25.0-100.0)	76.45 (22.0-100.0)	47.19 (26.5-67.77)	72.40 (60.49-89.0)	5.63 (n=1)	0.36 (n=1)	0.70 (0.408-0.899)	8.22 (1.28-17.99)	Strong
	≥ 50 - <100	2 (218)	56.0 (52.0-60)	61.6 (51.6-75.0)	62.25 (53.3-70.7)	42.5 (32.0-54.0)	77.7 (70.4-85.0)	1.85 (n=1)		0.670 (0.556-0.777)	1.69 (n=1)	
	≥ 100	6 (2270)	128.33 (100.0-200.0)	43.93 (12.0-80.0)	77.03 (41-100)	37 (33-41)	86.25 (82.50-90.0)			0.635 (0.60-0.667)		
NLCR	< 5	2 (1572)	3.0 (2.5-3.5)	22.20 (14.9-29.5)	89.75 (84.20-95.30)	57.40 (51.0-63.80)	67.50 (66.80-68.20)			0.656 (0.646-0.666)	2.86 (2.23-3.54)	Strong
	≥ 5 - <10	2 (251)	9.3 (8.6-10.0)	75.30 (65.60-85.0)	48.50 (31.0-66.0)	45.25 (26.0-64.50)	80.60 (67.20-94.0)			0.7253 (0.735-0.770)		

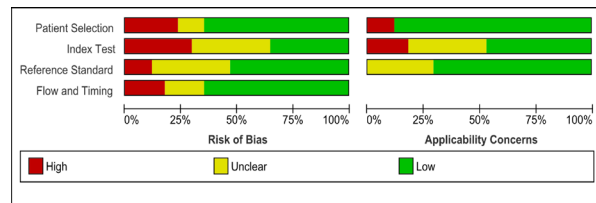
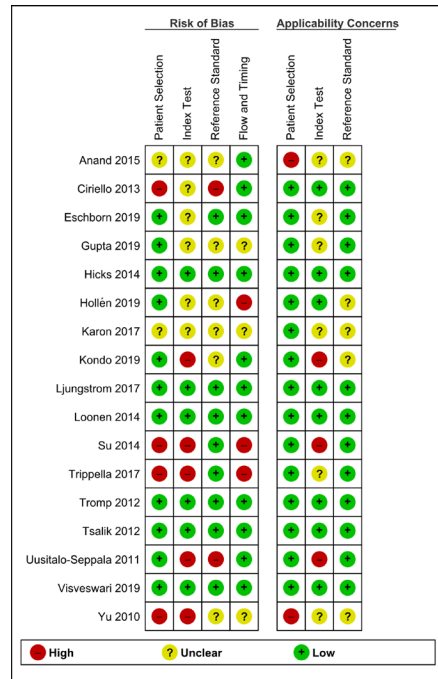
1. PCT cut off ¹⁷⁹ 0.5 ng/mL - systemic infection not likely; ≥0.5 - <2 ng/mL - significant, but moderate SIRS, sepsis likely; ≥2 - <10 ng/mL severe sepsis, SIRS most likely due to infection (sepsis) with high risk of developing organ dysfunction; ≥10 ng/mL – SIRS due to severe bacterial sepsis or septic shock; In healthy neonates, plasma PCT concentrations increase gradually after birth, reaching peak values at about 24 hours of age and then decrease to normal values below 0.5 ng/mL by 48-72 hours of age.¹⁸⁰

2. CRP cut off in the normal human population has a median of 0.8 mg/l (IQR 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples with levels above suggesting the presence of SIRS.³⁷ The discriminatory CRP level for sepsis is variable depending on the infective cause and population cohort but published data point to a CRP value between 50 and 100 mg/l.³⁷

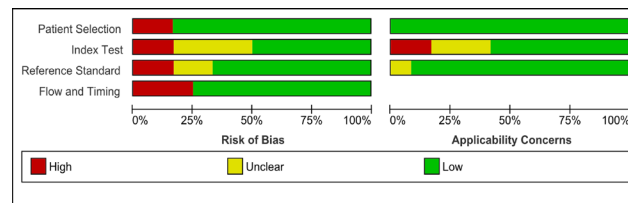
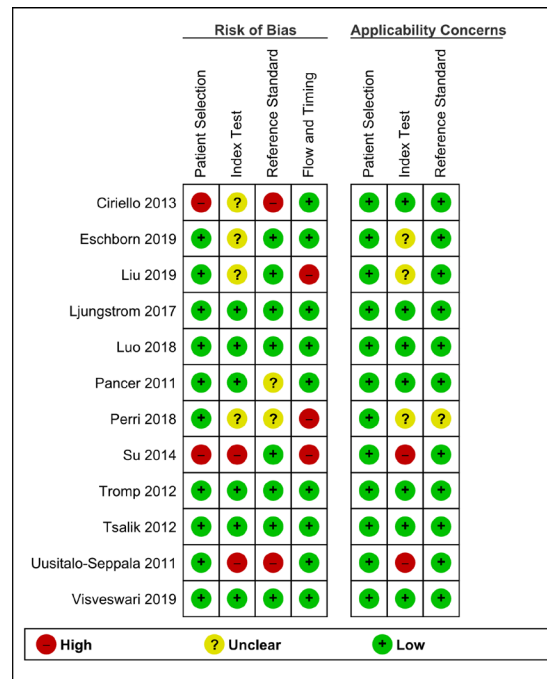
3. NLCR There are few studies that have set out to address NLCR cut off levels categorically but published studies have suggested the range is between 5 to 10.^{162,181}

Procalcitonin, CRP and NLCR studies methodological quality by study and combined summary graph

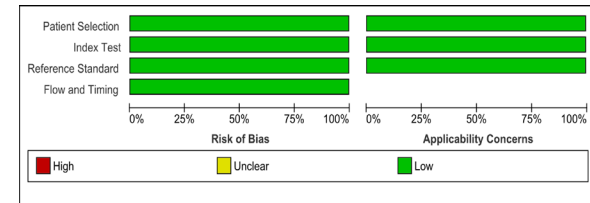
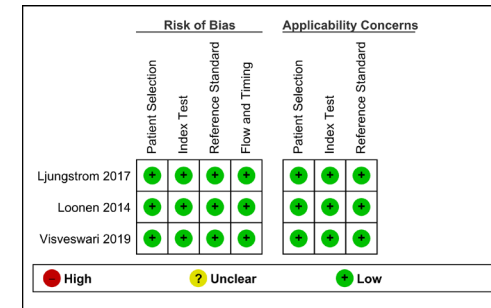
Procalcitonin



CRP



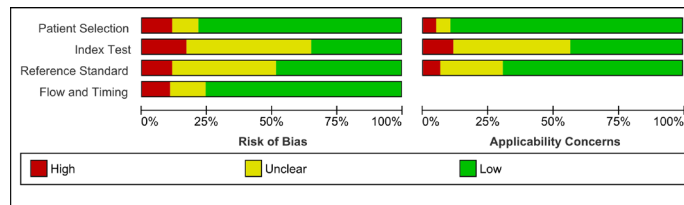
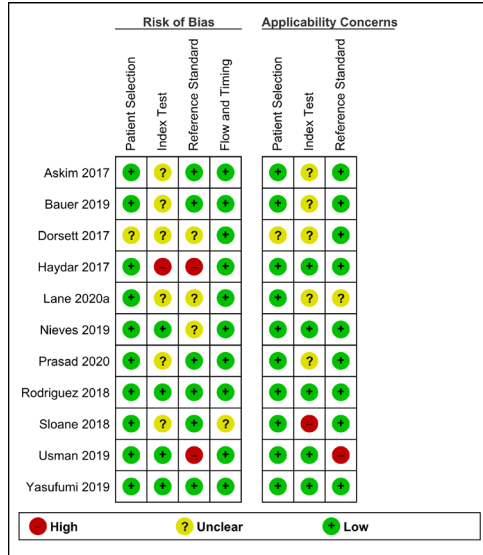
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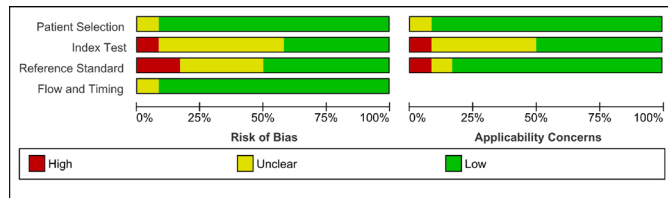
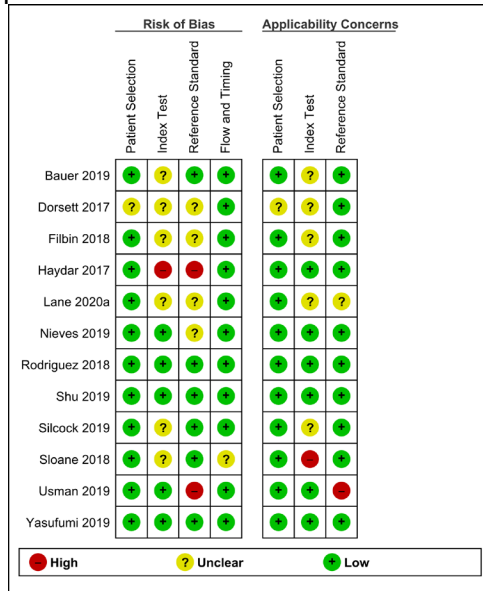
Appendix 9 Sepsis tool study quality

Sepsis tools study methodological quality assessment of study and combined

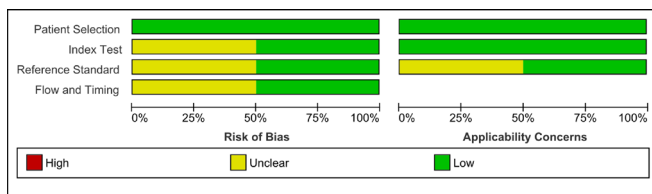
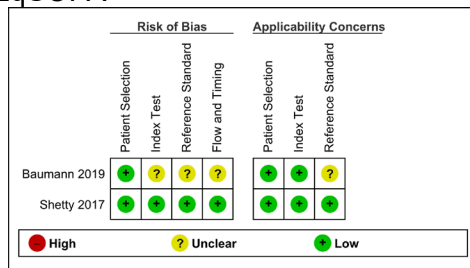
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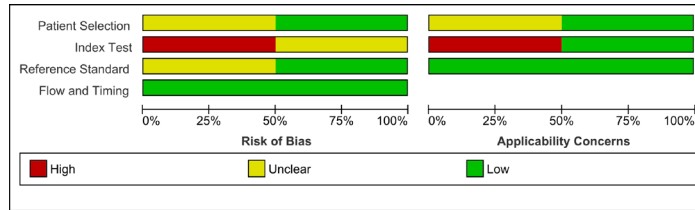
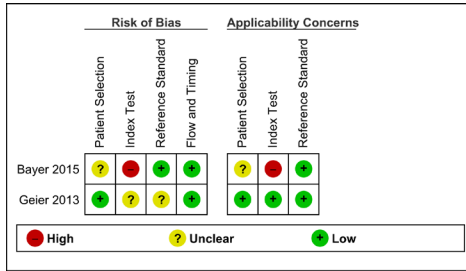
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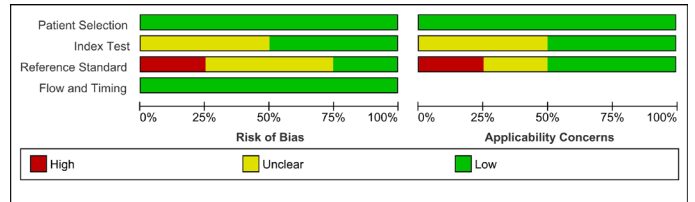
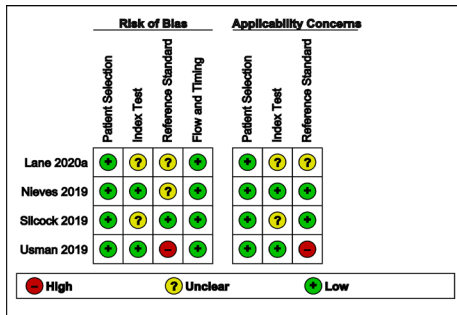
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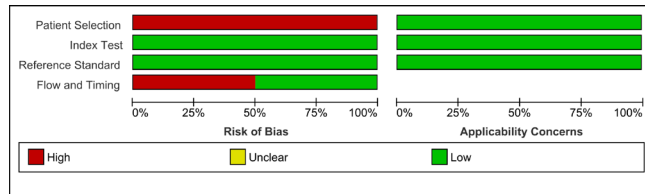
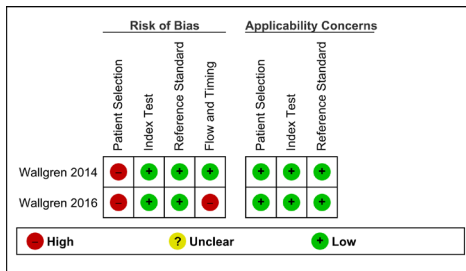
MEWS



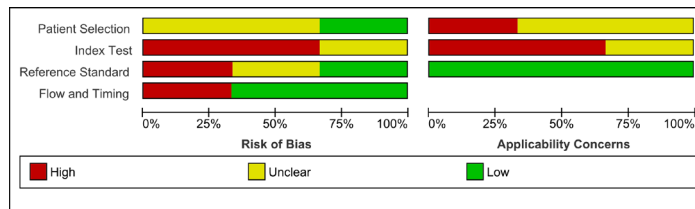
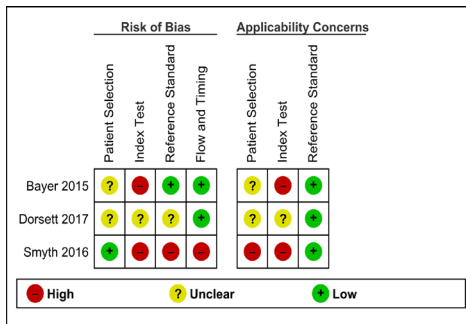
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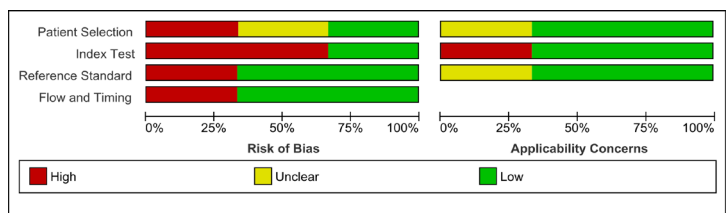
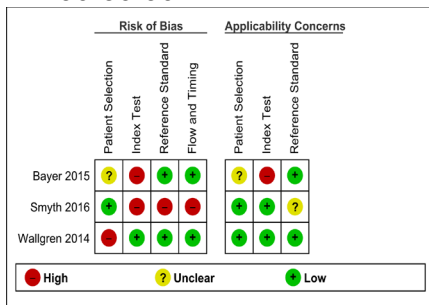
Robson Tool



Modified Robson Tool



BAS 90-30-90



Appendix 10 Prehospital tools

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
qSOFA								
Lane 2020	Prospective	131745	SIRS (cut-off ≥ 2) MEWS (cut-off ≥ 4) NEWS (cut-off ≥ 4) BAS (cut-off ≥ 1) Robson (cut-off ≥ 2) Others	40	99	PPV%: 68 NPV% 79 C-stats: 0.77 Predictive ability# At score 1: 0.25 At score 2: 0.60 At score 3: 0.87 PPV% (95% CI): 32.0 (25.8-38.8) NPV% (95% CI) 96.0 (95.1-96.8) +LR 6.86 (5.35 - 8.80) -LR 0.60 (0.53 - 0.70) AUROC (95% CI) 0.79 (0.74–0.83)	Mortality Sn: 40.6% Sp: 91.9%	qSOFA Sn = SIRS qSOFA Sn < MEWS, NEWS, BAS, Robson
Shu 2019	Retrospective	2292	Clinical diagnosis	42.9 (35.1- 51.0)	93.8 (92.6-94.7)		30-day Mortality AUROC: 0.68 (p = 0.01) 48 hrs ICU admission AUROC: 0.68 (p = 0.06) ICU LOS: 2.8 days	qSOFA Sn low for both identifying sepsis and mortality
Silcock 2019	Retrospective	1713	NEWS					qSOFA < NEWS in identifying adverse outcomes
Sloane 2018	Prospective	236	SIRS (cut-off > 2) 100-100-100 13-72 h prior admission <12h prior admission	7 27	96 88	+LR 2.53 - LR 0.72		qSOFA Sn < SIRS (cut-off ≥ 2) and 100-100-100
Dorsett 2017	Retrospective	152	SIRS (cut-off ≥ 2) Mod Robson Guerra	16.3 27.9 – 58.1 ^s	97.3 78 – 94.5 ^s	+LR 5.91 - LR 0.86		qSOFA Sn < SIRS and Mod Robson qSOFA Sn > Guerra

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key Findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
SIRS								
Lane 2020	Prospective	131745	qSOFA (cut-off ≥ 2) MEWS (cut-off ≥ 4) NEWS (cut-off ≥ 4) BAS (cut-off ≥ 1) Robson (cut-off ≥ 2) Others	45 43-47	72 71-73	PPV%: 31 NPV% 83 C-stats: 0.63 Predictive ability# At score 1: 0.17 At score 2: 0.24 At score 3: 0.33	SIRS (cut-off ≥ 2) Sn = qSOFA (cut-off ≥ 2) SIRS Sn < MEWS, NEWS, BAS, Robson	
Sloane 2018	Prospective	236	qSOFA 100-100-100 13-72 h prior admission <12h prior admission	10 36	94 86		SIRS (cut-off ≥ 2) Sn > qSOFA (cut-off ≥ 2)	
Dorsett 2017	Retrospective	152	qSOFA (cut-off ≥ 2) qSOFA plus Mod Robson Guerra	39.5	84.4	+LR 2.53 -LR 0.72	SIRS (cut-off ≥ 2) Sn > qSOFA (cut-off ≥ 2) and Guerra SIRS (cut-off ≥ 2) Sn < Mod. Robson	

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key Findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
NEWS								
Lane 2020	Prospective	131745	qSOFA (cut-off ≥ 2) MEWS (cut-off ≥ 4) NEWS (cut-off ≥ 4) BAS (cut-off ≥ 1) Robson (cut-off ≥ 2) Others			C-stats: 0.76 Predictive ability# At score 3: 0.12 At score 6: 0.26 At score 9: 0.49 At score 12: 0.72 At score 15: 0.88 At score 16: 0.93		NEWS predictive ability > qSOFA, SIRS MEWS, BAS, Robson
Silcock 2019	Retrospective	1713	qSOFA	10 36			30-day Mortality AUROC 0.7 ICU admission in 48h AUROC 0.7-0.8	NEWS > qSOFA in identifying adverse outcomes
					94 86			
MEWS								
Bayer 2015	Retrospective	375	MEWS (cut-off ≥ 4) PRESEP (cut-off ≥ 4) BAS 90-30-90 Mod. Robson Tool	74	75	AUROC 0.77 PPV% 45 NPV% 91		MEWS Sn (cut-off ≥ 4) > BAS 90-30-90 MEWS Sn (cut-off ≥ 4) < PRESEP (cut-off ≥ 4) & Mod Robson Tool

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key Findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
BAS 90-30-90								
Wallgren 2014	Retrospective	353	Robson	43* 70**	68.3	+LR 2.3 -LR 0.67		BAS 90-30-90 Sn < Robson Tool
Bayer 2015	Retrospective	375	MEWS (cut-off ≥4) PRESEP (cut-off ≥4) Mod. Robson Tool	62	83	PPV% 51 NPV% 89		BAS 90-30-90 Sn < MEWS (cut-off ≥4), PRESEP (cut-off ≥4), Mod. Robson Tool
Robson								
Wallgren 2016	Retrospective	353	Clinical judgment	63	68.3		Hospital mortality OR 4.0	Robson Tool Sn > clinical judgement
Wallgren 2014	Retrospective	577	BAS 90-30-90	75				Robson Tool Sn > BAS 90-30-90
Modified Robson Tool								
Dorsett 2017	Retrospective	152	SIRS (cut-off ≥2) qSOFA (cut-off ≥2) qSOFA plus Guerra	46.5	79.8	+LR 2.3 -LR 0.67 AUROC 0.54	Mortality AUROC 0.62	Mod Robson tool Sn > SIRS (cut-off ≥2), qSOFA (cut-off ≥2), qSOFA plus, Guerra
Smyth* 2016	Systematic review	147,320	CIS PRESS PRESEP Robson Tool BAS 90-30-90 MEWS	43 (28-58)* 30 (12-47)**	14 (1-40)** 77 (60-95)**			Mod Robson tool Sn < Robson, BAS 90-30-90, MEWS
Bayer 2015	Retrospective	375	MEWS (cut-off ≥4) PRESEP (cut-off ≥4) BAS 90-30-90 Mod. Robson Tool	95	43	PPV% 32 NPV% 97		Mod. Robson tool Sn > BAS 90-30-90, MEWS (cut-off ≥4) & PRESEP (cut-off ≥4)

Appendix 11 ED and acute care tools

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy				Outcome measures		Key findings
				Sn% (95% CI)	Sp% (95% CI)	Others				
qSOFA										
Bauer et al., 2019	Retrospective	410	MEW, SIRS	50 (33–67)	95 (91–98)					qSOFA < MEW < SIRS
Nieves 2019	Prospective	2523	SIRS NEWS ESI			+LR 5.13# /15## - LR 0.36# /0.85##		Hosp OR 4.6 (2.8-7.6) 30-d OR 3.9 (2.5-5.9)		qSOFA (cut-off ≥2) Sn < SIRS qSOFA (cut-off ≥1) = SIRS
Usman, 2019	Retrospective	115734	qSOFA (cut-off ≥1)# qSOFA (cut-off ≥2)## NEWS > 4 SIRS ≥ 2 qSOFA ≥ 2	69.2 (53.9–82.1)# 15.4 (5.1–28.2)## 28.5%	86.5 (85.1–87.8# 99.0 (98.5–99.4)## 98.9%	AUROC (95% CI) 0.81 (0.73–0.87)## AUROC: 0.81		ICU admission OR 4.2 (3.1–5.7)		qSOFA<NEWS<SIRS
Yasafumi, 2019	Retrospective	75	SIRS Q-CRT Q-CRT+qSOFA Lactate	66.7	100	AUROC (95% CI) 0.84 (0.73–0.91)				qSOFA Sn <SIRS, Q-CRT+qSOFA and Lactate qSOFA Sn > QCRT
Filbin 2018	Retrospective	19670	sPOT tCFI	28 (16–43%)	97 (96–97%)					QSOFA Sn < sPOT
Rodriguez, 2018	Retrospective	3743	SIRS qSOFA (cut-offs ≥1*/ ≥2**/≥3***) Lactate (cut-off ≥2/ ≥4)					Composite outcome§ Sn% 86.1*/53.5**/17.6*** Sp% 56.1*/89.1**/98.3** PPV% 24*/43.8**/61.6*** NPV% 96.3*/92.4**/88.3*** AUROC 0.79		qSOFA (cut-off ≥1) Sn = SIRS in predicting critical illness qSOFA (cut-off ≥2 & ≥3) Sn <SIRS in predicting critical illness
Dorsett 2017	Retrospective	152	Initial ED admission Entire ED course	27.9 (15.3–43.7) 67.4 (51.5–80.9)	93.6 (87.2–97.4) 86.2 (78.3–92.0)	+LR 4.35 4.9	- LR 0.77 0.38			Low to moderate qSOFA Sn
Haydar 2017	Retrospective	200	SIRS					Mortality Sn%: 90.9; Sp: 46% PPV%: 17.2; NPV%: 97.6 AUROC: 0.68		qSOFA Sn > SIRS in predicting sepsis-related mortality

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key Findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
LqSOFA								
Shetty 2017	Retrospective	12555	SOFA, qSOFA				Primary outcome ^{\$\$} Sn% (95% CI) 65.5 (62.6–68.4) Sp% (95% CI) 81.5 (80.8–82.2) PPV% (95% CI) 25.0 (23.9–26.1) NPV% (95% CI) 96.2 (95.9–96.5) RR 3.5 (3.3–3.8) NNT 2.1 (2.2–2.0) OR 8.4 (7.3–9.6)	LqSOFA (cut-off ≥2) > qSOFA LqSOFA (cut-off ≥2) < SOFA In identifying adverse outcomes
Baumann 2019	Retrospective	3743	LqSOFA (Multiple cut-offs) qSOFA (cut-off ≥1/ ≥2/ ≥3) Lactate (cut-off ≥2/ ≥4)				Primary outcome ^{\$\$\$} Sn% 17.4*/38.5**/57.0*** Sp% 98.7*/ 93.4**/81.5*** PPV% 75.0*/56.3**/40.3*** NPV% 84.5*/87.4**/89.6*** 72 Hrs Mortality Sn: 91.9** - 97.6*; Sp: 29.7* - 56.6**	qSOFA ≥1 & Lactate ≥2 > qSOFA & Lactate in predicting adverse outcomes including mortality
SIRS								
Askim 2017	Prospective	1535	qSOFA	74 (65-82)	72 (70-75)	PPV% 18 NPV% 97		SIRS (cut-off ≥2) Sn > qSOFA (cut-off ≥2)
Bauer et al., 2019	Retrospective	410	MEW, SIRS	93 (81–99)	63 (55–71)			SIRS > MEW > qSOFA
Haydar 2017	Retrospective	200	SIRS				Mortality Sn% 95.9; Sp%: 5.6 PPV%: 11.2; NPV%: 90.9 AUROC: 0.51	qSOFA Sn > SIRS in predicting sepsis-related mortality
Nieves 2019	Prospective	2523	qSOFA NEWS ESI	56.4 (41.0-71.8)	86.4 (85.0-87.8)	AUROC (95% CI) 0.81 (0.73-0.87)	Hosp mortality OR = 2.7 (2.0-3.7) 30-day mortality OR 2.2 (1.7-2.8) ICU admission OR = 2.3 (1.9-2.7) Tm to sepsis diagnosis 26 min Hosp mortality OR: 1.39 (1.20–1.61) (P<0.001 compared to SOFA) ICU LOS: 2.8 day Time to Ab: 2.7 hr (1.5-4-9)	SIRS (cut-off ≥2) Sn > qSOFA (cut-off ≥2)
Prasad 2020	Retrospective	16612	Sepsis 3 (SOFA)					Odds of mortality SIRS > SOFA Tm to Abs SIRS < SOFA
Rodriguez, 2018	Retrospective	3743	qSOFA (cut-off ≥1/ ≥2/ ≥3) Lactate (cut-off ≥2/ ≥4)				Composite outcome** Sn% 86.7 (83.5 to 89.5) Sp% 45.6 (43.9 to 47.3) PPV% 95.6 (94.5 to 96.4) NPV% 0.29 (0.23 to 0.36) AUROC 0.75	SIRS Sn > qSOFA ≥2 & ≥3 in predicting critical illness SIRS Sn = qSOFA ≥1 in predicting critical illness
Usman, 2019	Retrospective	115734	NEWS > 4 SIRS ≥ 2 qSOFA ≥ 2	86.1%	79.1%	AUROC: 0.88		SIRS > NEWS > qSOFA
Yasufumi 2019	Retrospective	75	Q-CRT, qSOFA Q-CRT+qSOFA, Lactate	81	40	AUROC (95% CI) 0.61 (0.49–0.72)		SIRS Sn > qSOFA, Q-CRT & Lactate SIRS Sn similar to Q-CRT+qSOFA

\$Death, vasopressor use or ICU admission within 72 hr \$\$Composite of mortality or prolonged ICU stay (≥72 h); \$\$\$composite of ICU stay, receipt of vasopressor support, and hospital death within 72 h of presentation; *qSOFA ≥2 & Lactate ≥4; ** qSOFA ≥2 & Lactate ≥2; *** qSOFA ≥1 & Lactate ≥2;

Author Year	Study type	N	Comparator(s)	Diagnostic accuracy			Outcome measures	Key Findings
				Sn% (95% CI)	Sp% (95% CI)	Others		
NEWS								
Nieves 2019	Prospective	2523	qSOFA (cut-off ≥ 1 & ≥ 2) SIRS (cut-off ≥ 2) NEWS (cut-off ≥ 4)	71.8 (56.4–84.6)	90.2 (89.1–91.3)	AUROC 0.85 (95% CI 0.77–0.92)	Overall/30-day Mortality & ICU admission OR 1.5	NEWS (cut-off ≥ 4) Sn > qSOFA (cut-off ≥ 1 & ≥ 2) and SIRS (cut-off ≥ 2) for sepsis diagnosis NEWS < qSOFA & SIRS for odds of adverse outcomes
Usman 2019	Retrospective	115,734	SIRS NEWS ≥ 4	Severe sepsis/ Septic shock 84.2 Septic shock 88.1	85 84.8	AUROC 0.91 0.93	Sepsis Mortality Sn% 92.9; Sp%: 84.5	NEWS (cut-off ≥ 4) > SIRS (cut-off ≥ 2) & qSOFA (cut-off ≥ 2) for sepsis diagnosis and mortality
Greier 2013	Retrospective	151	MEWS (cut-off ≥ 5) ESI (cut-off ≤ 2) MEDS (cut-off ≥ 8)	37	80	MEWS AUROC 0.64 (0.55–0.73) PPV% 62 NPV% 59 +LR 1.81 -LR 0.8	Mortality AUROC 0.62	MEWS (cut-off ≥ 5) Sn < ESI (cut-off ≤ 2) & MEDS (cut-off ≥ 8)

Appendix 12 Lactate results

Lactate diagnostic accuracy, process measures and patient outcomes

Lactate (mode & cut-off mmol/L)	Author, year	Study Type	N	Study Lactate	Sn% (95%CI)	Sp% (95%CI)	Diagnostic Accuracy		Process and outcome measures (95%CI)	Key findings	
							AUROC (95% CI)	Others			
ADULT											
Prehospital pLA	ns	Morris (13), 2014	Prospective	59	ns					Mortality (H) pLA 49.5 vs 55% sLA; p=0.78; LoS ED pLA 216 vs 396 min sLA;p=0.02	Reduced ED LoS
		Swan, 2018									
	≥2	Boland, 2016	Prospective	112	4	19	91				Does warrant ED pre-notification
	<2	Shetty, 2018	Retrospective	1234 9	1 2 3 4					Mortality (H) OR 2.93 (2.08 - 4.13)* Mortality (H) OR 2.77 (2.34 - 3.29)* Mortality (H) OR 3.26 (2.80 - 3.80)* Mortality (H) OR 4.01 (3.40 - 4.73)*	Screening algorithms for adverse outcomes should include an sLA ≥2 cut off
ED sLA	≥2	Freund 2012	Prospective	462	2	54	76	0.679	PPV% 39; NPV% 86 LR+ 2.31; LR- 0.59 DOR 10.88; p<0.05		sLA effective to diagnose severe sepsis
		Ljungstrom, 2017	Prospective	1572	3	95.1	11.7	0.415	PPV% 37.5; NPV% 81.1 DOR 2.58; p <0.05		sLA performed poorly (AUROC)
		Berkman et al. 2009	Prospective	1419	4	80	69	0.84	PPV% 29; NPV% 98; LR+ 2.5; LR- 0.3 AG r = 0.4; p<0.001		AG moderately correlated to sLA for sepsis

sLA = serum lactate; pLA = POC lactate *<0.0001; all 0.05 unless stated

Lactate (mode & cut-off mmol/L)	Author, year	Study Type	N	Study Lactate	Sn% (95%CI)	Sp% (95%CI)	Diagnostic Accuracy AUROC (95% CI)	Others	Process and outcome measures (95%CI)	Key findings		
ADULT												
ED	pLA	ns	Morris (10), 2015	Prospective	160	ns			Time to diag. pLA <1 hour OR 4.6; p<0.05	Reduced time to diag		
		ns	Morris (14) 2014	Retrospective	865	ns			Mortality (H) OR 0.6, p=0.001; Time to antib. <1Hour 15 vs 25.1% p=0.007	pLA reduces mortality and time to antib.		
		ns	Morris (15), 2014	Retrospective	1430	ns			Mortality (H) pLA OR 0.71; p=0.006	Reduced mortality		
		ns	Morris (16), 2010	Retrospective	210	ns			Time antib. <3hours pLA OR 4.2; p0.05	Reduced treatment time		
		ns	Morris (17), 2007	Prospective	92	ns			Mortality (H) pLA 14 vs 14% sLA; p=0.66	Reduced mortality		
		<2	Karon, 2017	Prospective	501	1.3	55.1	62.7	0.63	DOR 1.44; p<0.050	Low pLA has limited ability to predict sepsis	
			Contenti, 2014	Retrospective	103	2	81	42	0.759	pLA: sLA r= 0.96; p<0.0015	pLA sensitivity good but low specificity; highly correlated with sLA	
			Singer(a), 2014	Prospective	160	2				pLA: sLA r = 0.94 (0.91-0.97); p<0.001	Mortality (H) pLA 6 vs.19% sLA; p=0.02 LoS (H) pLA 7 vs 8 days sLA; p=0.27 ICU adm. pLA 33 vs 51% sLA p=0.02 Time to result pLA 34 vs 122 min sLA; p<0.001; Time to antib. pLa 89 vs. 88 min sLA; p= 0.35	pLA is rapid and highly accurate pLA improves processes and outcomes
			Singer (b), 2014	Retrospective	258	2	34	82	0.59	PPV% 89; NPV% 23; LR+ 2.5; LR- 0.3	Time to diagnosis pLA 21 vs 172 min sLA; p<0.05	Relatively low sensitivity but high specificity; combine clinical screening pLA and sLA have a strong correlation pLA is faster
			Goyal, 2010	Prospective	238	2.15				pLA: sLA r = 0.90; p<0.05		Very low sensitivity but high specificity especially in more severe pLA and sLA have a strong correlation pLA is faster
	Singer, 2014	Retrospective	258	4	7	98	0.59	PPV% 93; NPV% 20				
	Gaieski, 2013	Prospective	24	4				pLA: sLA r = -0.92; p<0.05	Time to diagnosis pLA 86 vs 151 min sLA; p<0.005			
Acute	sLA	<2	Visveswari, 2019	Prospective	126	1.55	67.2	47.00	0.577	PPV% 58.2; NPV% 58.6	NLCR is better marker (AUROC)	
		<2	Hunter, 2013	Prospective	201	1.7				sLA: ETC02 r = -0.421; p<0.01	Mortality 0.61 (AUROC)	sLA moderately neg correlated with ETC02; Moderate mortality prediction sLA increases LqSOFA sensitivity
		≥ 2	Baumann, 2019	Retrospective	2584	2	61.5	71.6	0.73	PPV% 32.2; NPV% 89.5		
		≥ 2	Rodriguez, 2019	Retrospective	3743	2	61.50	71.60	0.763	PPV% 32.2; NPV% 89.5; LR+ 2.2; LR- 0.54		
		≥ 2	Baumann, 2019	Retrospective	2584	4	26	96	0.59	PPV% 59; NPV% 85.5		sLA improves LqSOFA sensitivity
		≥ 2	Rodriguez 2019	Retrospective	3743	4	26	96	0.763	PPV% 59; NPV% 89.5 LR+ 6.6; LR- 0.77		sLA had low sensitivity: high specificity
pLA	≥ 2	Ismail 2015	Prospective	26	2.4				pLA: sLA r = 0.9999; p=NR	Time to result 5 vs 11 min; p<0.001	pLA comparable to sLA (ABG analysers)	

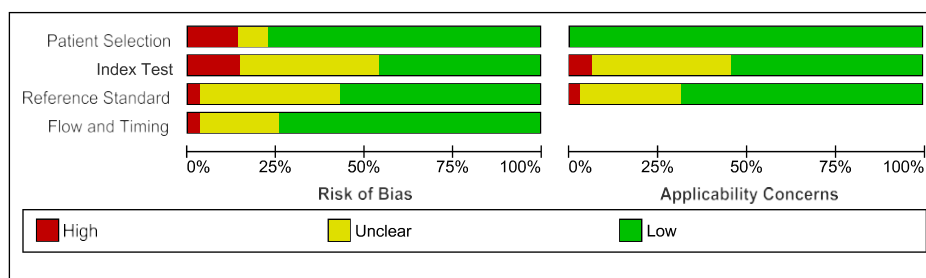
sLA = serum lactate; pLA = POC lactate * <0.0001 ; all 0.05 unless stated

Lactate	mmol/L	Author, year	Study type	N	Study ref Lactate	Sn% (95%CI)	Sp% (95%CI)	Diagnostic Accuracy		Process and outcome measures	Key findings	
								AUROC (95% CI)	Others			
PAEDIATRIC												
ED	sLA	≥ 2	Reed, 2013	Retrospective	283	2.04					sLA: Temp $r = -0.06$, $p=0.32$ sLA: HR $r = 0.35$, $p=0.0001$ sLA: RR $r = 0.30$, $p=0.0001$ sLA: SpO2% $r = 0.00$, $p=0.96$ sLA: WBC $r = 0.21$, $p=0.0004$ sLA: HC03 $r = -0.15$, $p=0.016$	Small positive correlation with HR, RR, and WBC; small negative correlation with HCO3; sLA is not a strong predictor of these variables
	pLA	ns	Morris (12), 2011	Prospective	247	ns				Mortality (H) pLA 5 vs 11% sLA; $p=0.11$ LoS (H) pLA 5.8 vs 7.5 days sLA; $p<0.05$	pLA reduces mortality and LoS	

sLA = serum lactate; pLA = POC lactate * <0.0001 ; all 0.05 unless stated

Appendix 13 Lactate study quality by study and combined

Lactate studies methodological quality assessment of study and combined



Appendix 14 Sepsis screening tools in use

Sample of screening and escalation tools by setting, cohort and alignment with the 3rd National Consensus Statement (NCS)

Adult

3 rd NCS	Prehospital		ED/Acute
Component	UK Sepsis Trust ¹ Adult	UK Sepsis Trust ² Adult	NSW CEC ³ Adult
Representation			< 48 hours
Impaired immunity	X	X	X
Indwelling device	X	X	X
Recent trauma/wound or invasive procedure	X	X	X
Age	> 75	> 75	> 65
Signs of infection Yes/No	X	X	X
Vomiting Diarrhoea			
Mental state	New/altered cognition	New/altered cognition	New/ altered LOC or cognition
RR	≥ 25	≥ 25	≤ 10 or ≥ 25
Nasal flaring			
HR	≥130	≥130	≤ 50 or ≥ 120
Temp (°C)	< 36 or >38	< 36 or >38	< 35.5 or > 38.5
Rigors			X
SBP mmHg	≤ 90	≤ 90	< 100
SpO ₂ %	Supp O ₂ needed to keep ≥92	Supp O ₂ needed to keep ≥92	< 95
Lactate mmol/l	≥ 2	≥ 2	≥ 2
Capillary refill time ≥ 3 sec.			
Reduced urine output	X	X	
Leg pain/cold extremities			
Non-blanching rash/mottled/ ashen / cyanotic	X	X	

1. <https://sepsistrust.org/wp-content/uploads/2018/06/PH-adult-NICE-Final-2-1.pdf>
2. <https://sepsistrust.org/wp-content/uploads/2018/06/ED-adult-NICE-Final-1107.pdf>
3. <http://cec.health.nsw.gov.au/keep-patients-safe/Deteriorating-patient-program/Sepsis/sepsis-tools>

Maternal

3 rd NCS Component	NSW CEC ¹ (yellow zone)	ACT Health ²	WA Health ³	UK Sepsis Trust ⁴
Representation				
Impaired immunity	X			X
Indwelling device	X			X
Recent trauma/wound or invasive procedure	X			X
Age				
Signs of infection Yes/No	X			X
Vomiting Diarrhoea	X			
Mental state	Altered LOC or V (AVPU) or cognition	Acute altered mental status		Altered cognition
RR	≤ 10 or ≥ 25	≤ 10 or ≥ 25	< 10 or ≥ 25	≥ 25
HR	≤ 50 or ≥ 120	≤ 50 or ≥ 120	≤ 50 or ≥ 120	≥ 130
Temp (°C) ⁵	< 35.5 or > 38.5	< 36 or ≥ 38	< 35.5° C or > 37.5	< 36 or > 38
Rigors	X		< 90	
SBP mmHg	80-90 or 140-170	< 90		≤ 90
SpO2%	< 95	< 95	< 95	Supp O2 needed to keep ≥ 92
Lactate mmol/L ⁶	≥ 2		≥ 2	≥ 2
Glucose mmol/L	2-4	> 7.7 mmol/L (in absence of diabetes)		
WBC		> 16.9 or < 4.0 x 10 ⁹ /L		
Capillary refill time ≥ 3 sec.				
Reduced urine output	Anuria or < 80mL over 4 consecutive hrs			
Skin - non-blanching rash/mottled/cyanotic				
Diabetes or gestational				X
Long labour/ruptured Membranes	X			X
Offensive vaginal discharge	X			X
Foetal distress HR >160	X			X
Blood loss	Cumulative 1-1.5L			

1. <http://cec.health.nsw.gov.au/keep-patients-safe/Deteriorating-patient-program/Sepsis/sepsis-tools>
2. <https://www.health.act.gov.au/sites/default/files/2018-09/Vital%20Signs%20and%20Early%20Warning%20Scores.pdf>
3. http://www.albanyhealthcampus.health.wa.gov.au/fileadmin/sections/policies/Managed/Prevention_of_Maternal_and_Newborn_Sepsis_Policy_TS4KSNFPVEZQ_210_19713.PDF
4. <https://sepsistrust.org/wp-content/uploads/2018/06/Inpatient-maternal-NICE-Final-1107-2.pdf>
5. Temperature instability is consistent with sepsis
6. Lactate may be raised in & immediately after normal delivery

Paediatrics, young children and neonates

3 rd NCS	NSW CEC Paediatric ¹ (yellow zone)	NSW CEC Newborn ² (yellow zone)	Queensland Paediatric ³	WA Paediatric (ED) ⁴	WA Newborn ⁵	UK Sepsis Trust < 5 years ⁶
Representation	< 48 hours					
Impaired immunity	X					
Indwelling device	X					
Trauma/wound or invasive procedure	X					X
Infection Yes/No	X			X	X	X
Mental state	Altered mental state: Agitation, combative, inconsolable.		Reduced LOC or GCS ≤12	Reduced LOC consciousness, lethargy, irritability, floppiness	Altered behaviour or responsiveness, floppiness	Drowsy/looks very unwell, weak, high-pitched, continuous cry
RR		60-80 or 25-30			Sign of respiratory distress OR apnoea	
< 3 mth.	65-75 or 20-25	Respiratory distress	>50	Tachypnoea +/- hypoxia ² or apnoea in neonates/infants		< 1yr 50-59
3 mth-1 yr.	55-65 or 15-25		>40			1-2 yrs. 40-49
1-4 yrs.	50-60 or 15-20		>40			3-4 yrs. 35-39
5-11 yr.	35-50 or 10-15		>30			
≥12 yrs.	30-40 or 5-10 Mod. distress					Nasal flaring
HR		160-190 or 70-90	<90 or >170	Tachycardia (persistent above limits for age) or bradycardia in neonates/infants.	Bradycardia or tachycardia	
< 3 mth.	170-190 or 80-100					< 1yr 150-9
3 mth-1 yr.	170-180 or 80-90					1-2 yrs. 140-9
1-4 yr.	150-170 or 70-80		<80 or >160			3-4 yr. 130-9
5-11 yr.	140-160 or 60-70		<70 or >150			< 60 bpm
≥12 yr.	130-150 or 40-50		<50 or >130			
Temp (°C)	≤ 35.5 or ≥38.5	≤ 36 or ≥38		≤ 36 or ≥38	≤ 36 or ≥38	≤ 36 or ≥38
SBP mmHg		90-100 or 40-60		Hypotension		Hypotension
< 3 mth	110-130 or 60-70		<65			
3 mth- 1 yr.	100-120 or 50-60		<70			
1-4 yrs.	120-150 or 70-80		<75			
5-11 yr.	130-160 or 80-90		<85			
≥12 yrs.	160-200 or 80-90					
SpO ₂ %	90-95 ⁴	90-95	<93 on O ₂ <85 on room air		Hypoxia i.e. central cyanosis or low SaO ₂	< 90 room air or increased O ₂ supp.
Lactate mmol/l	≥ 2		≥ 2			
Glucose mmol/L	2-3	> 10 or 1.7-2.5			Hypo or hyperglycaemia	
Capillary refill time ≥ 3 sec.	X			> 2		X
Reduced urine output	<1mL/kg/hr		Anuria 18 hrs or <0.5ml/kg/hr catheterised		Oliguria > 24 hrs after birth	
Leg pain/cold extremities						X
Non-blanching rash/mottled/cyanotic	X		X	X		X
Jaundice <24 h after birth		X			X	

1 & 2. <http://cec.health.nsw.gov.au/keep-patients-safe/Deteriorating-patient-program/Sepsis/sepsis-tools>
3. <https://www.childrens.health.qld.gov.au/guideline-sepsis-recognition-and-emergency-management-in-children/>
4. <https://pch.health.wa.gov.au/For-health-professionals/Emergency-Department-Guidelines/Sepsis-management/Management-summary>
5. www.albanyhealthcampus.health.wa.gov.au/fileadmin/sections/policies/Managed/Prevention_of_Maternal_and_Newborn_Sepsis_Policy_TS4KS_NFPVEZQ_210_19713.PDF
6. <https://sepsistrust.org/wp-content/uploads/2020/08/Sepsis-Acute-Under-5-Version-1.3.pdf>

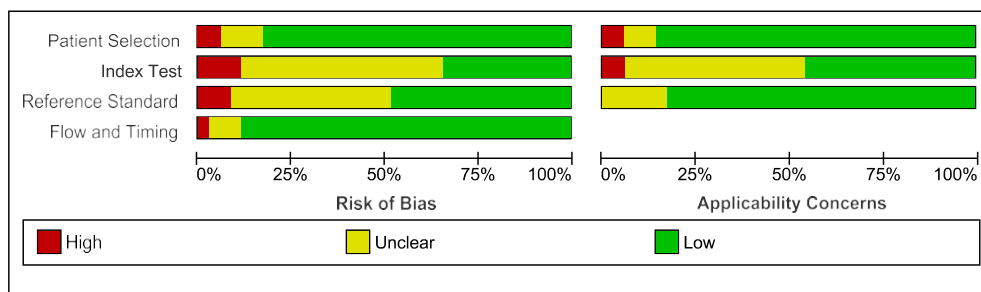
Appendix 15 Parameter metrics

		Parameter							
Tools	Pts ¹	RR min	SpO2 %	HR min	BP mmHg	Temp C°	GCS	New confusion/ Behaviour change	Additional
LqSOFA ²	1	≥ 22			SBP ≤ 100		<15	Lactate ≥ 2	
	3				SBP ≤ 70				
	2	≤ 8		≤ 40	SBP 71-80	≤ 35		UO <0.5 ³	
	1			41-50	SBP 81-100	35.1-36			
MEWS ²	0	9-14		51-100	SBP 101-199	36.1-38		A ⁴	
	1	15-20		101-110		38.1-38.5		V ⁴	
	2	21-29		111-129	SBP ≥ 200	≥ 38.6		P ⁴	
	3	>29		> 129				U ⁴	
	3	≤ 8	≤ 91	≤ 40	SBP ≤ 90	≤ 35			
	2		92-93		SBP 91-100			O2 supp	
	1		94-95	41-50	SBP 101-110	35.1-36			
NEWS ²	0		≥ 96	51-90	SBP 111-219	36.1-38		A ⁴	
	1			91-110		38.1-39			
	2			111-130		≥ 39.1			
	3			≥ 131	SBP ≥ 220			V, P or U ⁴	
Robson	1	>20		>90		< 36 or >38.3		√	BSL < 6.6 ⁵
Modified Robson	1	>20		>90		< 36 or >38.3	< 15		BSL < 6.6 ⁵
BAS 90-30-90	1	> 30	< 90		SBP < 90				
SIRS	1	> 20		> 90		< 36 or >38.0			WBC >1,200/mm ³ , <4,000/mm ³ Suspected infection
Triggers									
Anion Gap									> 12 ⁶
CRP									
ETCO ₂ ⁷									
NLCR									
Lactate									≥ 2
PCT									
Q-CRT ⁸									> 3.5 sec
Temp gradient ⁹									> 2 C°

1. Points score per parameter; 2. Significant score: qSOFA >2, LqSOFA >2 + lactate, MEWS ≥ 5, NEWS ≥ 5, Robson ≥ 2, Modified Robson ≥ 2, BAS 90-30-90 ≥ 1, SIRS ≥ 2; 3. Urine output ml/kg/hr; 4. **A**lert, **V**erbal, **P**ain, **U**nresponsive (AVPU) scale; 5. mmol/L; 6. Correlates to Lactate > 4; 7. ETCO₂ 8. Quantitative-Capillary Refill Time increases qSOFA sensitivity when combined¹⁶³; 8. Central (axilla)-peripheral (sole) temperature difference¹⁵⁰

Appendix 16 EHR - MLA study quality

EHR_MLA study methodological quality by study and combined



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