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Screening For Sepsis In General Hospitalised Patients: A Systematic Review

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Key words

Sepsis, sepsis screening, hospital wards, general hospitalised patients

Contributorship statement:

All authors were involved in the conception of the review and methodological design. LA conducted the literature search and article retrieval assisted by a librarian. LA and either RW, AM or LMA independently screened citations for eligibility. LA and LMA extracted data and reproduced accuracy tests. LA drafted the article. All authors revised critically the manuscript, provided important intellectual contribution and approved the final manuscript.

Summary

Introduction

Sepsis is a common condition observed outside critical care areas. The purpose of this review was to examine the application of sepsis screening tools for early recognition of sepsis in general hospitalised patients to: (i) identify the accuracy of these tools; (ii) determine the outcomes associated with their implementation and; (iii) describe the implementation process.

Method

A systematic review method was used. PubMed, CINAHL, COCHRANE, SCOPUS, Web of Science and EMBASE databases were systematically searched for primary articles, published from January 1990 to June 2016, that investigated screening tools or alert mechanisms for early identification of sepsis in adult general hospitalized patients. The review protocol was registered with PROSPERO (CRD42016042261).

Results

Over 8 thousand citations were screened for eligibility after duplicates were removed. Six articles met the inclusion criteria testing two types of sepsis screening tools. Electronic tools can capture, recognise abnormal variables and activate an alert in real time. However accuracy of these tools was found inconsistent across studies with only one demonstrating high specificity and sensitivity. Paper-based nurse-led screening tools appear to be more sensitive in the identification of septic patients but were only studied in small samples and particular populations. While process of care measures appears to be enhanced, demonstrating improved outcomes is more challenging.

Implementation details are rarely reported. Heterogeneity of studies prevented meta-analysis.

Conclusion

Clinicians, researchers and health decision makers should consider these findings and limitations when implementing screening tools, research or policy on sepsis recognition in general hospitalised patients.

Introduction

Sepsis is a physical response to a source of infection that triggers mechanisms that compromise organ function leading to death if not treated early. Over the past 25 years there has been an increasing interest in providing recommendations to diagnose and manage this condition.^{1,2} In spite of these efforts sepsis mortality remains unacceptably high. Global mortality rates based on data collected in 37 countries averaged 39%; but ranged from 22% in Australia to 56% in Brazil,³ with more recent reports of 38% across Americas and Europe,⁴ 32% in Uganda⁵ and 24% in Australia and New Zealand.⁶ Given these high mortality rates, timely recognition of sepsis is crucial to enable early and adequate intervention.

Septic patients were previously predominantly cared for in intensive care units (ICU),^{7,8} but this is now changing with more septic patients being cared for in hospital wards. In various countries across North American and Europe it is reported that 14-80% of patients in medical surgical wards develop sepsis.⁹⁻¹¹ Furthermore, within acute medical and surgical ward settings, sepsis is frequently the cause of organ failure,⁹ and clinical deterioration leading to rapid response activation^{12,13} or death.¹⁰ This growing evidence suggests identification of septic patients in hospital wards is paramount.

The earlier sepsis is identified the sooner the patient can be rescued from clinical deterioration.^{14,15} Timely recognition of this condition is a perennial concern stressed by clinicians and researchers.^{1,16,17} To address the issue, hospital wide quality improvement initiatives on sepsis recognition have been implemented, with some resulting in improved patient outcomes.^{18,19} Sepsis alerts mediated by technology,

embedded in electronic medical records have also been proposed as an effective screening mechanism.^{20,21} The most effective method of screening patients in acute care is not clear, therefore the purpose of this review was to examine the application of sepsis screening tools or alert mechanisms for early recognition of sepsis in general hospitalised patients to: (i) identify the accuracy of these screening tools; (ii) determine the outcomes associated with their implementation and; (iii) to describe the implementation process.

Methods

A systematic review method was used to search, identify, and appraise the available literature. The review was previously registered with the international prospective register of systematic reviews (PROSPERO registration number CRD42016042261).

Inclusion and exclusion criteria

Primary research that tested a screening tool or alert mechanism for early identification of sepsis in hospitalized general medical, surgical and trauma (including intermediate care) patients aged ≥ 16 years. Outcomes of interest included accurate diagnosis, early implementation of the 6-hour bundle,² shorter ICU and hospital length of stay and lower rates of mortality. Studies conducted in the emergency department and ICU were excluded, as were studies in patients aged ≤ 15 years, pregnant, obstetrics, haemodialysis, oncology and immuno-compromised (HIV, Bone Marrow Transplant, neutropenia) patients as these patients may have an altered response to sepsis and therefore not be representative of general hospitalised populations. Languages of publications were limited to English and Spanish. The search was limited to publications from January 1990 to June 2016. This time frame

was considered adequate as it preceded the publication of first sepsis consensus conference results.¹

Search strategy

US National Library of Medicine National Institutes of Health (PubMed), Cumulative Index to Nursing and Allied Health (CINAHL), COCHRANE, SCOPUS, Web of Science and EMBASE databases were systematically searched (Appendix 1). Medical subject headings and key words used were: screen, screening, early warning system, early identification, early diagnosis, mass screening, early detection, early recognition, sepsis, septic shock, severe sepsis, hospital, inpatient, hospital ward, hospitalised patient. The article search and retrieval process was undertaken by one author (LA) assisted by a librarian. Others articles were identified through manual searching reviewing the reference list section of relevant publications, and using the “cited by” function of Google Scholar with details of those publications. Identified citations were screened for eligibility by two independent reviewers (LA and either RW, AM or LMA). Disagreements were discussed and resolved within the entire team.

Appraisal and data extraction

An appraisal and data extraction tool was developed (Appendix 2) based on the BMJ Diagnostic test studies and critical appraisal,²² the Critical Appraisal Skills Programme (CASP) Diagnostic Test Study Checklist[©],²³ the STARD checklist for reporting of studies of diagnostic accuracy²⁴ and the template for intervention description and replication (TIDieR) checklist and guide.²⁵ The tool was used to assess the study validity, adequacy of population, blinding, testing and accuracy,

methods for the screening test, implementation of the test, its results and process if reported. Accuracy tests of the screening tools were reconstructed using the reported number of patients that did and did not activate the alerts, and the number of patients that were actually diagnosed as septic in both groups. If more than one cohort or group were studied, accuracy tests were combined when the sample characteristics and results of the groups were similar. If relevant information was not available in the publication, the author was contacted.

Results

The search resulted in 14 771 citations retrieved from 6 search engines and manual searching. After eliminating duplicates, 8456 citations including titles and abstracts were screened for eligibility (Figure 1).²⁶ Six articles met the inclusion criteria, including two prospective observational pilot studies,^{27,28} one prospective observational study,²⁹ two pre-post studies^{30,31} and one retrospective cohort study³² (Table I). Heterogeneity of studies in terms of instruments used to screen patients and outcomes measured (Table I, II and III) prevented meta-analysis and minimal detail was reported on the implementation of the screening tools.

Variables of screening tools and alert mechanism

The reviewed sepsis screening tools and alert mechanisms varied. Four of 6 tools were mediated by technology, with the alert criteria and mechanism embedded in electronic medical records.^{28,30-32} In one study it was not clear if the tool was paper or electronic.²⁹ The remaining study introduced a paper based screening tool.²⁷ The variables of all the alert/screening tools identified are summarised in Table II.

The electronic tools collected, in real time, a set of laboratory values and vital signs. One prediction tool was based on an algorithm with five levels of decision-criteria, with some variables used twice in different levels.³² The same prediction tool was later applied in the same setting.²⁸ The alerts were sent to a nurse who reviewed the patient and activated further referral to physicians in order to inform alert and patient condition.²⁸ Similarly, an electronic algorithm-based sepsis surveillance, provided additional prompts of isolated clinical changes, diagnostic variables and treatment reminder alerts.³¹ Nurses received the alerts and referred the patient to a physician.³¹ Another electronic sepsis alert using additional vital signs was investigated. The Early Warning and Response System (EWRS) for sepsis, comprised of a set of 6-point risk criteria, activated an alert when 4 of 6 criteria were met.³⁰ Similar clinical variables were applied in a three tier nurse-led paper-based screening tool.²⁷ Nurses assessed patients against the tool evaluating vital signs and inflammatory indicators (first tier), clues of infection (second tier), and tissue perfusion and organ dysfunction variables (third tier). If the screening process was positive, the nurse initiated a protocol and called the treating physician. Finally, based on vital signs the sepsis until proven otherwise (SUPO) protocol was examined.²⁹ If a positive screen was identified, nurses referred the patient to a medical provider and collected blood cultures and lactate samples unless advised otherwise. Screening processes are summarised in Table III.

Accuracy of screening tools

The accuracy of screening tools tested in these studies differed. References standards that were used varied across the studies and included ICD9 codes for sepsis,²⁷ ICD9 codes for acute infection matched to codes for acute organ dysfunction, and the need for vasopressors within 24 hours of ICU transfer,³² Systemic Inflammatory Response

Syndrome plus presence of infection,²⁹ and Surviving Sepsis Campaign definition.³¹ One study reported accuracy tests calculated against (1) any ICU transfer, (2) rapid response call, (3) death, or a composite of (1, 2 and 3) variables.³⁰ One study was not able to be included in this analysis because only positively screened patients were included and no data regarding patients who screened negative were available.²⁸

The sensitivity, specificity and predictive values of each of the screening tools are summarised in Table 1. In one case, the reproduced specificity (0.94) and positive predictive value (0.56) resulted in higher values than those reported by authors (specificity 0.88, positive predictive value 0.10).²⁹ High levels of accuracy were reported in the studies^{27,31} and reproduced for the purpose of this review²⁹ with the screening tools used in three studies. However two studies had small sample sizes with accuracy tests calculated on random numbers of negatively screened participants.^{27,29} The remaining study reported control data collected retrospectively outside of the study period.³¹ Lower sensitivity and positive predictive values were reproduced³⁰ and reported³² in the larger studies where arguably more robust designs were used. The more complex screening tools^{30,32} appear to be more effective in ruling out patients with sepsis, but they performed poorly in correctly identifying septic patients.

Response to sepsis alerts

Nurses were always the first responders to sepsis alerts²⁷⁻³¹ although sometimes the rapid response coordinator³⁰ and the covering medical provider³⁰ were also alerted at this time. Nurses were also responsible for initiating a sepsis protocol²⁹ or escalating the care^{27,28,31} (Table III). Sepsis management, mainly related to the 6-hour bundle,

including antibiotics prescription or escalation, fluid resuscitation and diagnostic tests were frequently specified^{27-29,31} and further consultation or transfer to ICU were outlined in one protocol.²⁷

Frequency of screening and review periods for variables to screen

The screening tools were used to identify clinical indicators of sepsis in two ways: continuously and at intervals (Table III). Tools that were applied continuously were electronically mediated and integrated into electronic medical records.^{28,30,31} In contrast, a paper based screening tool was used by nurses at the beginning of their shift.²⁷ SUPO was universally used across the study hospital but the format of the tool and frequency of screening were unclear.²⁹ In terms of the review periods for variables to be searched for when screening, different times were incorporated and ranged from two to 72 hours, with the most common being 24 to 48 hours.

Patient outcomes

Important improvements in sepsis management were identified in the reviewed studies and these are summarised in Table 1. Overall the frequency and time to use of diagnostic measures (lactate orders, blood cultures) improved significantly while results pertaining to treatment (fluids and vasopressors) were inconsistent across studies with some but not all demonstrating improvement. One study reported significant decrease in mortality and risk of death.³¹ Other studies showed positive trends in hospital mortality,^{28,30} hospital^{28,30} and ICU length of stay,³⁰ and ICU transfer.^{27,28,30}

Implementation of screening tools

The process used to implement the screening tools into routine practice was rarely reported. Gyang, et al. described support provided to nurses before and during the intervention.²⁷ Clinical nurse specialists, assistant nurse managers and educators provided more than 8 hours of education on infection and sepsis related topics six months before the implementation. In addition a sepsis education module was available with completion being optional. An extra hour of self-study time was provided a month before data collection was initiated where clinicians could learn about severe sepsis. In addition, designated champions conducted in-service training on completion of the screening tools the month prior to implementation. Manaktala et al. reported the governance process was led by nursing and physician steering committees and a ward nurses team.³¹ They were responsible for defining, training and following-up implementation processes, including conducting changes in the nursing documentation procedures that contained variables to be captured by the surveillance system.³¹ A “standardized education strategy” delivered during physicians and nurses meetings prior to the alert system going live was identified in other study.²⁸ Data about process compliance after sepsis alerts was reported in only one study and included the name of the provider, notifications sent to the provider, nurse review alert, nursing tasks, team presence at bedside within 30 mins, team awareness of sepsis before alert and changes in management.³⁰ Compliance results ranged from a low of 32% (any change in management) to 99% (nursing task verified: vital signs assessment).³⁰

Strengths and limitations of studies

The studies identified have some strengths and limitations to consider. Strengths included large sample sizes,^{30,32} common laboratory variables^{27,28,30,32} and vital signs

used for developing the tools,^{27,29,30} inter-rater agreement for sepsis diagnosis evaluated,³¹ details about implementation process,^{27,31} and details about process evaluation.³⁰ Limitations comprised small sample size,²⁷⁻²⁹ particular populations studied such as intermediate care²⁷ and patient's having abdominopelvic surgery,²⁹ a random sample of true negative patients studied,^{27,29} control group data collected out of the study period,³¹ and incomplete or lack of implementation details.²⁸⁻³⁰

Discussion

The evidence related to sepsis screening in acute care is examined in this review. Six studies were identified that investigated predominantly electronic tools, with only one paper-based tool reported. While process of care measures appear to be improved, demonstrating improved outcomes is more challenging. Electronic tools assisted by computing systems were able to capture, recognise abnormal variables and activate an alert immediately,^{28,30,31} or even facilitate prediction of organ dysfunction.³² However these tools performed poorly in identifying septic patients.^{30,32} When tools did perform better, comparisons were based on control data collected out of the study period.³¹ Paper-based nurse-lead tools and alert mechanisms appeared to be more sensitive in the identification of septic patients^{27,29} but were only studied in small samples and particular populations. Further investigation is needed to determine the effectiveness of the types of alerts, whether they are electronic³³ or health practitioner mediated.

Screening tools were comprised of a combination of laboratory indicators of organ dysfunction, hemodynamic, inflammatory, tissue perfusion, vital signs, and other variables. When considering the performance of a given combination of variables in

screening instruments, evidence is not consistent regarding accuracy. For example, a tool based on vital signs appears to perform better (sensitivity 1, specificity 0.94)²⁹ than a more complex prediction tool based on laboratory values (sensitivity 0.17, specificity 0.97)³² or a combination of laboratory and vital signs variables (sensitivity 0.23, specificity 0.98). It has been argued that sepsis has no gold standard for identification and diagnosis,^{34,35} with early signs and symptoms being non-specific. Thus the underlying spectrum of clinical variables may be difficult to capture³⁶ by the tools resulting in limitations in accuracy. Thus, the most accurate set of variables for sepsis screening is yet to be elucidated.

Nurses were the primary responders to sepsis alerts, even though on occasion rapid response system and medical providers also responded. Nurses' involvement in timely identification and response to sepsis alerts hospital-wide has been previously reported as decreasing overall mortality by 43% ($p < 0.01$) in a multicentre quality improvement program in the USA.³⁷ The initiative was based on (i) sepsis screening, (ii) diagnostic testing, and (iii) timely treatment. Nurses apply complex clinical reasoning about patient condition, respond according to protocols and serve as a safety mechanism.²⁷ Evidence favours nurses in responding to sepsis alerts, but to what extent their response influences patient outcomes in other settings merits further investigation.

Evidence identified was limited to hospital ward settings,^{28,30-32} intermediate care²⁷ or a particular type of surgery (abdominopelvic) patients²⁹ in the context of a developed economy, specifically the USA. The technology^{28,30-32} and the staff available such as the nurse patient ratio²⁷ and the supporting steering committees,³¹ played a pivotal

role in developing a strategy for sepsis screening in these studies. While quality improvement initiatives are frequently being implemented in developed health systems⁴ and technology is changing the way clinicians identify sepsis in well-resourced hospital ward settings,^{28,30-32} little is known about sepsis screening practices in less developed settings. For example, in Brazil, a hospital-wide paper-based sepsis screening strategy led by nurses resulted in a reduction in patient mortality from 61.7% to 36.5% ($p < 0.001$).¹⁹ Importantly, when technology is not available for assisting real time surveillance in hospital wards, nurses, physicians and other health care practitioners are the only safety mechanism patients have. However, health system decision makers play a key role in allocating resources for sepsis care. Whilst a nation wide “sepsis six” initiative has been implemented in the UK³⁹ low and middle-income countries decision makers are challenged by different priorities.^{40,41} Research to help understand the role of health care providers in sepsis care in diverse settings is urgently needed.

Details about implementation of screening tools and alert mechanisms were infrequently reported. Education on sepsis screening and care prior to, and throughout the implementation period,^{27,31} as well as compliance to the process³⁰ were the main components reported. Sepsis screening and response are complex processes of care that involve various disciplines necessitating roles of each of the professionals be made explicit. Details about implementation (such as activities for staff engagement and follow-up) provide evidence about intervention fidelity,³⁸ help to gain understanding of the setting, and promote future reproducibility.

This systematic review addressed early sepsis identification in acute care settings. It has a number of strengths and limitations. The review is limited to studies that tested a screening tool, were published in English and Spanish, and included quantitative analysis of accuracy and outcome measures. No publication that met the inclusion criteria was identified in Spanish. There may be strategies published in different languages that were not identified. The search was undertaken in six search engines only, but the key words and medical subject headings were purposively broad to capture as many studies as possible. Finally, studies identified were heterogeneous in terms of the settings resources, patients, and outcomes defined,³⁶ which prevented meta-analysis.

Implication for practice and research

The evidence examined uncovered important implications for practice and research. Reviewed screening tools have different levels of sensitivity and specificity which need to be considered prior to identifying an instrument for implementation; this applies not only to the variables incorporated in the instrument but also the medium that is used, specifically either electronic or paper based. If technology were available, electronic tools may be preferred over paper-based tools. However, given the resource-limited settings around the globe, implementation of paper based, nurse driven tools could make a difference in sepsis care. Frequency of screening practice and review periods of variables to screen may depend on patient characteristics, staffing and available technology. The roles of health professional within the multi-disciplinary team particularly nurse/physician to patient ratios and supporting staff, should be made explicit to promote optimal sepsis screening processes. Strategies to implement a new instrument should be carefully considered and explicitly described.

Robust prospective designs should be encouraged, as should hybrid trials. Larger sample sizes, across health settings, with differing levels of resource allocation should be studied, as should be the implementation process in these contexts.

Conclusion

Six studies were identified that examined predominantly electronic tools, with only one paper-based tool reported. Variables utilised were a combination of vital signs, laboratory indicators of organ dysfunction, inflammatory, tissue perfusion and other variables. After alert activation, nurses were the first responders and responsible for initiating a sepsis protocol to escalating the care. Electronic tools assisted by computing systems captured, recognised abnormal variables and activated alerts in real time and facilitated prediction of organ dysfunction. However these tools performed poorly in identifying septic patients. Only one tool performed better, but findings were based on control data collected prior to the study period. Paper-based nurse-led tools and alert mechanisms appeared to be more sensitive in the identification of septic patients but were only studied in small samples and in particular patient populations. The evidence regarding sepsis screening in hospitalised patients is limited. Clinicians, researchers and health decision makers should consider these findings and limitations when implementing screening tools, future research or policy on sepsis recognition in general hospitalised patients.

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Competing Interests

Authors have no competing interests to declare.

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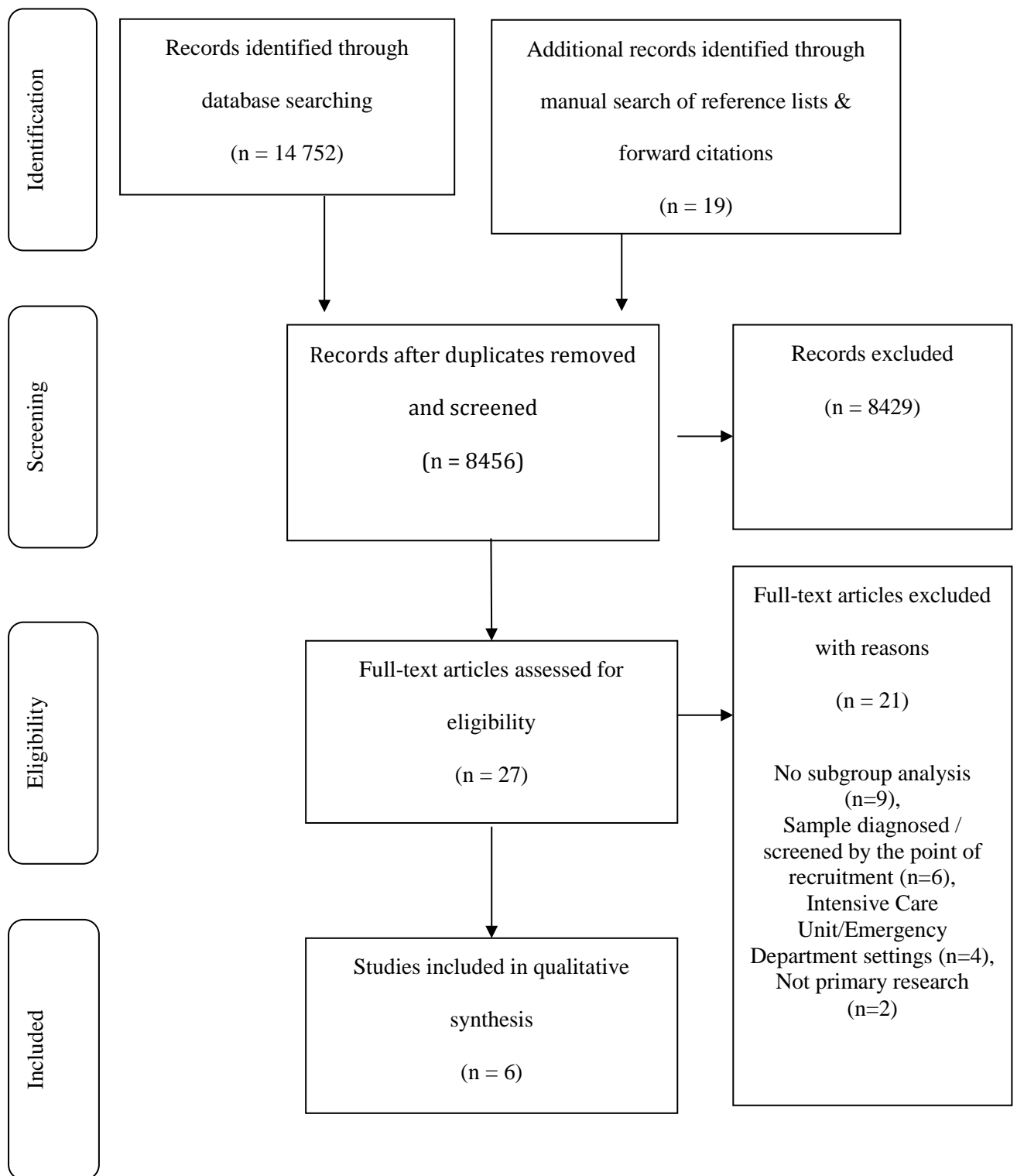


Figure 1. PRISMA Flow diagram

Table I. Study characteristics

Author (year) country	Aim	Design	Setting, Sample	Definition of sepsis	Accuracy tests	Outcomes NOT significant	Significant Outcomes (p)
Gyang et al., 2015, ²⁷ USA	To examine the performance of a nurse-driven sepsis screening tool	Prospective pilot study	26-bed medical/surgical intermediate care unit, 613-bed university tertiary referral hospital, n= 245	ICD-9 codes for sepsis, severe sepsis, or septic shock	Medical pts Se= 1 Sp= 0.96 PPV= 0.70 NPV= 1 Surgical pts Se= 0.93 Sp= 0.90 PPV= 0.48 NPV= 0.99	Fluids ICU transfer	ATB (0.006), Lactate (0.018), Blood culture (0.002)
MacQueen et al., 2015, ²⁹ USA	To evaluate the usage of a vital sign-based screening protocol for identifying sepsis	Observational, prospective screen	Non monitored, general surgical units, hospital network, n= 478 (abdominopelvic surgery only)	Systemic Inflammatory Response Syndrome plus presence of perioperative infection	Se ^a = 1 Sp ^a = 0.94 PPV ^a = 0.56 NPV ^a = 1	NR	NR
Manaktala et al., 2016, ³¹ USA	To develop and implement a clinical decision support system, and to evaluate its test characteristics and the resultant sepsis-related outcomes.	Quasi-experimental, with pre- and post-test analysis	Two hospital floors, respiratory and general medicine, 941 bed tertiary care hospital, n= 778 (pre and post)	ICD 9 codes for sepsis	Se= 0.95 Sp= 0.82 PPV= 0.50 NPV= 0.98	ICD 9 sepsis diagnosis Readmission rate Length of stay in the study units	Mortality (0.03) Lower risk of death (0.04)
Sawyer et al., 2011, ²⁸ USA	To evaluate whether the implementation of an automated sepsis screening and alert	Prospective pilot study with an intervention	6 medical wards, 1250-bed academic centre, n= 270 (non-intervention plus intervention)	Surviving Sepsis Campaign definition	NA	Microbiologic cultures and radiographic images ICU transfer	Sepsis related intervention <12h alert (0.018), ATB escalation (0.035),

	system facilitated early appropriate interventions					ICU transfer <12h after alert Mortality Hospital length of stay	Fluids (0.013), O2 therapy (0.005).
Thiel et al., 2010, ³² USA	To identify early predictors of septic shock	Retrospective cohort analysis	Medical, non-ICU units, 1200-bed academic centre, n= 27 674 (derivation plus validation)	ICD9 codes for acute infection matched to codes for acute organ dysfunction and the need for vasopressors within 24 hours of ICU transfer	Se ^b = 0.17 Sp ^b = 0.97 PPV ^b = 0.20 NPV ^b = 0.96	NA	NA
Umscheid et al., 2015, ³⁰ USA	To describe the development, implementation and impact of an early warning and response system for sepsis	Pre and post study	Non-ICU acute inpatient units, 3 urban academic hospitals of over 1500 beds, n= 31 069 (pre and post implementation)	Sepsis discharge diagnosis	Pre Se ^c = 0.22 Sp ^c = 0.97 PPV ^c = 0.39 NPV ^c = 0.94 Post Se ^c = 0.23 Sp ^c = 0.98 PPV ^c = 0.45 NPV ^c = 0.94	Hospital and ICU length of stay Vasopressors Mortality ICU transfer <6h after alert	Fluids, ATB, lactic acid and blood culture orders <3h after alert (0.01) Transfusion order <6h after alert (0.01) Chest radiograph, cardiac monitoring <6h after alert (0.02) Discharge home (0.04) Sepsis discharge diagnosis (0.02)

ICU, Intensive Care Unit; NA, Not applicable; NR, Not reported; ATB, Antibiotics; ICD, International Classification of Diseases; SE, Sensitivity; SP, Specificity; PPV, Positive Predictive Value; NPV, Negative Predictive Value; pts, patients; h, hours

^aTest reproduced using the negative alert patients (n=419) that did not develop sepsis (confirmed by author email communication)

^bTest reproduced combining 2006 and 2007 cohorts without arterial blood gas values for prediction

^cTest reproduced considering the sepsis discharge diagnosis instead of the composite variables reported by authors

Table II. Screening tool variables

Study	General variables	Inflammatory	Hemodynamic	Organ dysfunction	Tissue perfusion	Other
Gyang et al., 2015 ²⁷	Temperature >38°C, <36°C HR >90 beats/min RR >20 breaths/min Change mental status	WBC >12 000 or <4000 or more than 10% bands	SBP <90mmHg, >40 mmHg decrease in SBP from patient's baseline MAP <65mmHg	UO <0.5ml/kg/hr for 2 hs (or <30ml/h for 2hs) Increase O ₂ to maintain SpO ₂ >90% Absence bowel sounds (except recent post-surgery) Platelet count <100 000 μL ⁻¹ Serum creatinine increased by 0.3gm/dl in past 48hs INR >1.5 or PTT >60seconds Total bilirubin >4mg/d	Capillary refill >3 seconds Lactate >2.0 mmol/L	PCO ₂ <32 mmHg Question of possible sources
MacQueen et al., 2015 ²⁹	Temperature >38°C or <36°C HR >90 beats/min RR >20 breaths/min	-	SBP <90 mmHg, or MAP <65 mmHg	-	-	--
Manaktala et al., 2016 ³¹	Vital signs ^a	-	-	-	-	Demographics Medication Laboratory values ^a Documentation elements Medical problems Symptoms of infection
Sawyer et al., 2011 ²⁸	-	WBC ≥15.7x10 ³ /mcl	MAP <68 mmHg	INR ≥1.5, INR ≥1.6, Bilirubin <0.4 mg/dL, Bilirubin ≥2.5 mg/dL	-	Albumin ≥3.2 g/dl, Albumin <2.6 mg/dL Hemoglobin <10.9g/dL, Hemoglobin ≥11.7 g/dl Sodium ≥146 mmol/L Neutrophils ≥15.9x10 ³ /mcl, Shock index ≥1.2

Thiel et al., 2010 ³²	-	WBC $\geq 15.6 \times 10^3/\text{ul}$	MAP <68 mmHg	INR ≥ 1.5 , INR ≥ 1.6 Bilirubin <0.4 mg/dL, Bilirubin ≥ 2.5 mg/dL	-	Albumin ≥ 3.2 g/dl, Albumin <2.5 mg/dL Hemoglobin <11g/dL, Hemoglobin ≥ 12 g/dl Sodium ≥ 146 mmol/L Shock index ≥ 1.2 Neutrophils $\geq 16 \times 10^3$ uL
Umscheid et al., 2015 ³⁰	Temperature <36°C or >38°C HR >90 beats/min, RR >20 breaths/min	WBC <4000 or >12 000 or >10% bands	SBP <100 mmHg	-	Lactate >2.2 mmol/L	PaCO ₂ <32 mmHg

HR, Heart Rate; RR, Respiratory Rate; WBC, White Blood Cells; SBP, Systolic Blood Pressure; MAP, Main Arterial Pressure; INR, International normalised ratio; UO, Urinary Output; O₂, Oxygen; SpO₂, Pulse Oximeter Oxygen Saturation; PTT, Partial Thromboplastin Time; PaCO₂, partial pressure of carbon dioxide

^a No cut off values of variables were provided

Table III. Screening process and response

Study	Screening tool name	Review periods for variables to screen	Frequency of screening	Screening mechanism	Alert mechanism	Response
Gyang et al., 2015 ²⁷	Severe-Sepsis Screening Tool	Within the previous 8h of the time of assessment	At the beginning of every nursing shift,	Nurse driven, paper based	Nurse to call primary team	Nurse to initiate guideline Primary team to order diagnostic tests, administration of broad spectrum ATB and fluids, ICU consultation/ transfer
MacQueen et al., 2015 ²⁹	Sepsis Until Proven Otherwise	NR	NR	Nurse based	Nurse to call a provider	Provider to prescribe antibiotics and intravenous fluid boluses as recommended by the protocol
Manaktala et al., 2016 ³¹	Electronic sepsis surveillance and alerting system	NR	Real time surveillance	Electronic	Alert sent to nurses on mobile and desktop computer 4 types of alerts could be activated: informational, diagnosis, advice and reminders	Nurses accepted or override the alert, they were directed to contact physicians about all diagnosis alert
Sawyer et al., 2011 ²⁸	Prediction tool	Immediately after registered in electronic medical record	Continuously	Electronic	Automatic alert sent to the nurse	Nurse assess the patient, and referred the patient to a physician, Physician to prescribe antibiotic, escalation, administration of fluids and oxygen, diagnostic tests
Thiel et al., 2010 ³²	Prediction tool	24 to 2h previous ICU admission (cases) 48h controls	NA	NA	NA	NA
Umscheid et al., 2015 ³⁰	Early warning and response system	Vital signs 24h Laboratory values 48h	Continuously	Electronic	Alert sent to bedside nurse, RRC and covering provider	Bedside nurse, RRC and covering provider to evaluate the patient within 30min and enact changes in management

NR, Not reported; NA, Not applicable; ICU, intensive care unit; RRC, Rapid Response Coordinator; ATB, antibiotics; h, hours

