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REVIEW

Early warning scores for sepsis identification and prediction of in-hospital mortality in adults with sepsis: A systematic review and meta-analysis

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Abstract

Aim: The early warning scores (EWS), quick Sequential Organ Failure Assessment (qSOFA) and systemic inflammatory response syndrome (SIRS) criteria have been proposed as sepsis screening tools. This review aims to summarise and compare the performance of EWS with the qSOFA and SIRS criteria for predicting sepsis diagnosis and in-hospital mortality in patients with sepsis.

Design: A systematic review with meta-analysis.

Review Methods: Seven databases were searched from January 1, 2016 until March 10, 2022. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Sensitivity, specificity, likelihood ratios and diagnostic odd ratios were pooled by using the bivariate random effects model. Overall performance was summarised by using the hierarchical summary receiver–operating characteristics curve. This paper adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines.

Results: Ten studies involving 52,474 subjects were included in the review. For predicting sepsis diagnosis, the pooled sensitivity of EWS (65%, 95% CI: 55, 75) was similar to SIRS ≥2 (70%, 95% CI: 49, 85) and higher than qSOFA ≥2 (37%, 95% CI: 20, 59). The pooled specificity of EWS (77%, 95% CI: 64, 86) was higher than SIRS ≥2 (62%, 95% CI: 41, 80) but lower than qSOFA ≥2 (94%, 95% CI: 86, 98). Results were similar for the secondary outcome of in-hospital mortality.

Conclusions: Although no one scoring system had both high sensitivity and specificity, the EWS had at least equivalent values in most measures of diagnostic accuracy compared with SIRS or qSOFA.

Implications for the profession: Healthcare systems in which EWS is already in place should consider whether there is any clinical benefit in adopting qSOFA or SIRS.

No patient or public contribution: This systematic review did not directly involve patient or public contribution to the manuscript.

KEYWORDS
early warning score, meta-analysis, mortality, qSOFA, sepsis, SIRS

1 | INTRODUCTION

Sepsis is a leading cause of morbidity and mortality worldwide (Rudd et al., 2020). A global estimated burden of sepsis is reported to be 48.9 million cases, with a mortality rate of 20% (Rudd et al., 2020). Timely administration of antibiotics is associated with an increased survival rate in patients with sepsis, thus screening and early recognition of sepsis are paramount (Im et al., 2022; Liu et al., 2017). As such, sepsis screening tools have been devised and integrated as part of nurses' routine patient assessment to facilitate early identification of sepsis, which can lead to more timely investigations and treatment of sepsis (Kleinpell, 2017).

For many years before the updated definitions of sepsis (Sepsis-3) by the Third International Consensus Definitions for Sepsis and Septic Shock in 2016, the systemic inflammatory response syndrome (SIRS) criteria was used for screening and diagnosing sepsis. However, the updated sepsis-3 definitions–'life-threatening organ dysfunction caused by a dysregulated host response to infection'–have moved away from the centrality of inflammation and the SIRS criteria, which have been shown to be lacking in specificity (Singer et al., 2016, p. 804). The Quick Sequential Organ Failure Assessment (qSOFA) score, which uses three clinical parameters–systolic blood pressure, mental status and respiratory rate–is proposed as a surrogate for organ dysfunction and may act as a screening tool for clinicians to consider the diagnosis of sepsis among patients with known or suspected infection.

The Early Warning Score (EWS), calculated from a patient's vital signs and mental status, has gained widespread use in detecting acutely deteriorating patients. Although the EWS was originally designed to grade the severity of physiologic derangement and assess risk for all-cause clinical deterioration, it is increasingly being implemented in both hospital and pre-hospital settings as a sepsis screening tool, with studies comparing the performance of SIRS, qSOFA and national early warning score (NEWS) for identification of sepsis and mortality prediction (Brunetti et al., 2022; Churpek et al., 2017; Lane et al., 2020; Oduncu et al., 2021). In particular, the NEWS of ≥5 has been widely adopted by National Health Service England as a trigger for possible sepsis (National Health Service England, 2017).

Notwithstanding the recommendation to use a qSOFA score ≥2 for sepsis screening by the 2016 Sepsis Task Force, the 2021 Surviving Sepsis Campaign recommended against using qSOFA compared with SIRS, NEWS, or modified early warning score (MEWS) as a single screening tool for sepsis or septic shock (Evans et al., 2021). This is because of concerns related to the low sensitivity of qSOFA (Tusgul et al., 2017; Williams et al., 2017) and sepsis identification only in the later course of the disease with less reversibility and worse prognosis (Sprung et al., 2016).

What does this paper contribute to the wider global clinical community?

- The review demonstrates that the EWS had similar or superior values in most measures of diagnostic accuracy compared with SIRS or qSOFA in predicting sepsis diagnosis and in-hospital mortality in adult patients with sepsis, calling into question the value of SIRS or qSOFA in institutions where EWS is already in use.
- While the findings also suggest that the EWS is not an ideal standalone screening tool for sepsis nor prognosticating patients with sepsis, it could offer utility either in a two-stage screening approach or in combination with other clinical risk factors or point-of-care biomarkers.

Notably, three recent reviews studied the performance accuracy of EWS in the diagnosis and mortality prediction of adult patients with sepsis (Adegbite et al., 2021; Hamilton et al., 2018; Wang et al., 2022). However, two of the reviews included articles that had a mixture of sepsis definitions—both sepsis-3 definitions and the old sepsis-2 definition, defined as proven or suspected infection in combination with at least 2 SIRS criteria (Adegbite et al., 2021; Hamilton et al., 2018). While the recent review by Wang et al. (2022) included articles published after 2016 and reported that the qSOFA had a higher overall prediction accuracy of mortality than SIRS and NEWS, the result is limited by pooling together different mortality measures (in-hospital mortality or 30/28/60-day mortality) and including patients with sepsis or suspected sepsis (Wang et al., 2022).

To date, no published meta-analysis compares the diagnostic accuracy of SIRS, qSOFA, and EWS for diagnosing sepsis according to the sepsis-3 definitions. Furthermore, given that the EWS is being more routinely used clinically, there will be little operational benefit in introducing additional screening tools if the EWS is shown to perform better or is comparable with other sepsis screening tools. Therefore, this review aimed to (1) summarise the diagnostic accuracy of EWS in predicting sepsis and in-hospital mortality in patients with sepsis and (2) compare the performance of EWS with that of the qSOFA and SIRS.

2 | METHODS

2.1 | Design

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines (Data S1—Supplemental Material 1) (McInnes et al., 2018). The review was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42021259829).

2.2 | Search strategy and study selection

A search strategy was developed with the keywords, Medical Subject Headings (MeSH) terms and free text variations for sepsis linked by the Boolean operator 'AND' to the keywords MeSH terms, and free text variations for EWSs (Data S1—Supplemental Material 2). Seven electronic databases (MEDLINE, Embase, Scopus, Web of Science, The Cochrane Central Register of Controlled Trials, CINHAL and PsycINFO) were searched from 01/01/2016 to 10/03/2022 to identify full-text, peer-reviewed, English language studies published after the release of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) that described the clinical criteria of sepsis-3 definitions (Singer et al., 2016). The reference lists of relevant articles, reviews, commentaries and views identified by the search strategy were searched manually for additional articles.

Studies were eligible for inclusion if they involved adult patients (≥16 years old) in any setting and provided sufficient data for the construction of 2×2 contingency tables using true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values, (1) on the diagnostic value of any form of EWS for sepsis diagnosis or outcomes of sepsis; or (2) that directly compared the diagnostic value of EWS with the qSOFA or SIRS criteria for sepsis diagnosis or outcomes of sepsis in the same population. EWS were included if they generated a score by combining commonly measured physiological parameters, including pulse rate, blood pressure, respiratory rate, oxygen saturation and level of consciousness. A diagnosis of sepsis was considered if it adhered to the clinical criteria of sepsis-3 definition—the presence of suspected or confirmed infection with a concurrent rise in ≥2 in SOFA score (Singer et al., 2016)—or the presence of suspected or confirmed infection with at least one organ or system dysfunction.

Two reviewers independently screened titles, abstracts, and full text for eligibility. Any disagreement was resolved with discussion in the presence of a third reviewer.

2.3 | Quality appraisal

Two reviewers independently assessed the quality of the included studies by using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Whiting et al., 2011). Four key domains (patient selection, index test, reference standard, and flowing and timing) were assessed for risk of bias and applicability (first three domains only). No overall summary score was calculated; however, each domain was rated 'low', 'high' or 'unclear'. No study was excluded from the review based on its methodological quality to maintain a comprehensive analysis. Discrepancies were discussed between the two independent reviewers until a consensus was reached.

2.4 | Data extraction

The following information was extracted using a predesigned form by one reviewer from each article: author and year, country, setting, study design, participant characteristics (e.g. age, sample size), type of EWS used and its threshold, presence of comparators (qSOFA or SIRS criteria), criteria to diagnose sepsis, outcomes assessed (i.e. sepsis-3 diagnosis and in-hospital mortality) and data required to construct the 2×2 contingency tables of TP, FP, TN and FN counts. Authors were contacted for data where required. Another reviewer cross-checked all extracted data for accuracy.

2.5 | Data analysis and synthesis

The primary outcome of the review was the diagnosis of sepsis, and the secondary outcome was in-hospital mortality among patients with sepsis. The diagnostic values of the EWS for the studied outcomes were evaluated and compared head-to-head with those of the qSOFA and SIRS criteria. Where studies reported data for multiple thresholds, the threshold that was consistent with other studies was used.

The meta-analysis was conducted using Review Manager software, version 5.4 (Review Manager, 2020), and MetaDTA: Diagnostic Test Accuracy Meta-Analysis Version 2.01 (Freeman et al., 2019). The pooled sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−, respectively), and diagnostic odds ratios (DOR) with 95% CI were calculated under bivariate random-effects and hierarchical summary receiver operating characteristic (HSROC) modelling (Rutter & Gatsonis, 2001). The summary estimates of sensitivity and specificity with a 95% confidence interval for each test were presented graphically on the coupled forest plots and the HSROC curves. The overall diagnostic performance of the index tests could also be determined by the HSROC curves, whereby the closer the curve approaches the upper-left corner, the higher the overall performance. Heterogeneity between studies was evaluated through visual assessment of study results in the ROC space and forest plots. Subgroup analyses were performed to investigate the effect of the type of EWS, setting, and threshold.

3 | RESULTS

3.1 | Search results

The search identified a total of 5394 records and were exported into the EndNote software where duplicates were removed. After removing 1915 duplicates, the resulting 3479 records were screened

for relevance by their title and abstract. Subsequently, 62 articles were considered potentially relevant and screened as full-text articles. A final 10 articles (52,474 participants) were included in this review (Figure 1; rejected articles are listed in Data S1—Supplemental Material 3).

3.2 | Study characteristics

Table 1 presents an overview of the included studies. Eight studies were single-site studies, with four conducted in the emergency department (ED) (Boonmee et al., 2020; Oduncu et al., 2021; Ortega et al., 2019; Prasad et al., 2021), one in both the ED and inpatient wards (Churpek et al., 2017), one in inpatient wards (Pairattanakorn et al., 2021), one in medical intensive care unit (ICU) (Khwannimit et al., 2019), and one in acute geriatric unit (Brunetti et al., 2022). Two studies were conducted in the prehospital settings (Lane et al., 2020; Wallgren et al., 2021), with EWS evaluated based on ambulance or prehospital service records; both were multi-site studies.

The most frequently evaluated version of the EWS was the NEWS ($n=7$). Six studies compared EWS with both the qSOFA and SIRS criteria (Boonmee et al., 2020; Churpek et al., 2017; Lane et al., 2020; Oduncu et al., 2021; Ortega et al., 2019; Pairattanakorn et al., 2021), and three studies compared EWS with qSOFA (Brunetti et al., 2022; Khwannimit et al., 2019; Prasad et al., 2021). A summary of the parameters included in each EWS, the score range and the recommended threshold for sepsis diagnosis and/or predicting in-hospital mortality among patients with sepsis can be found in Data S1—Supplemental Material 4.

The diagnosis of sepsis was evaluated at varied timings across all studies. For the reference standard of sepsis, four studies employed the clinical criteria of sepsis-3 definition (Oduncu et al., 2021; Ortega et al., 2019; Prasad et al., 2021; Wallgren et al., 2021) while three studies employed the definition of presence of infection with at least one organ dysfunction (Brunetti et al., 2022; Lane et al., 2020; Pairattanakorn et al., 2021). Except for Ortega (Ortega et al., 2019), patients included in the evaluation of sepsis diagnosis were either suspected or confirmed with an infection that was based on blood cultures drawn with concomitant administration of antibiotics (Brunetti et al., 2022; Oduncu et al., 2021; Prasad et al., 2021), clinical judgement (Pairattanakorn et al., 2021; Wallgren et al., 2021) or infection diagnosis codes (Lane et al., 2020). One prehospital study setting further examined a sub-cohort of patients in which a suspicion of infection that was based on the paramedic's clinical judgement of the patient's chief complaint and clinical presentation (Lane et al., 2020).

Among studies that evaluated the diagnostic ability of EWS to predict in-hospital mortality in sepsis, two studies used the clinical criteria of the sepsis-3 definition as the basis of their sepsis diagnosis (Boonmee et al., 2020; Khwannimit et al., 2019) and two studies used the sepsis definition of presence of infection with at least one organ dysfunction (Churpek et al., 2017; Pairattanakorn et al., 2021).

3.3 | Assessment of study quality

In general, all the studies had limitations in study quality (Figure 2). The domain with the lowest risk of bias was the patient selection.

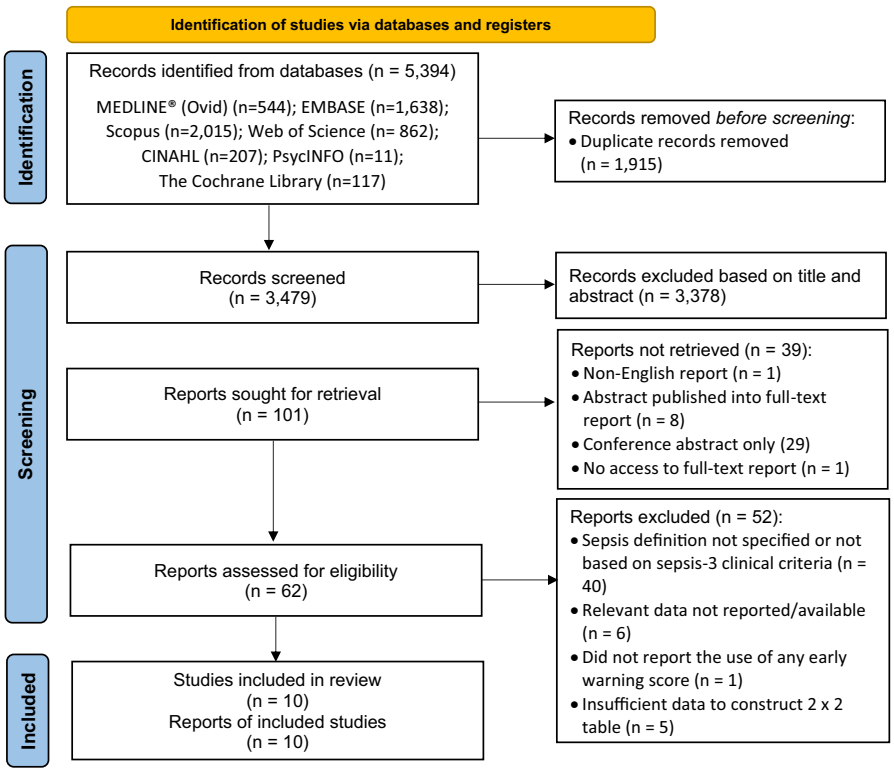

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

TABLE 1 Characteristics of included studies.

Author/year	Design	Country/setting/sites	*N*	Mean/median age, years	Inclusion & exclusion criteria	Definition of suspected infection	EWS/comparator (C)	EWS/comparator timing	Sepsis diagnosis	Relevant outcomes
Boonmee et al. (2020)	Retrospective cohort	Thailand—ED of tertiary hospital Single site	1616	NR	Adults ≥18 years old with sepsis	Physicians' clinical judgement + blood culture + intravenous antibiotics	NEWS ≥5 C: qSOFA ≥2; SIRS ≥2	On ED triage or time of culture or antibiotics, whichever came first	Sepsis-3	In-hospital mortality
Brunetti et al. (2022)	Prospective cohort	Italy—acute geriatric unit of university hospital Single site	230	86 (IQR: 66–99)	Admitted with ≥1 risk factor for sepsis and suspected infection at admission or during hospital stay	Oral/parenteral antibiotic prescription within the time frame of 24 h before and 72 h after obtaining culture	NEWS ≥7 MEWS ≥5 C:qSOFA ≥2	Worst recorded value throughout hospital stay; measurements taken at least twice daily	ICD-9-CM codes for infection with simultaneous presence of ≥1 acute organ dysfunction	Sepsis diagnosis
Churpek et al. (2017)	Retrospective cohort	United States—ED and wards of tertiary centre Single site	8744 (Subset sample)	NR	Adult patients who met Angus ICD-9 abstraction criteria for sepsis	Intravenous antibiotic prescription (1) followed by culture taken within 24 h or (2) within 72 h after culture obtained	NEWS ≥5 NEWS ≥7 MEWS ≥5 C: qSOFA ≥2; SIRS ≥2	Highest value of each score when patient first met suspicion of infection.[a]	Angus ICD-9 abstraction criteria for sepsis	In-hospital mortality
Khwannimit et al. (2019)	Retrospective cohort	Thailand—medical ICU of a teaching hospital Single site	1589	63 (IQR 48–76)	Adult patients admitted to medical ICU for sepsis or septic shock	NR	NEWS[b] C: qSOFA ≥2[d]	Worst values within 24 h of ICU admission	Suspected infection + SOFA score ≥2	In-hospital mortality
Lane et al. (2020)	Retrospective Cohort	Canada prehospital—EMS linked to population-based emergency administrative and inpatient databases Multi-site	Main cohort: 12,740 Sub-cohort: 4138	NR	Adults ≥18 years old brought to ED by EMS and had confirmed infection. Exclusion[c]	Main cohort: Infection diagnosis codes used in ED Sub-cohort: Based on patient's chief complaint & paramedic's impression	HEWS ≥2 MEWS ≥4 C: qSOFA ≥2; SIRS ≥2	First encounter with paramedic	Hospital billing codes for organ dysfunction	Sepsis diagnosis
Oduncu et al. (2021)	Prospective cohort	Turkey—ED of tertiary referral hospital Singe site	463	63 ± 18	Patients ≥18 years old with suspected infection Exclusion[c]	Culture samples and parenteral antibiotics	NEWS ≥5 C: qSOFA ≥2; SIRS ≥2	On arrival at ED	Suspected infection + SOFA score ≥2	Sepsis diagnosis

(Continues)

TABLE 1 (Continued)

Author/year	Design	Country/setting/sites	*N*	Mean/median age, years	Inclusion & exclusion criteria	Definition of suspected infection	EWS/comparator (C)	EWS/comparator timing	Sepsis diagnosis	Relevant outcomes
Ortega et al. (2019)	Prospective cohort	Switzerland—ED of a tertiary hospital Single site	2523	52 (IQR 38)	Adult patients presented to ED. Exclusion[c]	NR	NEWS C: qSOFA ≥2; SIRS ≥2	At triage[e]	Suspected infection + SOFA score ≥2	Sepsis diagnosis
Pairattanakorn et al. (2021)	Prospective cohort	Thailand—inpatient wards hospital Single site	409	65.7 ± 17.8	Adults ≥18 years old who had blood cultures taken	Determined by attending physicians at the time blood cultures were taken	NEWS ≥5 MEWS ≥4 C: qSOFA ≥2; SIRS ≥2	Worse values of each parameter taken at time of or within 6 h before blood culture drawn	Presence of infection with at least one organ dysfunction	Sepsis diagnosis In-hospital mortality
Prasad et al. (2021)	Retrospective cohort	United States—ED of 1 academic teaching hospital Single site	23,837	62 (IQR: 48–75)	Patients ≥18 years old who had blood cultures taken and intravenous antibiotics within 24 h presented to ED	Blood cultures ordered within 24 h of ED presentation and administration of intravenous antibiotics within 24 h	NEWS2 ≥5 C: qSOFA≥2	Most abnormal readings within 30 min of ED presentation[e]	EHR-based diagnosis of sepsis[f]	Sepsis diagnosis
Wallgren et al. (2021)	Prospective cohort	Sweden prehospital—EDs of 7 major hospitals Multi-site	323	78 (IQR 72–85)	Non-trauma ambulance patients ≥18 y.o with clinically suspected infection transported to hospitals. Exclusion[c]	New onset infection according to clinical judgement of ambulance personnel	NEWS2 ≥5 NEWS2 ≥7	Ambulance records	Infection + increased in SOFA score[g]	Sepsis diagnosis

Abbreviations: ED, emergency department; EMS, emergency medical service; EWS, early warning score; HEWS, hamilton early warning score; ICD-9-CM, international classification of diseases, ninth revision, clinical modification; ICU, intensive care unit; MEWS, modified early warning score; NEWS, national early warning score; NR, not reported; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

[a]Missing values were pulled from previous values and imputed using median (normal) values if no previous values available.

[b]Threshold score was not pre-specified.

[c]Excluded patients who were discharged from ED (Lane et al., 2020); Excluded pregnant women and patients with trauma, cardiac or respiratory arrest, intoxication and epilepsy (Oduncu et al., 2021); Excluded paediatric, obstetric and ophthalmologic patients (Ortega et al., 2019); Excluded patients with incomplete EWS (Wallgren et al., 2021).

[d]Insufficient data to form 2 × 2 table of true positive, true negative, false positive and false negative.

[e]Missing values were assumed as normal in analysis.

[f]EHR-based diagnosis of sepsis: (1) Suspected infection + SOFA ≥2 within first 48 h and (2) received ≥4 days of sequential antibiotic therapy or experience death or discharge to hospice before 4 days of antibiotic therapy; or have a validated sepsis discharge billing code.

[g]No previous record of baseline data were assumed as normal in analysis.

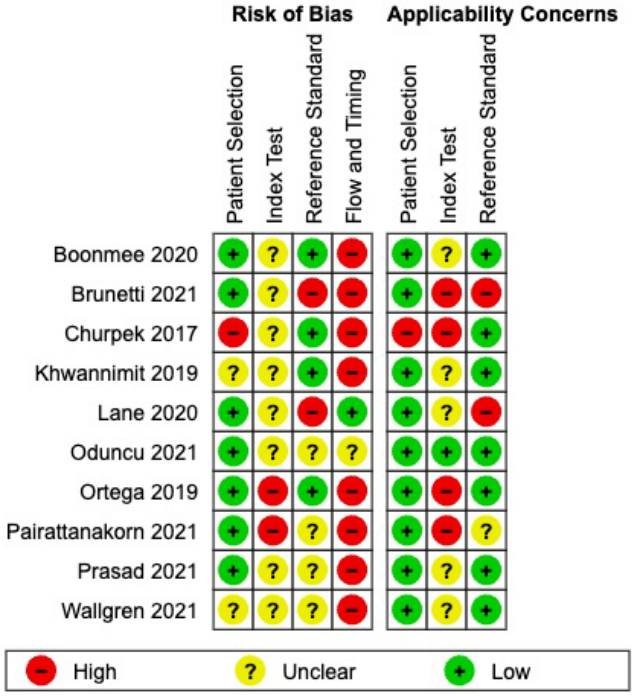

FIGURE 2 Risk of bias and applicability concerns of studies using QUADAS-2 tool.

The primary source of bias was related to the flow and timing, where most of the index test and reference standard–the assessment of sepsis diagnosis–were not collected at the same time. The index tests collected could have changed over time during the evolution of sepsis. For the index test and reference standard domains, blinding of interpretation of index test results to the outcomes of interests and vice versa was either lacking or not reported (Data S1—Supplemental Material 5). Concerns regarding the applicability of the index tests were related to insufficient information on whether the index tests were calculated based on the worst values for each item of the scoring systems at different time points or based on the entire set of parameters collected at one time point. A few studies also evaluated the index tests based on the worst values obtained.

3.4 | Sepsis diagnosis

Seven studies with 15 EWS tests in 40,525 patients assessed the diagnostic accuracy of EWS on sepsis diagnosis (Brunetti et al., 2022; Lane et al., 2020; Oduncu et al., 2021; Ortega et al., 2019; Pairattanakorn et al., 2021; Prasad et al., 2021; Wallgren et al., 2021). Data S1—Supplemental Material 6 shows the summary statistics of the seven studies that assessed the diagnosis of sepsis. As shown in Table 2a, the pooled sensitivity and specificity of the EWS were 65% (95% CI: 55, 75) and 77% (95% CI: 64, 86) respectively. However, visual inspection of the forest plot (Data S1—Supplemental Material 7) and plotted points in the HSROC curve (Figure 3) revealed considerable variation in individual estimates of the sensitivity and specificity across studies. The prediction region covered over one-third of the SROC space and was substantially larger relative to the confidence region, suggesting moderate to substantial heterogeneity beyond chance alone.

The estimated DOR for EWS was 6.49 (95% CI: 4.47, 9.44), which is significantly greater than 1, suggesting that the EWS has a good accuracy of the overall diagnostic power (Table 2a). The pooled positive and negative likelihood ratios were 2.89 (95% CI: 2.00, 4.18) and 0.45 (95% CI: 0.36, 0.55), respectively.

3.4.1 | Subgroup analyses

The effect of the type of EWS, threshold, and setting were investigated (Table 2a and Figure 4). The HSROCS curves for the analyses are presented in Figures e1–e5 in Data S1—Supplemental Material 8. The prediction regions for NEWS/NEWS2 and MEWS ≥4 were similar to the prediction region for EWS. The performance of the NEWS/NEWS2 ≥7 was slightly better in predicting sepsis diagnosis (LR+: 4.00, 95% CI [1.45, 11.00]) than NEWS/NEWS2 ≥5 (LR+: 2.76, 95% CI [1.49, 5.08]) and MEWS ≥4 (LR+: 2.49, 95% CI [1.93, 3.22]). Although the NEWS/NEWS2 ≥7 performed poorer in sensitivity than NEWS/NEWS2 ≥5 and MEWS ≥4, it had better pooled specificity estimates (Table 2a).

3.4.2 | Direct comparison of the EWS with qSOFA and SIRS

Data from 40,202 patients in six studies investigated the accuracy of both the EWS and qSOFA ≥2 on sepsis diagnosis (Brunetti et al., 2022; Lane et al., 2020; Oduncu et al., 2021; Ortega et al., 2019; Pairattanakorn et al., 2021; Prasad et al., 2021). While estimates of the pooled sensitivity were in favour of the EWS, the qSOFA (LR+: 6.06, 95% CI [3.72, 9.88]) performed better than the EWS (LR+: 2.75, 95% CI [1.76, 4.30]) in predicting sepsis (Data S1—Supplemental Material 9). In the subgroup analyses for the direct comparison of (i) NEWS/NEWS2 ≥5 and qSOFA ≥2, and (ii) MEWS ≥4 and qSOFA ≥2, the qSOFA ≥2 was found to be better in predicting sepsis diagnosis than both the NEWS/ NEWS2 ≥5 and MEWS ≥4 although it had lower pooled sensitivity (Data S1—Supplemental Material 10 and 11). The removal of the ward setting in the direct comparison of NEWS/NEWS2 ≥5 and qSOFA ≥2 did not change with the result.

Four studies incorporating 16,135 patients reported the accuracy of both the EWS and SIRS ≥2 on sepsis diagnosis (Lane et al., 2020; Oduncu et al., 2021; Ortega et al., 2019; Pairattanakorn et al., 2021). While estimates of the pooled sensitivity were in favour of the SIRS, the EWS (LR+: 3.18, 95% CI [1.80, 5.61]) performed better than the SIRS (LR+: 1.85, 95% CI [1.29, 2.67]) in predicting sepsis (Data S1—Supplemental Material 12). In contrast to a comparable pooled sensitivity estimates when MEWS ≥4 (73%, 95% CI [51, 87]) was compared directly to SIRS ≥2 (72%, 95% CI

TABLE 2 Summary estimates of sensitivity, specificity, diagnostic odd ratios and likelihood ratios for the primary analysis and sensitivity analyses.

Group/subgroup	No. of dataset (No. of patients)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odd ratio (95% CI)
(a) Sepsis diagnosis						
All studies (EWS)	15 (40,525)	65 [55, 75]	77 [64, 86]	2.89 [2.00, 4.18]	0.45 [0.36, 0.55]	6.49 [4.47, 9.44]
NEWS/NEWS2 only	9 (27,785)	58 [47, 68]	84 [69, 93]	3.65 [2.02, 6.59]	0.50 [0.42, 0.59]	7.33 [4.04, 13.30]
NEWS/NEWS2 ≥5 only	5 (27,092)	65 [56, 72]	77 [59, 88]	2.76 [1.49, 5.08]	0.46 [0.36, 0.61]	5.94 [2.60, 13.54]
NEWS/NEWS2 ≥5 in ED only	3 (26,823)	58 [53, 63]	82 [59, 94]	3.25 [1.19, 8.88]	0.51 [0.39, 0.68]	6.33 [1.78, 22.45]
NEWS/NEWS2 ≥7 only	3 (3076)	52 [28, 75]	87 [55, 97]	4.00 [1.45, 11.00]	0.55 [0.40, 0.77]	7.23 [3.33, 15.70]
MEWS ≥4 only	4 (13,379)	67 [46, 83]	73 [60, 83]	2.49 [1.93, 3.22]	0.45 [0.29, 0.71]	5.51 [3.38, 9.00]
qSOFA	7 (40,202)	37 [20, 59]	94 [86, 98]	6.06 [3.72, 9.88]	0.67 [0.50, 0.89]	9.07 [5.56, 14.80]
SIRS	5 (16,135)	70 [49, 85]	62 [41, 80]	1.85 [1.29, 2.67]	0.49 [0.32, 0.72]	3.82 [2.19, 6.67]
(b) In-hospital mortality						
All studies (EWS)	7 (12,358)	94 [83, 98]	21 [12, 35]	1.18 [1.08, 1.29]	0.31 [0.17, 0.57]	3.86 [2.12, 7.00]
NEWS/NEWS2 only	5 (12,358)	96 [80, 99]	18 [9, 31]	1.16 [1.07, 1.25]	0.26 [0.09, 0.76]	4.47 [1.55, 12.87]
NEWS/NEWS2 ≥5 only	3 (10,769)	90 [85, 94]	20 [14, 27]	1.12 [1.07, 1.18]	0.50 [0.39, 0.65]	2.25 [1.69, 2.99]
qSOFA	3 (12,358)	65 [48, 75]	59 [48, 69]	1.58 [1.29, 1.92]	0.59 [0.41, 0.85]	2.66 [1.59, 4.46]
SIRS	3 (10,769)	92 [86, 96]	12 [7, 19]	1.04 [1.02, 1.07]	0.69 [0.56, 0.84]	1.52 [1.23, 1.87]

Abbreviations: EWS, early warning score; MEWS, modified early warning score; NEWS, national early warning score; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

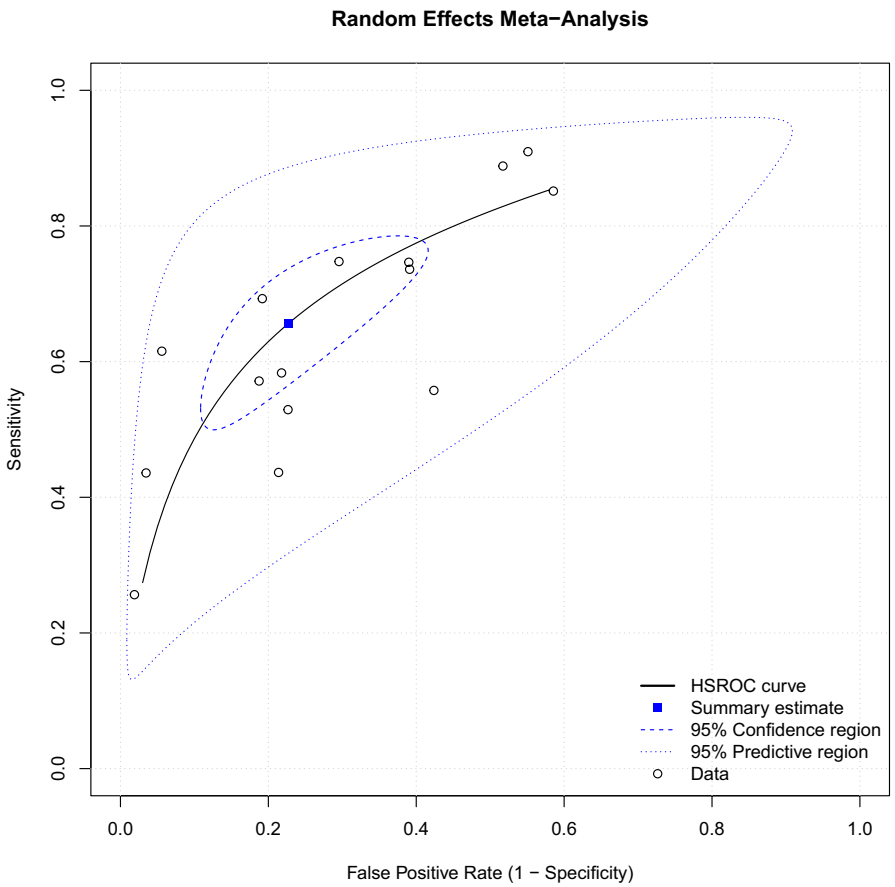

FIGURE 3 Summary receiver operating characteristic plot for all studies evaluating the early warning scores for detection of sepsis.

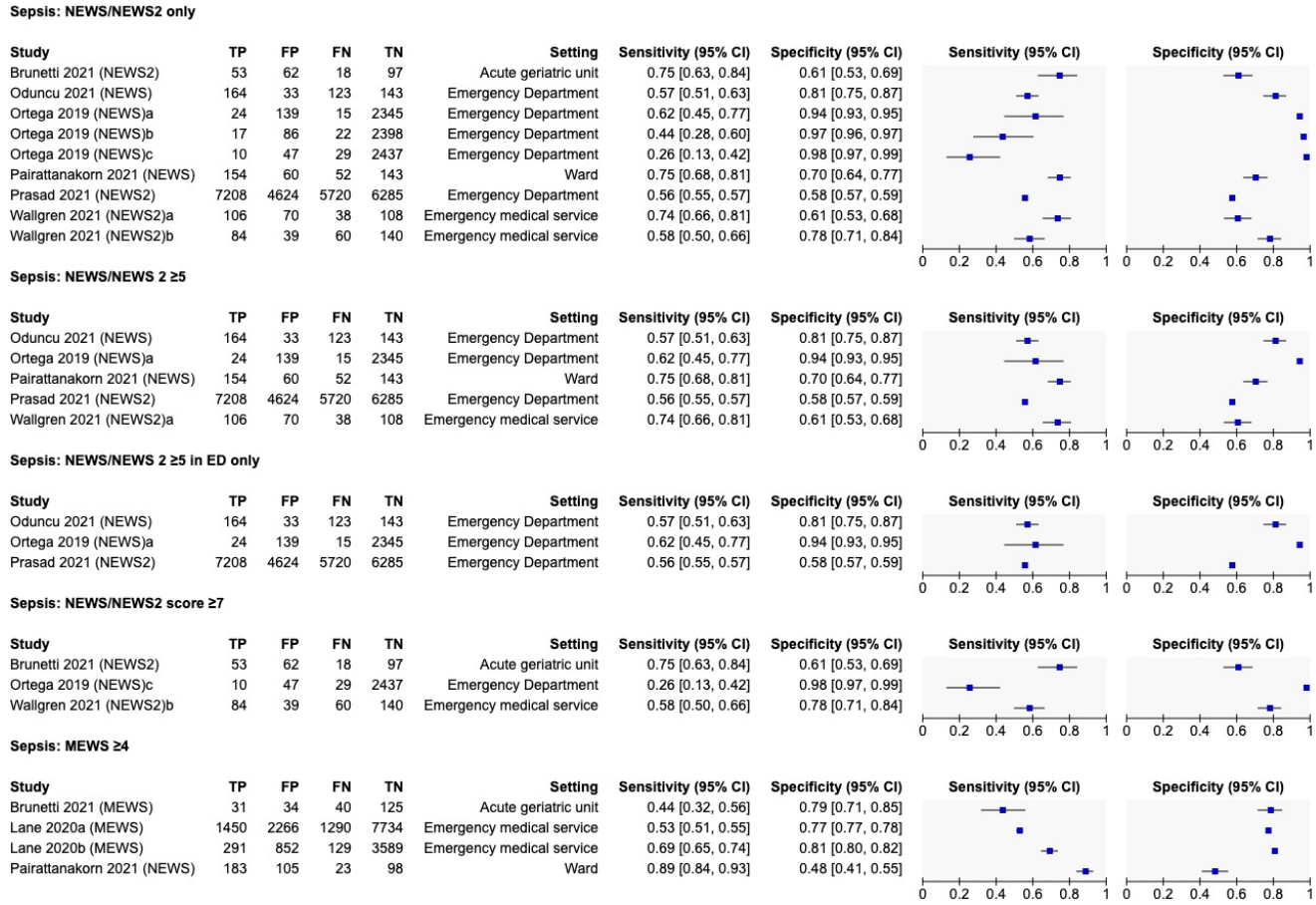

FIGURE 4 Forest plot of sensitivity and specificity of the early warning scores for detection of sepsis sorted by type of EWS, threshold and setting.

[40, 92]) (Data S1—Supplemental Material 13), the direct comparison between NEWS/NEWS2 ≥5 (64%, 95% CI [52, 74]) and SIRS ≥2 found a higher pooled sensitivity estimates in SIRS ≥2 (79%, 95% CI [56, 92]) (Data S1—Supplemental Material 14). Nevertheless, both the MEWS ≥4 and NEWS/NEWS2 ≥5 had higher DOR and LR+ than the SIRS ≥2 (Data S1—Supplemental Material 13 and 14).

3.5 | In-hospital mortality

Four studies, incorporating seven EWS tests, examined the diagnostic accuracy of EWS on in-hospital mortality among 12,358 patients with sepsis (Data S1—Supplemental Material 6) (Boonmee et al., 2020; Churpek et al., 2017; Khwannimit et al., 2019; Pairattanakorn et al., 2021). The pooled sensitivity and specificity of the EWS was 94% (95% CI: 83, 98) and 21% (95% CI: 12, 35), respectively (Table 2b). As seen in Figure 5 and Data S1—Supplemental Material 15, the forest plot and HSROC curve revealed variation in individual estimates of the sensitivity and specificity across studies. In addition, the prediction region was substantially larger relative to the confidence region, suggesting moderate heterogeneity beyond chance alone.

The estimated DOR for EWS was 3.86 (95% CI: 2.12, 7.00), suggesting that EWS has a satisfactory overall diagnostic accuracy for in-hospital mortality among patients with sepsis (Table 2b). However, the pooled LR+ of 1.18 (95% CI: 1.08, 1.29) indicates that the EWS is associated with minimal difference in the probability of predicting in-hospital mortality among patients with and without sepsis.

3.5.1 | Subgroup analyses

Sufficient data were available to perform subgroup analysis only of studies that evaluated NEWS/NEWS2 ($n=5$) and NEWS/NEWS2 ≥5 ($n=3$) (Figure 6 and Data S1—Supplemental Material 16). Despite the high pooled sensitivity estimates of >90% in both subgroup analyses, both subgroups had pooled specificity estimates of ≤20%. Furthermore, both subgroups had LR+ close to one, suggesting both tests had negligible ability to predict in-hospital mortality (Table 2b).

3.5.2 | Comparison of the EWS, qSOFA and SIRS

Three studies incorporating 12,358 patients evaluated the accuracy of the EWS, qSOFA ≥2 and SIRS ≥2 in predicting in-hospital mortality in sepsis (Boonmee et al., 2020; Churpek et al., 2017;

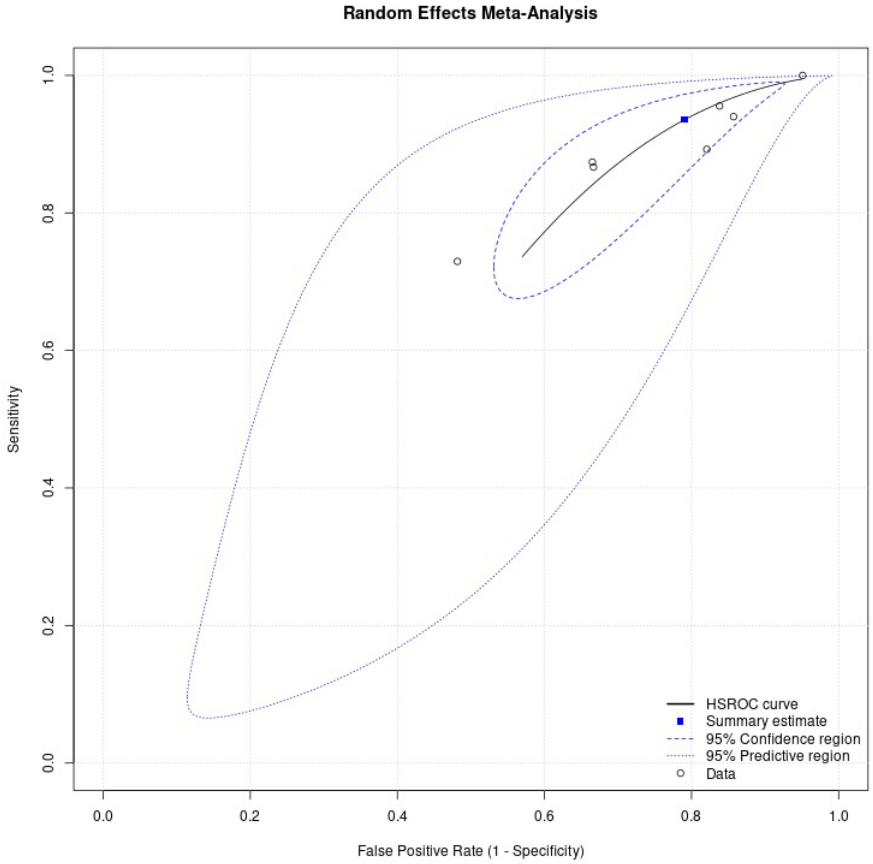

FIGURE 5 Summary receiver operating characteristic plot for all studies evaluating the early warning scores for in-hospital mortality in sepsis.

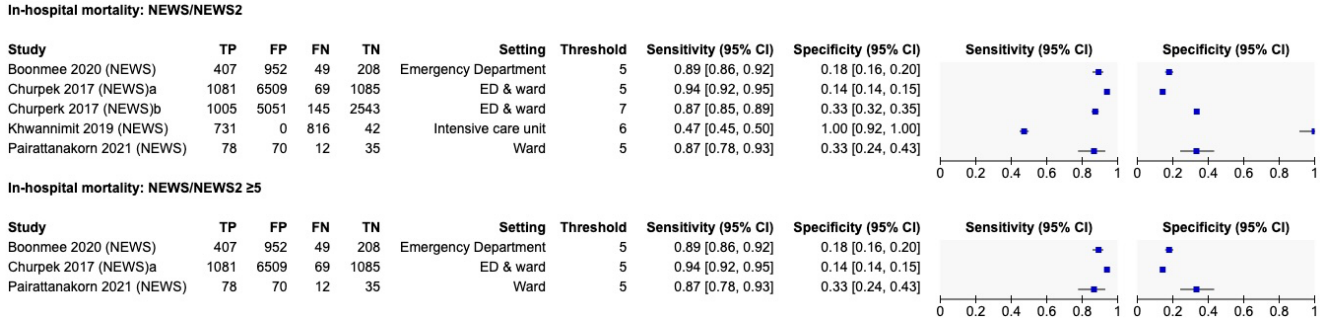

FIGURE 6 Forest plot of sensitivity and specificity of the studies of NEWS/NEWS2 in predicting in-hospital mortality in sepsis.

Khwannimit et al., 2019; Pairattanakorn et al., 2021). While the pooled sensitivity estimate was less in favour of the qSOFA ≥2 (65%, 95% CI [48, 75]) when compared against the EWS (94%, 95% CI [83, 98]), the qSOFA (LR+: 1.58, 95% [1.29, 1.92]) performed slightly better than the EWS (LR+ 1.18, 95% CI [1.08, 1.29]) in predicting in-hospital mortality in sepsis (Data S1—Supplemental Material 17). The results were similar in the subgroup analysis for directly comparing the NEWS/NEWS2 ≥5 and qSOFA ≥2 (Data S1—Supplemental Material 18). Despite the lower pooled sensitivity, the qSOFA ≥2 (LR+: 1.58, 95% CI: [1.29, 1.92]) performed better than the NEWS/NEWS2 ≥5 (LR+: 1.12, 95% CI [1.07, 1.18]) in predicting in-hospital mortality in sepsis.

On the other hand, a comparison between the EWS and SIRS ≥2 revealed comparable pooled sensitivity estimates and LR+ (Data S1—Supplemental Material 19). However, the NEWS/NEWS2 ≥5 yielded better DOR between the two tests (Data S1—Supplemental Material 20). In addition, with an LR+ of 1.04 (95% CI: 1.02, 1.07), the SIRS ≥2 is associated with almost no difference in the probability of predicting in-hospital mortality among patients with and without sepsis.

4 | DISCUSSION

A meta-analysis of 10 relevant studies was conducted to investigate the diagnostic accuracy of EWS on the new sepsis-3 definition and predicting in-hospital mortality in adult patients with sepsis, and to compare the performance with that of the qSOFA and SIRS. However, there is no single screening tool that has both high

sensitivity and specificity to predict the diagnosis of sepsis and in-hospital mortality among patients with sepsis.

In this meta-analysis, EWS had an intermediate sensitivity and specificity compared to qSOFA and SIRS in predicting the diagnosis of sepsis. Our findings suggest that EWS performed slightly poorer than qSOFA but outperformed SIRS in terms of DOR and prediction ability while avoiding the low sensitivity of qSOFA. Considering the lethality and high mortality in sepsis, high sensitivity is preferred over specificity for a sepsis screening tool because the cost of delayed or missed treatment caused by FNs far outweighs the cost of unnecessary antibiotics caused by FPs (Goulden et al., 2018; Wang et al., 2022). Hence, the qSOFA might not be an appropriate screening tool for initiating investigation and treatment in the earlier course of sepsis, which has more reversibility.

By contrast, both the EWS and SIRS provide higher sensitivity for detecting sepsis compared with qSOFA, rendering both better options than qSOFA as screening tools for early sepsis care and preventing missed sepsis diagnosis. Of note, EWS provides better discriminatory and prediction ability and superior specificity than SIRS with comparable pooled sensitivity estimates. This finding may suggest that EWS could outperform SIRS in detecting patients with sepsis. The lack of specificity in SIRS limits its utility as a sepsis screen, and this was manifested in the results of one large database study conducted in the United States, whereby only 14% of the 270,000 patients hospitalised on regular wards developed organ dysfunction despite almost half of the cohort presenting with SIRS during their hospital stay (Churpek et al., 2015). The high false-positive rates in SIRS could lead to a risk of overtreatment, and there are legitimate concerns about excessive fluid administration and overuse of antibiotics (McLymont & Glover, 2016). Nonetheless, echoing Adegbite et al. (2021), the SIRS still has value in screening patients with infections who might require higher level care owing to its high sensitivity. However, it is not necessarily capable of identifying patients with sepsis due to its low specificity (Adegbite et al., 2021).

In this review, the MEWS and NEWS/NEWS2 were the two commonly identified EWS. Our subgroup analyses, though limited by the small number of studies, provided some initial evidence to suggest that the pooled sensitivity estimates of MEWS ≥4 and NEWS/NEWS2 ≥5 were comparable to those of SIRS criteria. Although both outperformed SIRS in specificity, the EWS generally lacks the ability to differentiate between all-cause clinical deterioration and deterioration due to sepsis. Notwithstanding this limitation, the EWS has three notable advantages. First, with the EWS being commonplace in hospitals as an integral part of patient monitoring and initial patient assessment at triage, doubling the EWS to screen for sepsis would ease nurses' workload and confusion about implementing an additional sepsis screening tool. Second, unlike SIRS, EWS has no reliance on laboratory values and is readily available, especially for screening at triage, which will avoid delays in initiating time-critical interventions for possible sepsis (Keep et al., 2016). A few studies suggest that adding biomarkers such as serum lactate to EWS may provide greater specificity (Almutary et al., 2020; Hargreaves et al., 2020). To that end, MEWS ≥4 or NEWS/NEWS2 ≥5 may be a useful initial tool to trigger systematic screening for sepsis, followed by looking specifically for signs of infection and obtaining point-of-care biomarkers and, where needed, starting fluid resuscitation and antibiotic therapy. However, further prospective validation is required. Third, the EWS is a predictive scoring system that uses simple clinical assessment, which may be valuable to resource-poor settings to facilitate the recognition of patients at greater risk of sepsis, allowing optimal use of limited critical care resources.

Although three recent systematic reviews have evaluated the ability of EWS to predict mortality in patients with sepsis, none of them measured specifically on in-hospital mortality (Adegbite et al., 2021; Hamilton et al., 2018; Wang et al., 2022). More importantly, most of the studies included in the three reviews reported on the predictive ability of EWS in sepsis patients diagnosed according to the previous sepsis-1 or 2 guidelines, which might create bias, favouring the SIRS criteria. Generally, this meta-analysis demonstrates that all three scoring systems have poor prognostic value in predicting in-hospital mortality in patients diagnosed with sepsis according to the new criteria. The pooled likelihood ratios ranged from 1.04 to 1.58, and pooled negative likelihood ratios ranged from 0.26 to 0.69, indicating that they are not sufficiently accurate to rule in or rule out in-hospital mortality in patients with sepsis. This finding is consistent with earlier systematic reviews (Adegbite et al., 2021; Hamilton et al., 2018; Wang et al., 2022), further iterating that none of these three scoring systems is suitable for prognosticating sepsis or is a true sepsis-specific scoring system.

Furthermore, two reviews had warned about the possibility of a biased estimate of the predictive accuracy of EWS due to a reduced risk of mortality in prospective studies as the 'track and trigger' nature of EWS would have encouraged actions to be taken on the higher EWS scores (Hamilton et al., 2018; Patel et al., 2018). One of the four included studies in this review was potentially at risk of this (Pairattanakorn et al., 2021). However, there were too few studies with a variation in patient study groups to determine whether there is a true difference in mortality. Nevertheless, the EWS had the highest DOR and pooled sensitivity among the three scoring systems in predicting in-hospital mortality in patients with sepsis, suggesting its clinical utility as an initial screening tool to identify patients 'suspicious' of sepsis and subsequently with a more sepsis-specific tool to guide management decision.

5 | STRENGTHS AND LIMITATIONS

To our knowledge, this is the first systematic review to evaluate the performance of traditional sepsis scoring systems against the updated sepsis-3 definitions. We devised a comprehensive search strategy to locate as many relevant studies as possible. Although a formal assessment of publication bias was not conducted due to the lack of suitable and reliable methods for systematic reviews of diagnostic test accuracy (Macaskill et al., 2022), all stages of the review process involved two investigators, which minimises bias and errors. The validated QUADAS-2 tool was used to assess the quality of each study.

However, results from the meta-analysis, especially those from the subgroup analyses, should be interpreted prudently due to the limitations of this review. First, this meta-analysis has considerable heterogeneity of sources of data and selection bias because of the variations in study populations, clinical settings, sample sizes, study designs, criteria for suspected infection, criteria for sepsis diagnosis, timing of index tests collected and timing of sepsis diagnosis made relative to index test. A few studies also had patients with a high possibility of having sepsis or a clinical diagnosis of sepsis. Furthermore, most studies were judged to be of low quality. Second, we could not include five studies in the review due to insufficient data to construct the 2×2 contingency tables despite efforts to contact the authors. The addition of these studies could produce different results. Third, despite the variations of existing EWS, our analysis of EWS was only limited to NEWS/NEW2 and MEWS and based on the predefined cut-off values with sufficient data to perform meta-analysis.

6 | CONCLUSION & RELEVANCE TO CLINICAL PRACTICE

In conclusion, neither the EWS, SIRS, nor qSOFA are ideal standalone screening tools for sepsis or prognosticating patients with sepsis. However, the EWS had similar or superior values in most measures of diagnostic accuracy compared with SIRS or qSOFA, calling into question the value of SIRS or qSOFA in institutions where EWS is already in use. Our study suggests that the EWS could offer utility, even in resource-constrained settings, either (1) in a staged approach, whereby the EWS is used to first screen all cases to identify patients requiring a higher level of care followed by a more sepsis-specific tool to aid clinical decision-making or (2) in combination with other clinical risk factors or point-of-care biomarkers that were not investigated in this review. Large-scale, multi-centre studies are needed to investigate the performance of an EWS two-staged sepsis screening or combination of EWS with sepsis point-of-care biomarkers. To improve the quality of evidence, future studies should use more homogenous methodologies to evaluate EWS in sepsis screening.

AUTHOR CONTRIBUTIONS

Wei Ling Chua: Conceptualisation, methodology, acquisition of data, formal analysis, writing—original draft. Khairul Dzakirin Bin Rusli: Acquisition of data, interpretation of data, writing—review and editing. Leanne M. Aitken: Conceptualisation, methodology, analysis and interpretation of data, writing—review and editing. All the listed authors have given final approval of the version to be submitted and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data used to generate the analyses presented in the manuscript are not available via a publicly available data repository. However, all the dataset and data that supports the findings of this manuscript are available within the article and its supplementary material.

AUTHORS' STATEMENT

The authors have checked to make sure that our submission conforms as applicable to the Journal's statistical guidelines. The authors affirm that the methods used in the data analyses are suitably applied to our data within our study design and context, and the statistical findings have been implemented and interpreted correctly. The authors agree to take responsibility for ensuring that the choice of statistical approach is appropriate and is conducted and interpreted correctly as a condition to submit to the Journal.

SYSTEMATIC REVIEW REGISTRATION STATEMENT

The review was registered in the International Prospective Register of Systematic Reviews (CRD42021259829). https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=259829.

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SUPPORTING INFORMATION

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