BMJ Open

Does lactate enhance the prognostic accuracy of the quick Sequential Organ Failure Assessment for adult patients with sepsis? A systematic review

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To cite: Gill A, Ackermann K, Hughes C, *et al*. Does lactate enhance the prognostic accuracy of the quick Sequential Organ Failure Assessment for adult patients with sepsis? A systematic review. *BMJ Open* 2022;**12**:e060455. doi:10.1136/bmjopen-2021-060455

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-060455).

Received 23 December 2021
Accepted 03 October 2022

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ABSTRACT

Objectives To investigate whether adding lactate to the quick Sequential (sepsis-related) Organ Failure Assessment (qSOFA) improves the prediction of mortality in adult hospital patients, compared with qSOFA alone.

Design Systematic review in accordance with Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies guidelines.

Data sources Embase, Medline, PubMed, SCOPUS, Web of Science, CINAHL and Open Grey databases were searched in November 2020.

Eligibility criteria Original research studies published after 2016 comparing qSOFA in combination with lactate (LqSOFA) with qSOFA alone in adult patients with sepsis in hospital. The language was restricted to English.

Data extraction and synthesis Title and abstract screening, full-text screening, data extraction and quality assessment (using Quality Assessment of Diagnostic Accuracy Studies-2) were conducted independently by two reviewers. Extracted data were collected into tables and diagnostic test accuracy was compared between the two tests.

Results We identified 1621 studies, of which 11 met our inclusion criteria. Overall, there was a low risk of bias across all studies. The area under the receiver operating characteristic (AUROC) curve for qSOFA was improved by the addition of lactate in 9 of the 10 studies reporting it. Sensitivity was increased in three of seven studies that reported it. Specificity was increased in four of seven studies that reported it. Of the six studies set exclusively within the emergency department, five published AUROCs, all of which reported an increase following the addition of lactate. Sensitivity and specificity results varied throughout the included studies. Due to insufficient data and heterogeneity of studies, a meta-analysis was not performed.

Conclusions LqSOFA is an effective tool for identifying mortality risk both in adult inpatients with sepsis and those in the emergency department. LqSOFA increases AUROC over qSOFA alone, particularly within the emergency department. However, further original research is required to provide a stronger base of evidence in lactate measurement timing, as well as prospective trials to strengthen evidence and reduce bias.

PROSPERO registration number CRD42020207648.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review search was comprehensive and systematic, using multiple databases and hand searching to investigate whether combining lactate with quick Sequential Organ Failure Assessment better stratified the risk of mortality in adult inpatients.
⇒ The review search was restricted to studies published in English, and thus placed a bias towards English-speaking countries.
⇒ Two team members worked independently on study screening, data extraction and the risk of bias assessment, with a third team member available to settle disagreements, reducing the risk of confirmatory bias.
⇒ Due to insufficient data and heterogeneity of the included studies, a valid meta-analysis could not be performed.

INTRODUCTION

Throughout the last few decades, sepsis has persisted as a leading cause of mortality worldwide.[1–3] In 2017, sepsis was associated with an estimated 19.7% of all global deaths, and in 2013 cost the USA an estimated $24 billion.[3–5] Initiating sepsis treatment as early as feasible is critical to reducing sepsis mortality and improving patient outcomes.[6 7] As such, many clinical tools have been developed to assist in the rapid clinical recognition of sepsis upon patient presentation.[8–10]

The quick Sequential Organ Failure Assessment (qSOFA) pathway is a rapid bedside tool that 'provides simple bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes'.[10] The qSOFA score is classified as: (1) altered mentation; (2) a systolic blood pressure <100 mm Hg; and (3) a respiratory rate ≥22 breaths/min, with patients who meet two or more out of the three criteria considered higher risk.[11] However, there have been recent concerns regarding the low

sensitivity of qSOFA, resulting in attempts to improve its accuracy.[12–15]

Lactate, a metabolite resulting from cellular anaerobic metabolism, is associated with sepsis and septic shock.[16] Hyperlactatemia in isolation has been shown to increase the risk of 90-day mortality in patients with sepsis by 1.7 times.[17] As such, lactate alone has been postulated as a diagnostic and prognostic tool for sepsis.[18 19] Point-of-care lactate has shown promise as a marker of sepsis severity and has been validated in several studies to improve the performance of bedside recognition algorithms.[20 21] Combining biomarkers, such as lactate, with pre-existing clinical scores, such as qSOFA, could enhance swift sepsis recognition,[22 23] improving overall patient mortality and morbidity. Kashyap *et al* investigated qSOFA and lactate during a larger review on the enhancement of sepsis identification scores, but did not study this tool in detail.[24]

This review aimed to identify and provide high-level evidence as to whether lactate as an additive to qSOFA (LqSOFA) will enhance the rapid stratification of sepsis risk in adult patients with sepsis in various hospital settings, compared with qSOFA alone.

METHODS

This study is a systematic review searching multiple online databases using a PROSPERO-registered search strategy (CRD42020207648). We have followed the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines for reporting throughout the review.[25 26] A completed PRISMA-DTA checklist is attached in online supplemental appendix 1.

Search strategy

To identify relevant papers, we searched Embase, Medline (both via Ovid), Web of Science, Scopus, PubMed, and the Cumulative Index to Nursing and Allied Health Literature. To capture grey literature, we used the Open Grey database. The search strategy was developed by two authors (AG, KA) with the assistance of a clinical librarian, and reviewed by a third reviewer (LL). Search strategies for all databases can be seen in online supplemental appendix 2. Only papers written in English or with readily available English translations were considered for inclusion due to time and resource constraints.

All references retrieved by the search were imported into an EndNote V.X9 library (Clarivate) and duplicates removed. Two reviewers (AG, KA) then independently applied the predefined eligibility criteria (below) for study selection through first title and abstract screening, followed by full-text retrieval and screening. Disagreements on included research were resolved by discussion, or by a third independent reviewer (LL) if required.

Eligibility criteria

Studies were included if they: (1) were original research; (2) were published after 2016; (3) examined adult hospital patient populations only; (4) reported combined qSOFA and lactate score results, as well as qSOFA alone as a comparator; (5) had a population defined as having a confirmed diagnosis or a suspected diagnosis of sepsis, systemic inflammatory response syndrome or septic shock; (6) were published in English.

Original research only was included, defined as published original research with relevant clinical results, including randomised controlled trials, observational studies, prospective and retrospective cohort analyses, as well as grey literature such as published conference abstracts. Opinion pieces, such as editorials and commentaries, reviews and other references containing unpublished non-original research were excluded. Papers published before 2016 were excluded as this was prior to the publication of the qSOFA criteria.[11] Following discussion and full-text screening, the inclusion criteria were further clarified to require papers to look at the use of qSOFA and lactate specifically within the context of sepsis as defined in the included studies.

Quality assessment

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool.[27] Two reviewers (AG, KA) independently performed the quality assessment, with disagreements resolved through discussion or by a third reviewer (LL). Any biases of selected papers found, as well as the implications of bias, were discussed in narrative synthesis.

Patient and public involvement

This is a systematic review. No patients are involved.

Data extraction

Data were extracted from the selected studies using a data extraction form in Microsoft Excel. Data extracted included year of publication, study author(s), country of study setting, funding sources, number of participants, patient demographics, study design (eg, prospective or retrospective cohort), length of stay, intensive care unit (ICU) admission status and mortality. Data related to the implementation of qSOFA and combined qSOFA and lactate tools, and the threshold values of lactate used, were also extracted from papers. The type of mortality investigated, sensitivity, specificity, area under the receiver operating characteristic (AUROC) curve or data related to calculating these metrics were extracted if available. Seven authors were contacted to request missing data,[21 28–33] three of which replied.[21 29 31]

Data synthesis

Data were analysed in the style of a narrative review with accompanying summary statistics due to the high variability within the included studies. Extracted data were collated within tables to allow for better comparison and analysis between studies.

We calculated sensitivity and specificity from data made available by authors if needed. The change in sensitivity, specificity and AUROC after the addition of lactate was

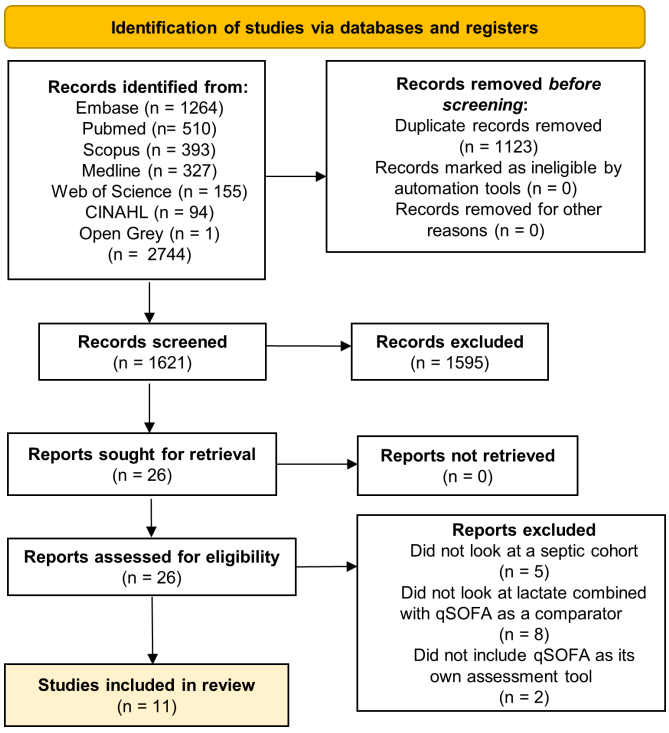

Figure 1 PRISMA flow chart for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; qSOFA, quick Sequential Organ Failure Assessment.

calculated for each study. Studies involving the ICU only and emergency department (ED) were analysed as subgroups. Mortality outcomes were also stratified as subgroups and analysed. Additional data, including positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic OR (DOR) and raw outcome data (ie, true positive, false positive, true negative and false negative), were calculated from available data (reported and via author correspondence) and included in online supplemental tables 1–3.

RESULTS

Search results

Our search strategy was executed on the 2 November 2020, returning 2744 citations. After deduplication, 1621 articles remained. Following title and abstract screening, 26 articles remained, excluding 1595 articles. From this, full texts were retrieved, and 11 studies selected for inclusion.[20 21 28–36] A flow chart demonstrating this process can be seen in figure 1.

Study characteristics

The characteristics of included studies are presented in table 1. Eleven studies were identified ranging from 2017 to 2020 in publication year. These studies were conducted in a diverse range of countries, with studies set in Australia (n=1), the USA (n=3), China (n=2), South Korea (n=2), Brazil (n=1) and across multiple countries (n=1). Only one study did not report the country it was set in. Six studies recruited only from the ED, with two recruiting from ICU, one from both ED and inpatient wards, and two from a hospital-wide cohort. Study population sizes ranged from 165 to 55 945.

The main outcome for all studies was mortality. The type of mortality reported varied (table 1). Three studies used 30-day or 28-day mortality as their primary outcome,[29 30 36] four studies used in-hospital mortality,[20 31 33 35] one study used 7-day mortality[32] and one other did not specify (table 2).[34] Of the final two studies, one used a composite of ICU length of stay, vasopressor use and mortality within 72 hours of presentation,[28] and the other looked at a composite of adverse outcomes, specified as either a prolonged stay in ICU ≥72 hours or in-hospital mortality.[21]

Study outcomes

Nine of the 10 studies reporting an AUROC found an improvement following the addition of lactate regardless of the type of mortality investigated (table 2), with the greatest increase being 23.9% demonstrated by Liu *et al*.[33] In addition, sensitivity was increased by the addition of lactate in three of seven studies that reported sensitivity, and specificity was increased in the other four. The greatest change in sensitivity was demonstrated by Machado *et al*, with a 69.4% increase with the addition of lactate (table 2).[35] The greatest change in specificity was demonstrated by Zhou *et al*, with a 63.4% increase in specificity in LqSOFA over qSOFA.[36]

Four studies reported data specifically on in-hospital mortality (table 1). The AUROC was improved by the addition of lactate in all four studies (table 2). Liu *et al* (2019) demonstrated the largest rise in AUROC, from 0.544 to 0.674 for qSOFA and LqSOFA, respectively; a 23.9% increase over qSOFA alone.[33]

Six studies were set exclusively within the ED, five of which recorded AUROCs (table 2). The AUROC increased after the addition of lactate in five studies. Chae *et al* demonstrated the largest increase in AUROC in LqSOFA, with a +16.7% increase.[29] Sensitivity was increased by the addition of lactate in two of the five studies reporting it and specificity was increased in the other three (table 2). Given the heterogeneity across studies, for example, study population, lactate thresholds, outcome types and time points of outcome measurement, meta-analysis would not provide meaningful results. A summary ROC plot (sensitivity vs 1-specificity) of five ED studies shows that results of all studies are above the chance level (online supplemental figure 1).

Six studies reported the PPV and NPV following the addition of lactate to qSOFA with four studies reporting an increase to PPV, two reporting a decrease and vice versa for the NPV (online supplemental table 1). Similarly, the seven studies demonstrating a change in PLRs and NLRs are relatively evenly split with three studies demonstrating a decrease in PLR, four demonstrating an increase, four studies demonstrating an increase in NLR and three studies a decrease (online supplemental table 2). Of the

Table 1 Study characteristics

Study	Year of publication	Country of study population	Study population	N	% male	Study design*	Setting	Main outcome	Other outcomes
Ho and Lan[31]	2017	Australia	ICU patients not intubated within the first hour of ICU stay	2322	61	Prospective audit	ICU	Hospital mortality	LOS (ICU) >10 days, invasive mechanical ventilation within 24 hours of ICU admission
Said Ahmed *et al*[34]	2017	USA	Patients with suspected infection admitted to the medical centre ED	581	NR	Retrospective study	ED	Mortality	LOS, ICU admission
Shetty *et al*[21]	2017	Multinational (Australia and the Netherlands)	Adult patients with suspected infection or suspected/confirmed sepsis	12 555	52.4	Retrospective cohort	ED	Combined adverse events: composite of death in hospital or ICU stay ≥72 hours	None
Chou *et al*[30]	2019	NR	Adults with suspected infection	55945	NR	Retrospective study	Hospital-wide	30-day mortality	None
Liu *et al*[33]	2019	USA	Adult patients diagnosed with sepsis, severe sepsis or septic shock	1865	57	Retrospective study	ICU	Hospital mortality	30-day, 90-day and 1-year mortality
Baumann *et al*[28]	2020	USA	Adult patients admitted to hospital from the ED with presumed infectious disease-related illnesses	2584	51.9	Multicentre retrospective cohort	ED	Composite of ICU admission, vasopressor use or death within 72 hours of ED presentation	None
Chae *et al*[29]	2020	South Korea	Adult patients with active cancer with sepsis as defined by SIRS	301	49.5	Retrospective cohort	ED	30-day mortality	None
Hwang *et al*[32]	2020	South Korea	Adult patients who visited the ED with confirmed sepsis based on bacterial culture and MAP <60 mm Hg	165	47	Retrospective study	ED	7-day mortality	In-hospital mortality, mechanical ventilation, ICU admission
Liu *et al*[20]	2020	China	All adult patients diagnosed with sepsis based on Sepsis-3 criteria	821	64.3	Retrospective observational study	Hospital-wide	In-hospital mortality	ICU admission

Continued

Table 1 Continued

Study	Year of publication	Country of study population	Study population	N	% male	Study design*	Setting	Main outcome	Other outcomes
Machado *et al*[35]	2020	Brazil	All patients with suspected sepsis in the ED or ward	5460	46.1	Observational prospective	ED+wards	In-hospital mortality	ICU admission within 24 hours after diagnosis, composite of ICU admission within 24 hours and ICU LOS >48 hours
Zhou *et al*[36]	2020	China	Adult patients with discharge diagnosis of CAP and a SOFA score of ≥2	336	63.4	Retrospective cohort	ED	28-day mortality	ICU admission, mechanical ventilation, vasopressor use

*Study design as described by study authors in text.
CAP, community-acquired pneumonia; ED, emergency department; ICU, intensive care unit; LOS, length of stay; MAP, mean arterial pressure; NR, not reported; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

seven studies with DOR, six reported an increase when lactate was added to qSOFA (online supplemental table 2).

qSOFA and LqSOFA cut-off thresholds and lactate measurement timing

Seven studies reported a lactate threshold of ≥2 mmol/L (table 3). Other lactate threshold levels used were ≥4 mmol/L (n=1), ≥3.225 mmol/L (n=1), and groups of <2 mmol/L, 2–4 mmol/L, and >4 mmol/L (n=1). Only one study did not report their lactate threshold. The definition of a positive 'LqSOFA' varied widely between studies, with seven studies reporting five different score thresholds (table 3). The time of lactate measurement and collection of clinical data also varied between studies (table 3).

Risk of bias

The risk of bias was generally low as seen in figure 2. Five studies demonstrated a low risk of bias among all domains. The index test domain was the most likely to introduce bias among the included studies, with two studies judged as high, and three as unclear risk of bias (figure 2). In addition, one study demonstrated a high risk of bias in the flow and timing domain (figure 2).

DISCUSSION

Overall, LqSOFA demonstrated an increased accuracy for the identification of patients at higher risk of mortality compared with qSOFA alone, as evidenced by an improvement in the AUROC upon the addition of lactate in 9 of the 11 included studies. This increased accuracy will translate to earlier identification of patients who would otherwise be overlooked, followed by earlier treatment initiation, escalation of care and better patient outcomes.[6 7] In addition, most studies reported an increase in DOR following the addition of lactate to qSOFA, suggesting that there has been an increase in the test's ability to diagnose the risk of mortality in patients with suspected sepsis correctly, further reinforcing the merit of adding lactate to qSOFA.

Our findings regarding changes in sensitivity and specificity following the addition of lactate to qSOFA are more inconsistent. Unsurprisingly, studies reporting an increase in sensitivity also reported a decrease in specificity, and vice versa. Of the included seven studies reporting sensitivity and specificity values, three[21 34 35] reported an increase in sensitivity and decrease in specificity, and four[28 29 31 36] reported an increase in specificity and decrease in sensitivity. High sensitivity of a sepsis recognition tool is beneficial as sepsis deteriorates rapidly.[37] The earlier patients are identified, the earlier treatment begins, and therefore it is critical to identify as many sepsis cases as early as possible.[38] However, a high-test specificity is also beneficial as it can reduce unnecessary antibiotic use or fluid resuscitation treatment, both of which have been linked to negative outcomes.[39–41] This is particularly true in low-income to middle-income

Table 2 qSOFA versus LqSOFA mortality outcome measurement

	Sensitivity (CI)*			Specificity (CI)*			AUROC (CI)*		
Study	**qSOFA**	**LqSOFA**	**Change (%)**	**qSOFA**	**LqSOFA**	**Change (%)**	**qSOFA**	**LqSOFA**	**Change (%)**
Ho and Lan†[31]	0.46 (0.40 to 0.51)	0.291‡ (0.233 to 0.350)§	−0.169 (−36.7)	0.81 (0.80 to 0.83)	0.922‡ (0.909 to 0.935)§	+0.112 (+13.8)	0.672 (0.638 to 0.707)	0.730 (0.694 to 0.765)	+0.058 (+8.6)
Said Ahmed *et al*[34]	0.595 (NR)	0.795 (NR)	+0.2 (+33.6)	0.688 (NR)	0.487 (NR)	−0.201 (−29.2)	NR	NR	NR
Shetty *et al*[21]	0.476 (0.446 to 0.506)	0.655 (0.626 to 0.684)	+0.179 (+37.6)	0.891 (0.885 to 0.896)	0.815 (0.808 to 0.822)	−0.076 (−8.5)	0.68 (0.68 to 0.69)	0.74 (0.73 to 0.74)	+0.06 (+8.8)
Chou *et al*[30]	NR	NR	NR	NR	NR	NR	0.66 (0.65 to 0.66)	0.57 (0.57 to 0.58)	−0.09 (−13.6)
Liu *et al*[33]	0.234 (NR)	NR	NR	0.822 (NR)	NR	NR	0.544 (0.518 to 0.571)	0.674 (0.650 to 0.699)	+0.130 (+23.9)
Baumann *et al*[28]	0.557 (0.551 to 0.603)	0.385 (0.341 to 0.431)	−0.172 (−30.9)	0.854 (0.838 to 0.868)	0.934 (0.923 to 0.944)	+0.08 (+9.4)	0.772 (0.750 to 0.794)	0.821 (0.800 to 0.842)	+0.049 (+6.3)
Chae *et al*[29]	0.256 (0.125 to 0.386)§	0.186‡ (0.070 to 0.302)§	−0.07 (−27.3)	0.953 (0.928 to 0.979)§	0.973‡ (0.953 to 0.993)§	+0.02 (+2.1)	0.66 (0.56 to 0.75)	0.77 (0.69 to 0.85)	+0.11 (+16.7)
Hwang *et al*[32]	NR	NR	NR	NR	NR	NR	0.698 (NR)	0.787 (0.697 to 0.877)	+0.089 (+12.8)
Liu *et al*[20]	NR	NR	NR	NR	NR	NR	0.717 (0.685 to 0.748)	0.751 (0.720 to 0.780)	+0.034 (+4.7)
Machado *et al*[35]	0.539 (0.503 to 0.575)	0.913 (0.890 to 0.932)	+0.374 (+69.4)	0.836 (0.825 to 0.846)	0.360 (0.346 to 0.374)	−0.476 (−56.9)	0.750 (0.732 to 0.769)	0.824 (0.808 to 0.839)	+0.074 (+9.9)
Zhou *et al*[36]	0.910 (NR)	0.640 (NR)	−0.27 (−29.7)	0.538 (NR)	0.879 (NR)	+0.341 (+63.4)	0.807 (0.754 to 0.859)	0.833 (0.786 to 0.881)	+0.026 (+3.2)

*These values reported correspond to the main outcome reported in table 1, and to the lactate and qSOFA thresholds reported in table 3. Other sensitivity, specificity, and AUROC values may be presented in the studies for other outcomes and threshold values.
†For Ho and Lan,[31] the n values given for the total cohorts in the provided data from the authors did not match the n values reported in the published study (from authors data: qSOFA score n=2303, LqSOFA score n=1893; from study data: qSOFA score n=2322, LqSOFA score n=1910).
‡Calculated data from author correspondence.
§CIs are assumed to be 95% CI and are calculated using a CI web calculator[61] based on data received from author correspondence.
AUROC, area under the receiver operating characteristic curve; LqSOFA, lactate combined with qSOFA; NR, not reported; qSOFA, quick Sequential Organ Failure Assessment.

Table 3 LqSOFA characteristics

Paper	Lactate level threshold	qSOFA score threshold	LqSOFA score threshold	Timing of all measurements
Ho and Lan[31]	Groups of <2 mmol/L, 2–4 mmol/L and >4 mmol/L	≥2	qSOFA ≥2 AND lactate ≥2 mmol/L*	Obtained within the first hour of admission to ICU
Said Ahmed *et al*[34]	≥2 mmol/L	≥2	Score of 2 or more	NR
Shetty *et al*[21]	≥2 mmol/L	≥2	Score of ≥2 out of 4	Study uses large, merged dataset. Time of measurements depends on the specific patient cohort
Chou *et al*[30]	NR	NR	NR	≤24 hours after admission
Liu *et al*[33]	≥3.225 mmol/L	NR	NR	Worst qSOFA scores within the first 24 hours of ICU admission, average lactate level measured within the first 24 hours of ICU admission
Baumann *et al*†[28]	≥2 mmol/L	≥2	qSOFA ≥2 and lactate ≥2. The threshold used to calculate the reported AUROCs was not specified.	Most abnormal physiological results within first 6 hours of ED stay and the first lactate measurement (if taken within 6 hours of ED presentation)
Chae *et al*[29]	≥2 mmol/L	≥2	qSOFA+1 if lactate ≥2 mmol/L	qSOFA calculated at ED admission. Lactate measurement time not specified
Hwang *et al*†[32]	≥4 mmol/L	≥2	NR	ED triage‡
Liu *et al*[20]	≥2 mmol/L	NR	NR	NR
Machado *et al*‡§[35]	≥2 mmol/L	≥2	≥1 qSOFA OR >2 mmol/L lactate	Worst values at moment of sepsis suspicion used. Collected ED data from admission to sepsis suspicion and ward patient data for previous 24 hours. Lactate timing not reported
Zhou *et al*[36]	≥2 mmol/L	≥2	qSOFA ≥2 or lactate ≥2 mmol/L	ED admission

*Data retrieved from author correspondence.
†Study investigated multiple lactate and/or LqSOFA and/or qSOFA thresholds. The thresholds reported in this table were chosen to improve homogeneity, and correspond with the sensitivity, specificity, and AUROC scores reported. See study for details on other thresholds.
‡Also took measurements after therapy initiation. We chose to report the measurements associated with ED triage to improve homogeneity and to better mimic real-life situations.
§Only used data from cohort 1 as only cohort 1 investigated LqSOFA versus qSOFA.
AUROC, area under the receiver operating characteristic curve; ED, emergency department; ICU, intensive care unit; LqSOFA, lactate combined with qSOFA; NR, not reported; qSOFA, quick Sequential Organ Failure Assessment.

countries, as studies have shown unnecessary treatment to be associated with mortality in sepsis.[42] Therefore, while our findings regarding the sensitivity and specificity of LqSOFA are heterogenic, both an increase in sensitivity or specificity would be beneficial in sepsis screening.

The qSOFA tool was designed to be fast, simple, and highly specific for predicting organ dysfunction and mortality, and is therefore ideal for use as a bedside tool in the ED.[11 43–45] Lactate is often taken as part of normal screening and sepsis management within the ED, making it a viable and attractive candidate to add to the qSOFA score.[46 47] Furthermore, lactate is a known marker of illness severity and septic shock, reinforcing its suitability for combination with qSOFA.[10 47] We found all studies investigating LqSOFA in the ED demonstrated an increased AUROC, and hence ability to accurately predict mortality, after the addition of lactate (table 2). Thus, lactate would be a useful and valuable addition to qSOFA in the ED and other emergency situations.

Further to this, there is some evidence for the use of lactate in guiding sepsis therapy.[47–49] Lactate levels have been shown to correlate with disease severity, and increased lactate clearance has long been known to correlate with survivability.[47 49–51] Using lactate kinetics as part of lactate clearance-driven therapy could improve patient outcomes.[52–55] Adding lactate to qSOFA would enhance the ability of qSOFA to not only identify patients at high risk of sepsis-related poor outcomes, but to also guide the management of patients treated as septic. Increasing the frequency of LqSOFA measurement could facilitate its use throughout the entirety of a patient's hospitalisation. This would provide clinicians an

	Risk of bias				Applicability concerns		
	Patient Selection	Index test	Reference standard	Flow and timing	Patient selection	Index Test	Reference standard
Ho, 2017	✓	✗	✓	✓	✓	✓	✓
Said Ahmed, 2017	✓	✓	✓	✓	✓	✓	✓
Shetty, 2017	✓	✓	✓	✓	✓	✓	✓
Chou, 2019	✓	!	✓	✓	✓	✓	✓
Liu, 2019	✓	✓	✓	✓	✓	✓	✓
Baumann, 2020	✓	✓	✓	✓	✓	✓	✓
Chae, 2020	✓	✓	✓	✓	✓	✓	✓
Hwang, 2020	✓	✗	✓	✓	✓	✓	✓
Liu, 2020	✓	!	✓	✓	✓	✓	✓
Machado, 2020	✓	✓	✓	✓	✓	!	✓
Zhou, 2020	✓	!	✓	✗	✓	✓	✓

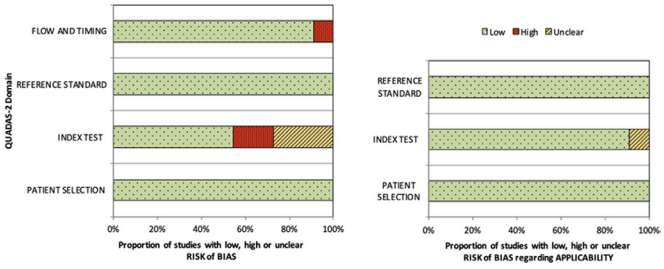

Figure 2 Risk of bias. In accordance with QUADAS-2 tool guidelines.[27] Green or (√) symbol denotes low risk of bias. Red or (X) denotes high risk of bias. Yellow or (!) denotes unclear risk of bias. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

additional tool for the simple and efficient assessment of a patient's health, supporting regular patient monitoring. This may improve patient outcomes and is thus highlighted as an area for future research. However, lactate scores can be altered by several different mechanisms.[47 49] Other conditions that interfere with tissue oxygenation or alter metabolic demand, such as diabetic ketoacidosis, seizures, metabolic liver disease as well as iatrogenic causes, can result in a raised lactate.[47 49 56] Clinicians and researchers should be aware of these confounding factors when using or investigating the use of LqSOFA for both prognosis and sepsis management.

The studies included in this review use a range of lactate thresholds, including 2, 3.25 and 4 mmol/L (table 3). The lactate threshold used when screening a patient for sepsis risk will greatly affect the following risk estimation. Within the literature currently, there is a poor consensus for the appropriate lactate cut-off. Some studies indicate a lower lactate threshold, such as 1.3 mmol/L, can still have a significant correlation with prognosis, while others indicate a ≥2 mmol/L or ≥4 mmol/L concentration is the optimal threshold.[57–59] Furthermore, we have highlighted considerable diversity in what lactate measurements are used when calculating the LqSOFA score (table 3). Some studies make use of the worst score within the first 24 hours, while others use parameters collected at ED triage. Given the dynamic nature of blood lactate levels,[49] this difference in measurement timing will likely affect the final LqSOFA score. Furthermore, as many of these studies are retrospective, this does not give an accurate reflection of how LqSOFA will be measured when implemented in real time. Future research should aim to maintain pragmatic and consistent lactate thresholds and measurement timings, better reflecting the real-world use of the LqSOFA tool, and hence improving the evaluation validity.

Lastly, there is some evidence that venous lactate does not always correlate well with arterial and central lactate values, especially during hyperlactatemia.[47] However, taking arterial lactate is difficult and not always practical, and venous lactate may be more suitable for a quick and simple tool such as LqSOFA.[47] Clinicians and researchers should be aware of how the source of the lactate may influence the test result. Future large multicentre studies investigating the correlation between arterial and venous lactate would better elucidate this relationship and shed light on how this may influence LqSOFA.

To our knowledge, this systematic review is the first examining the addition of lactate to the qSOFA pathway. We used multiple databases to ensure a comprehensive and systematic search of the literature and completed this review to current PRISMA-DTA standards. However, we were unable to perform a valid meta-analysis due to insufficient data and heterogeneity of studies. Across the 11 included studies, there were six different measures of mortality reported. A total of four studies used the same time point to measure mortality; however, these four studies examined very different study populations, including all hospital patients, only ED patients or only ICU patients. Each of these populations is uniquely different, particularly in terms of sepsis severity, and therefore combining these studies for meta-analysis would not result in valid conclusions. Future meta-analyses could consider certain focused subsets as published studies accumulate on a specific mortality measure or among certain population (eg, ED patients). With enough studies, a valid meta-analysis could model sensitivity and specificity jointly using either the Hierarchical Summary Receiver Operating Characteristic Model or the Bivariate Model.[60] In addition, we only reviewed trials available in English due to the time and resource constraints, and therefore may have missed articles published in other languages.

CONCLUSION

LqSOFA increased the accuracy of qSOFA alone in detecting patients at higher risk of sepsis-related mortality in many hospital settings, including the ED. Further research should investigate the use of LqSOFA prospectively, with focus on a more standardised or dynamic lactate measurement timing.

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Contributors LL was responsible for the overall study as the guarantor. AG drafted the protocol. LL and KA reviewed the protocol. AG and KA conducted the literature search. AG, KA, LL, CH and VL all contributed to the production and review of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study did not receive nor require ethics approval, as it does not involve human and animal participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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