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ORIGINAL RESEARCH

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Combining C-reactive protein and quick sequential organ failure assessment (qSOFA) to improve prognostic accuracy for sepsis and mortality in adult inpatients: A systematic review

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Abstract

Background and Aims: Infections are common in hospitals, and if mismanaged can develop into sepsis, a leading cause of death and disability worldwide. This study aimed to examine whether combining C-reactive protein (CRP) with the quick sequential organ failure assessment (qSOFA) improves its accuracy for predicting mortality and sepsis in adult inpatients.

Methods: PubMed, MEDLINE, EMBASE, Scopus, Web of Science, Science Direct, CINAHL, Open Grey, Grey Literature Report, and the Clinical Trials registry were searched using CRP and qSOFA search terms. Title, abstract, and full-text screening were performed by two independent reviewers using pre-determined eligibility criteria, followed by data extraction and a risk of bias assessment using the Quality Assessment tool for Diagnostic Accuracy Studies 2 (QUADAS-2). Disagreements were settled through discussion and consultation with a third reviewer.

Results: Four retrospective studies with a total of 2070 patients were included in this review. Adding CRP to qSOFA improved the Area Under the Receiver Operating Characteristic Curve up to 9.7% for predicting mortality and by 14.9% for identifying sepsis. The sensitivity and specificity of the combined score for mortality prediction were available in two studies. CRP improved the sensitivity of qSOFA by 43% and 71% while only decreasing the specificity by 12% and 7%, respectively. A meta-analysis was not performed due to study heterogeneity.

Conclusion: This comprehensive review provided initial evidence that combining CRP with qSOFA may improve the accuracy of qSOFA alone in identifying sepsis or patients at risk of dying in hospital. The combined tool demonstrated the potential to improve patient outcomes, with implications for low-resource settings given its simplicity and low-cost.

Registration PROSPERO registration No. CRD42020190973

KEYWORDS
C-reactive protein, early diagnosis, hospital mortality, infections, organ dysfunction scores, sepsis

1 | INTRODUCTION

Infection is common and if left untreated can develop into sepsis,[1] a leading cause of death and disability worldwide.[2] Sepsis is particularly prevalent in countries with a low to middle socio-demographic index (SDI), where 85% of the global sepsis incidence is reported.[2] Furthermore, countries with the lowest SDI suffer the highest sepsis-related mortality.[2] Patients with sepsis can rapidly deteriorate if not promptly identified and carefully managed.[3,4] Thus, identifying high-risk infection patients and initiating evidence-based bundle care is paramount to improving patient outcomes.[2] However, despite numerous efforts to develop effective diagnostic tools, rapid identification of infection, especially sepsis, remains challenging.[5]

In 2016, the quick sequential (sepsis-related) organ failure assessment (qSOFA) was introduced as a simple bedside scoring system aimed to identify patients at higher risk of poor outcomes related to sepsis, including death or ICU admission.[3] Compared with established sepsis scores, such as the systemic inflammatory response syndrome (SIRS) criteria, qSOFA better predicts in-hospital mortality in emergency department (ED) patients with suspected infection.[6] Its use for the prediction of mortality or poor outcomes in low resource settings, defined by financial pressure, geographical, or environmental factors,[7] and in other sepsis-related conditions, such as suspected infection and pneumonia, has been investigated.[8–12] However, in recent years, the poor sensitivity of qSOFA for mortality prediction and identification of suspected sepsis has raised concerns.[13–17] Notably, the most recent surviving sepsis campaign guidelines recommend against using qSOFA alone as a screening tool for sepsis, although the guidelines do not comment on its use for the prediction of poor outcomes as originally designed.[18]

C-reactive protein (CRP) is an acute phase reactant released by the liver in the early stages of inflammation and infection, and has demonstrated high sensitivity for sepsis identification.[19–23] As part of the initial immune response, CRP can activate the complement system, recruit leukocytes to the site of inflammation, and mark pathogens for phagocytosis by identifying and binding foreign molecules, such as phosphocholine, on pathogen cell walls.[21] Critically, CRP is one of the first biomarkers to rise in response to infection, with CRP blood levels rising 6 h after stimulus.[21,24] Studies have demonstrated the use of CRP for assisting clinicians in determining bacterial infection severity in Nepal[19] and rural Congo,[25] in guiding antibiotic use for febrile patients in low resource settings,[26–29] and most recently in estimating COVID-19 severity.[30] Including CRP in qSOFA may improve qSOFA's sensitivity and ability to identify patients at high-risk of mortality or sepsis. Other acute phase reactants such as interleukin-1 beta, tumor necrosis factor-alpha, procalcitonin, and interferon gamma can also act as inflammatory biomarkers.[31–36] However, CRP testing is very accessible, relatively inexpensive, and well-established in low-resource clinical settings,[19,22,23,25–27,29,30] making it an ideal choice for combination with qSOFA, a rapid and simple bedside scoring system.[3,37]

Current evidence evaluating the performance of a combined qSOFA and CRP score is limited. Preliminary studies have suggested adding CRP to qSOFA yields improved performance when compared to qSOFA alone.[38] However, there has been no systematic approach appraising the literature. This paper aimed to comprehensively evaluate whether combining CRP with qSOFA improves sepsis identification and mortality prediction among adult hospital patients compared with qSOFA alone.

2 | METHODS

2.1 | Protocol registration

This study complied with the recommendations for the conduct and reporting of systematic reviews and meta-analyses, set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Diagnostic Test Accuracy (PRISMA-DTA) statement.[39] The study protocol was developed and registered with PROSPERO (Registration No. CRD42020190973).

2.2 | Literature search and study selection

A comprehensive electronic search of 10 databases, including PubMed, Embase, MEDLINE, Scopus, CINAHL, Web of Science, Science Direct, Clinical Trials Registry, Open Grey, and the Grey Literature Report was performed using search terms for CRP and qSOFA (see Appendix for MEDLINE search strategy). Reference lists were also hand-searched for any additional relevant studies.

No restrictions were placed on the publication date, allowing complete coverage of included databases. The search was executed in May 2022. Following the deduplication of search results, two review authors (AZ and KA) independently performed title, abstract and keyword screening by applying pre-decided eligibility criteria to all studies. References that were relevant to the topic after the title, abstract and keyword screening had full-text articles retrieved. These articles underwent full-text screening, and the same pre-decided eligibility criteria were applied. Any disagreements during the search and screening process were settled via discussion or consultation with a third team member (LL).

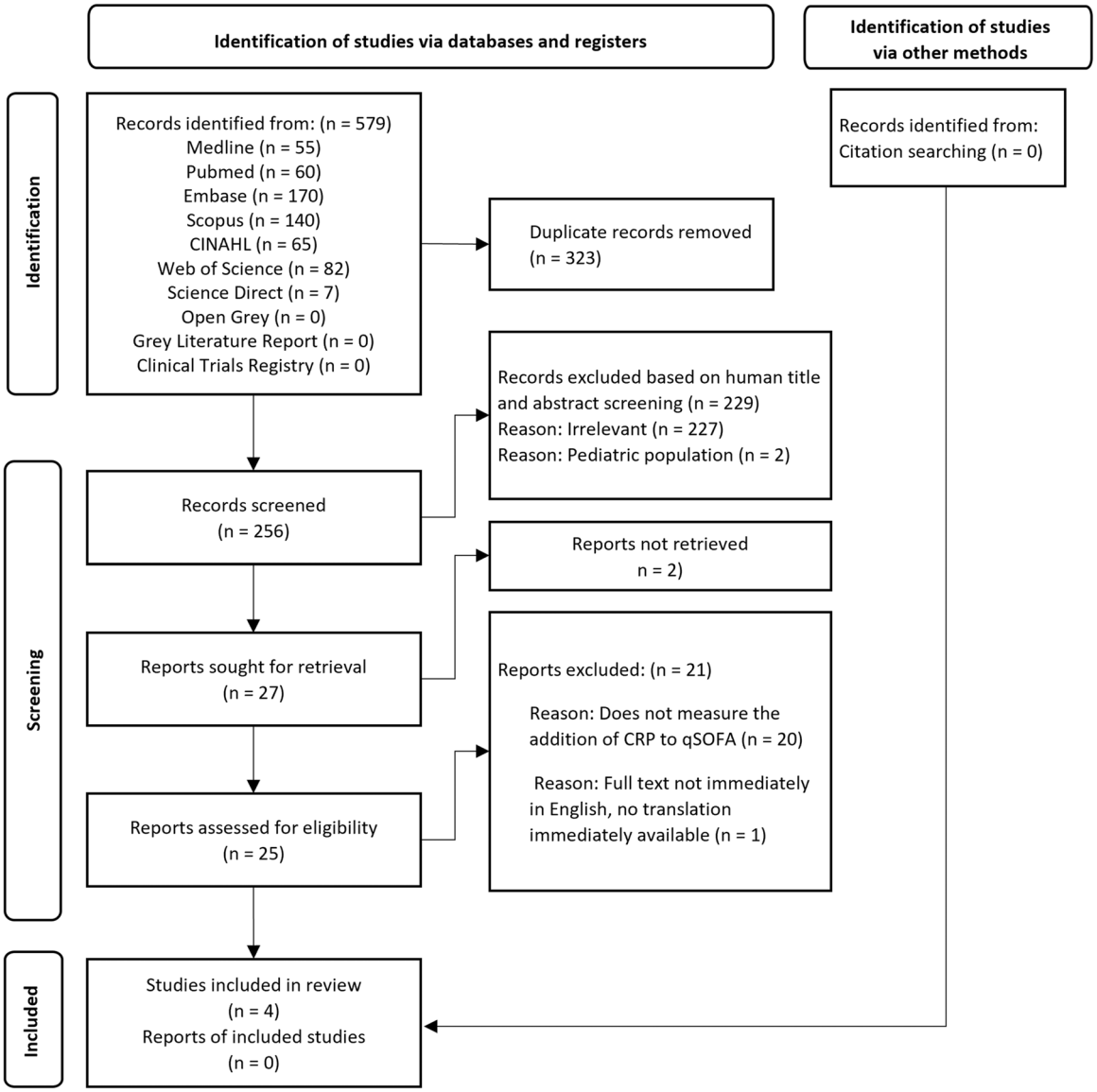

FIGURE 1 PRISMA flowchart.

2.3 | Eligibility criteria

Studies had to meet all inclusion criteria and no exclusion criteria to be included in this review. The inclusion criteria were: (i) the study population was aged ≥18 years or defined as an adult by study authors, (ii) the study compared qSOFA (reference test) to qSOFA combined with CRP (index test), (iii) the study was set in a hospital environment, (iv) the study was original research regardless of design, and (v) the study was published in English or with a readily available English translation. The study population was confined to adult patients as pediatric and neonatal populations have a physiologically distinct sepsis presentation.[40] We accepted any combination of CRP and qSOFA used by the study authors and defined hospital setting as either ED, intensive care unit, or inpatient wards. We only accepted papers in English or with English translations readily available due to time and resource constraints.

2.4 | Data extraction

Our study outcomes were the accuracy of predicting patient mortality risk or identifying sepsis. All relevant study characteristics and study outcome information were extracted into a pre-designed excel template, which included: country of study, study design, sample size, clinical context of study, setting of the study, study population demographics (sex, age, and comorbidities), and performance outcomes for qSOFA and qSOFA combined with CRP (i.e., sensitivity, specificity, area under receiving operating characteristics curve (AUROC), negative predictive value (NPV), and positive predictive value (PPV)).

TABLE 1 Characteristics of included studies.

Study	Country	Study design	Number of participants	Clinical context	Setting	CRP cut-off (mg/L) (point)	Cut-off score for qSOFA + CRP	Patient outcome
Dimitrov et al.[38]	Bulgaria	Retrospective study	78	Patients referred from ED who underwent surgery for complicated abdominal infections	Department of surgical diseases - in hospital	>100 (1 point)	≥2	In-hospital mortality
Yu et al.[43]	China and Taiwan	Retrospective multi-center cohort study	1318	Patients presenting to ED or who were admitted to hospital with symptoms that indicated systemic infection	ED & inpatients	60–120 (1 point); >120 (2 points)	≥2	In-hospital mortality
Kim et al.[42]	Korea	Retrospective chart review	125	Patients admitted to ED with discharge diagnosis of community acquired pneumonia	ED	>128.8 (1 point)	≥2	28-day mortality
Woo et al.[33]	Korea	Prospective study	549	Patients presenting to ED with a completed blood count collected	ED	>40 (1 point)	NR	Sepsis diagnosis

NR = Not reported.

2.5 | Quality assessment

The quality of each full-text article was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool as recommended by the Cochrane Collaboration for the quality assessment of diagnostic studies.[41]

Data extraction and quality assessment were performed independently by two reviewers (AZ and KA), with any disagreements being settled through discussion or by consultation with a third team member (LL).

2.6 | Data synthesis

Data were synthesized through narrative synthesis and summary statistics. Data regarding study characteristics (country, study design, sample size, clinical context, setting) and participant characteristics (sex, age, comorbidities) were collected into tables, enabling comparison across studies. For papers with available data, 2 × 2 tables were used to compare qSOFA and qSOFA combined with CRP. The sensitivity, specificity, NPV, and positive PPV of the tests for mortality risk prediction and sepsis identification were calculated if not provided in the original papers, and the data was available. Study authors were contacted via email if relevant data were not available.[33,42,43] Only Kim et al.[42] provided additional data.

3 | RESULTS

3.1 | Search results

Database searching retrieved 594 studies, which were published from 2006 onwards. After duplicates were removed, 256 articles underwent title, abstract and keyword screening (Figure 1). Of the 27 studies included in full-text screening, four met the inclusion criteria and were included in the final analysis (Figure 1).[33,38,42,43]

3.2 | Characteristics of studies

The characteristics of included studies and patient populations are presented in Tables 1 and 2, respectively. The four included studies were published in 2017,[42] 2019,[43] 2020,[38] and 2021.[33] Two studies were set in the ED, one in the ED and inpatient wards, and one in the hospital's department of surgical diseases. All four studies had similar age and comorbidity distributions within their study population.[33,38,42,43] The studies varied in their CRP cut-off value, ranging from 40 mg/L[33] to 128.8 mg/L.[42] Three of the included studies investigated the accuracy of the combined score for predicting mortality risk, one in pneumonia patients,[42] one in sepsis patients,[43] and one in complicated intra-abdominal infection patients.[38] The last study[33] investigated the accuracy of the score for sepsis identification, defined using the Sepsis-3 definition.[3]

TABLE 2 Patient population characteristics.

	Dimitrov et al.[38]		Yu et al.[43]		Kim et al.[42]		Woo et al.[33]	
	Survivor (*n* = 58)	Nonsurvivor (*n* = 20)	Survivor (*n* = 1140)	Nonsurvivor (*n* = 178)	Survivor (*n* = 112)	Nonsurvivor (*n* = 13)	Sepsis diagnosis (*n* = 188)	Total (*n* = 549)
Age, years; mean ± SD	54.21 ± 18.29	73.25 ± 12.18	62 (47–74) (median, IQR)	71 (55 –81) (median, IQR)	67.2 ± 18.0	76.4 ± 9.5	63.4 ± 11.0	59.2 ± 13.3
Male; *n* (%)	33 (56.9)	10 (50)	708 (62.2)	118 (66.3)	70 (62.5)	8 (61.5)	110 (58.5)	302 (55)
Diabetes mellitus; *n* (%)	6 (10.3)	3 (15.0)	253 (22.2)	47 (26.4)	30 (26.8)	5 (38.5)	NR	NR
Hypertension; *n* (%)	20 (34.5)	10 (50.0)	NR	NR	46 (41.1)	9 (69.2)	NR	NR
Malignancy; *n* (%)	7 (12.1)	8 (40.0)	76 (6.7)	26 (14.6)	25 (22.3)	2 (15.4)	117 (62.2)	267 (48.6)
Chronic renal failure; *n* (%)	1 (1.7)	5 (25.0)	NR	NR	11 (9.8)	4 (30.8)	NR	NR
Chronic liver disease; *n* (%)	NR	NR	84 (6.4)	67 (5.9)	3 (2.7)	0	NR	NR

Abbreviation: NR, not reported.

TABLE 3 Combined sensitivity, specificity, PPV, NPV and AUROC for qSOFA and qSOFA + CRP.

Study	Test	Patient outcome	AUROC (95% CI)	Sensitivity	Specificity	PPV	NPV
Dimitrov et al.[38]	qSOFA	In-hospital mortality	0.746 (0.603–0.889)	0.350	0.983	0.875	0.814
	qSOFA+CRP		0.818 (0.704–0.932)	0.600	0.914	0.706	0.869
			+0.072 (+9.7%)[a]	**+0.25 (+71.4%)**	**−0.069 (−7.0%)**	**−0.169 (−19.3%)**	**+0.055 (+6.8%)**
Yu et al.[43]	qSOFA	In-hospital mortality	0.670 (0.620–0.710)	NR	NR	NR	NR
	qSOFA+CRP		0.690 (0.640–0.730)	NR	NR	NR	NR
			+0.02 (+3.0%)				
Kim et al.[42]	qSOFA	28-day mortality	0.810 (0.730–0.87)	0.538[b]	0.892[b]	0.368[b]	0.943[b]
	qSOFA+CRP		0.870 (0.790–0.920)	0.769[b]	0.785[b]	0.294[b]	0.967[b]
			+0.06 (+7.4%)	**+0.231 (+42.9%)**	**−0.107 (−12.0%)**	**−0.074 (−20.1%)**	**+0.024 (+2.5%)**
Woo et al.[33]	qSOFA	Sepsis diagnosis	0.670 (0.620–0.720)	NR	NR	NR	NR
	qSOFA+CRP		0.770 (0.730–0.810)	NR	NR	NR	NR
			+0.1 (14.9%)[a]				

Note: Highlighted rows indicate changes (%) from qSOFA to qSOFA+CRP.

Abbreviations: AUROC, area under receiving operating characteristics curve; CRP, C-reactive protein; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; qSOFA, quick sequential (sepsis-related) organ failure assessment.

[a]Studies reported a statistically significant change in AUROC.

[b]Supplemental data supplied by study authors via email.

3.3 | Predicting mortality risk and identifying sepsis

The AUROC values were extracted from each paper as illustrated in Table 3.[33,38,42,43] Across all studies there was a universal increase in AUROC values with the addition of CRP to qSOFA.[33,38,42,43]

The sensitivity, specificity, PPV, and NPV for mortality prediction of qSOFA combined with CRP and qSOFA alone were calculated for two studies, Dimitrov et al.[38] and Kim et al.[42] (see Appendix), and presented in Table 3. With the addition of CRP the sensitivity of qSOFA for mortality, prediction increased by 71.4%[38] and 42.9%,[42] respectively. Conversely, the specificity of qSOFA for mortality prediction decreased with the addition of CRP by 7.0%[38] and 12.0%.[42] The PPV for mortality prediction using qSOFA combined with CRP decreased by 19.3%[38] and 20.1%,[42] respectively. Whereas adding CRP to qSOFA increased the NPV for mortality prediction by 6.8%[38] and 2.6%.[42]

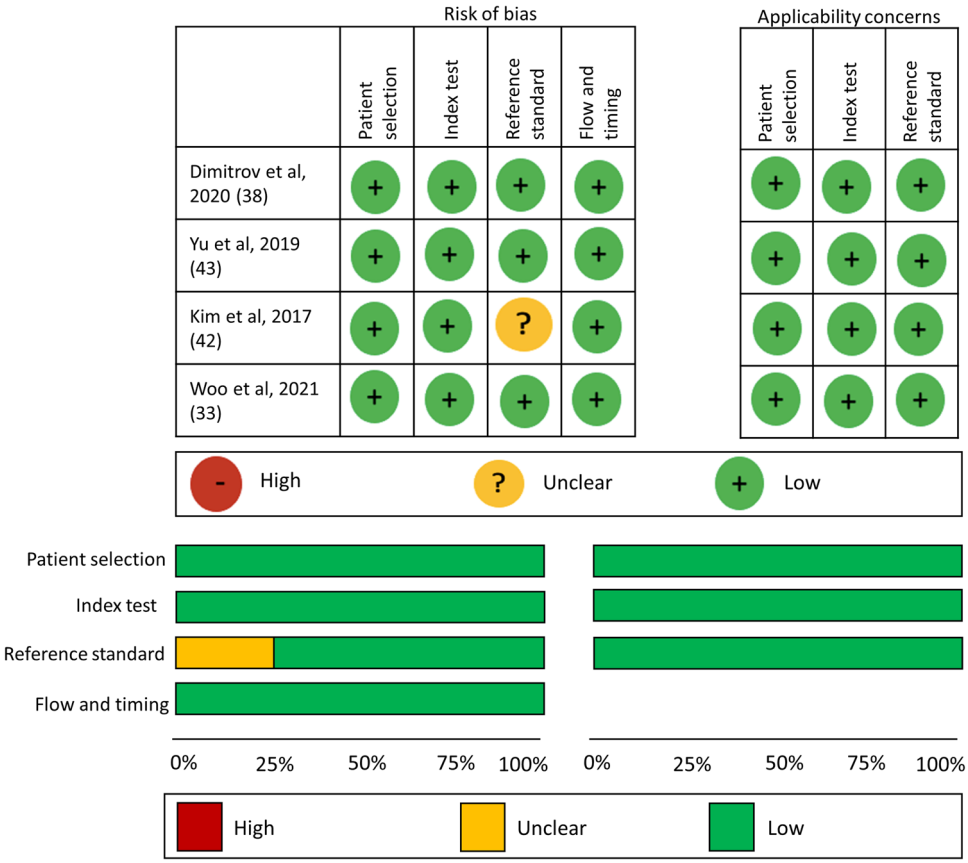

FIGURE 2 Quality assessment of diagnostic accuracy studies-2 risk of bias summary of assessment.

3.4 | Risk of bias results

Applying QUADAS-2[41] to the four studies found no concerns regarding risk of bias or applicability for any paper, with only one unclear point in regard to the reference standard used for Kim et al.[42] (Figure 2).

4 | DISCUSSION

This comprehensive review demonstrated the improved accuracy of qSOFA for mortality prediction and sepsis identification when combined with CRP, as shown by the global improvement in AUROC values (Table 3). Notably, adding CRP to the qSOFA tool increased the sensitivity and NPV for mortality prediction in the two studies with available data.[38,42] As sepsis, as well as other infections, are highly-fatal and time-critical conditions, having a higher sensitivity results in a greater likelihood of identifying patients earlier in the disease course, and consequently, offers improved chances of better outcomes.[44]

Our findings present an opportunity for improved early detection of sepsis patients in low-resource and emergency settings. Research has shown the need for such a tool as countries with a low to middle SDI carry the majority of sepsis incidence and mortality globally.[2,37,45] Earlier recognition of such patients can improve time to antibiotics initiation, and hence could improve patient outcomes.[27,28,44] As qSOFA is a fast, easy and inexpensive tool to use, it is ideal for identifying sepsis and predicting mortality risk in high patient flow settings where rapid, cost-effective, and sensitive assessments are essential.[3,43,46] CRP is inexpensive, simple, and widely available in clinical settings, with measurements taken via venous collection and results returned rapidly.[26,27,29,30,47] It is also one of the earliest biomarkers to rise in response to infection, and thus is well-placed to be implemented in a clinical environment where patients are initially presenting.[24,30] Furthermore, the recent review by Plebani[30] has demonstrated the broad applicability of CRP as a sensitive systemic marker of inflammation and tissue damage across a diverse range of conditions, including COVID-19. Therefore, the combined qSOFA and CRP score offers a low-cost and widely accessible tool ideal for sepsis early identification in the emergency setting and is a valuable area for future research.[26,27,30]

The studies included in this systematic review implemented a wide spectrum of CRP cut-off values, ranging from 40 mg/L to 128.8 mg/L.[33,38,42,43] The CRP threshold used during testing influences the reported score accuracy, and therefore future CRP tests should use an appropriate and consistent cut-off to improve validity and reliability between studies. Previous studies have indicated the optimal CRP cut-off value for sepsis identification in adults is

61–84 mg/L.[19,24] However, this value can be influenced heavily by age.[48–50] Additionally, studies included in this review involved patients with community-acquired pneumonia, complicated abdominal infections, and a range of comorbidities which may affect the reliability of CRP cut-off values.[33,38,42,43] As infections impact a diverse range of patients with varying and often complex medical histories, future research should investigate whether age, comorbidities, and common concurrent conditions impact CRP cut-off values for the prediction of mortality and identification of sepsis.

A strength of this review was the systematic and comprehensive literature search performed using a robust search strategy that included multiple databases, grey literature and hand searching. Thereby, obtaining the best likelihood that all relevant papers were included. The quality of evidence reported in the four included studies was of an acceptable standard with a low risk of bias and low concerns regarding the applicability, as evaluated using the QUADAS-2 tool.[41] This review is limited by its restriction to only papers written in English or with an English translation readily available due to time and financial constraints. Additionally, a valid meta-analysis could not be performed for two primary reasons. Firstly, there was not enough data to calculate standardized effect sizes. Study authors were contacted via email to seek additional information, however, only one replied and supplied additional data.[42] Secondly, the limited number of studies included ($n = 4$) displayed substantial heterogeneity in the clinical setting, CRP cut-off values, and included patient populations.

5 | CONCLUSION

Infection remains a global challenge, with the best outcomes yielded from rapidly identifying and predicting the mortality risk of patients. This is especially pertinent in low-resource settings, which often have a high infection and sepsis burden. Our comprehensive review demonstrates that the addition of CRP to qSOFA confers improved performance for identifying sepsis patients and for predicting mortality risk, compared to qSOFA alone. Critically, the addition of CRP to qSOFA improved the sensitivity of qSOFA for mortality prediction. Further research into the combined CRP and qSOFA score is encouraged to confirm these promising preliminary findings, with a focus on determining the optimal cut-off level for CRP and investigating the performance of CRP combined with qSOFA in larger patient cohorts.

AUTHOR CONTRIBUTIONS

Alexandra Zacharakis: Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing—original draft; writing—review & editing. **Khalia Ackermann**: Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing—review & editing. **Clifford Hughes**: Conceptualization; writing—review & editing. **Vincent Lam**: Conceptualization; writing—review & editing. **Ling Li**: Conceptualization; methodology; project administration; supervision; validation; writing—review & editing.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data are relevant to the study are included in the article or uploaded as supplementary information. The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Not applicable. Ethics approval is not required as this is a systematic review and used data already published.

TRANSPARENCY STATEMENT

The lead author Ling Li affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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