

# Prognostic value of combining c-reactive protein and quick sequential organ failure assessment for adult inpatients: A systematic review

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## Research

**Keywords:** qSOFA, PubMed, MEDLINE, EMBASE, Scopus, Web of Science, Science Direct, CINAHL, Open Grey, Grey Literature Report

**Posted Date:** October 21st, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-968626/v1>

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# Abstract

## Objective

To examine the prognostic performance of combining the biomarker c-reactive protein (CRP) with the quick sequential organ failure assessment (qSOFA) bedside tool on mortality prediction in adult inpatients.

## Methods

We searched PubMed, MEDLINE, EMBASE, Scopus, Web of Science, Science Direct, CINAHL, Open Grey, Grey Literature Report, and the Clinical Trials registry. Title, abstract, and full text screening were performed by two independent reviewers using pre-determined eligibility criteria. The eligibility criteria were (i) original research, (ii) adult populations, (iii) a comparison between qSOFA and qSOFA combined with CRP, and (iv) set in a hospital environment. The same two reviewers independently extracted data into a pre-designed form and performed a risk of bias assessment using the Quality Assessment tool for Diagnostic Accuracy Studies version 2 (QUADAS-2). Disagreements were settled through discussion and a third reviewer was consulted if necessary. Our primary outcome is mortality.

## Results

Three retrospective studies with a total of 1521 patients were included in the review. Adding CRP to qSOFA improved the Area Under the Receiver Operating Characteristic Curve (AUROC) value in all three studies by 3-10%. In the two studies with available data, the addition of CRP improved the sensitivity of qSOFA for mortality risk stratification by 43% and 71%, while decreasing the specificity by 12% and 7% respectively. The cut-off values of CRP ranged from 60 to 128.8mg/L across the three studies. A meta-analysis was not performed due to the heterogeneity across studies and the small sample size.

## Conclusions

This comprehensive review provides initial evidence that combining CRP with qSOFA could improve the prognostic performance of qSOFA alone in identifying patients at risk of dying in hospital. The combined tool demonstrates potential to improve patient outcomes, especially in low resource settings. The review also reveals research gaps in this area.

## Registration

PROSPERO registration No. CRD42020190973

# Introduction

Sepsis is a leading cause of mortality, with global estimates attributing 11 million deaths to sepsis in 2017 alone.[1] The most recent definition of sepsis, published in 2016, is “life threatening organ dysfunction caused by a dysregulated host response to infection”.[2] Patients who do not receive prompt identification and management rapidly deteriorate, contributing to the high mortality rate.[2, 3] Thus, identifying septic patients and initiating evidence based bundle care is paramount to improving sepsis outcomes.[1] However, despite numerous efforts to develop effective diagnostic tools, rapid sepsis identification remains a global challenge.[4]

In 2016, the quick sepsis-related organ failure assessment (qSOFA) was introduced as a simple bedside scoring system aimed to identify patients at higher risk of poor sepsis related outcomes.[2] qSOFA implements 3 clinical components: altered mentation determined via a Glasgow Coma Scale (GCS) less than 15, a respiratory rate of 22 breaths per minute or greater, and a systolic blood pressure of 100mmHg or less.[2] A score of 2 or more indicates a patient is more likely to experience poor outcomes typical of sepsis, such as ICU admission or death.[2] Since its integration into clinical care, the poor sensitivity of qSOFA for mortality prediction and risk stratification of sepsis has raised concerns.[5, 6]

C-reactive protein (CRP) has been shown to be highly sensitive for identifying sepsis.[7, 8] CRP is an acute phase reactant released by the liver in the early stages of inflammation and infection.[9–11] Circulating levels of CRP are impacted by a myriad of factors, including; age, sex, smoking status, weight, blood lipid levels, and blood pressure.[9] Critically, CRP is one of the first biomarkers to rise in response to infection.[9] Studies have shown CRP blood levels to rise six hours after stimulus, peaking at 48 hours, with a half-life of approximately 19 hours.[12] In addition, CRP is accessible and inexpensive.[10, 13] Studies in low resource settings, such as

Nepal[7] and rural Congo[14] have shown the merit of CRP in assisting clinicians to determine the severity of bacterial infections. Studies have also shown CRP point of care testing to be accessible and cost-effective in guiding antibiotic use in febrile patients. [15– 18] Therefore, including CRP in qSOFA may improve qSOFA's sensitivity and ability to accurately stratify a patient's mortality risk in both high and low resource settings.

The current evidence evaluating the performance of qSOFA combined with CRP is limited. Preliminary searches suggest a combined approach of qSOFA and CRP yields improved performance when compared to qSOFA alone.[19] However, study populations have been small and constrained to specific patient conditions.[19] Moreover, there has been no systematic approach appraising the literature, and therefore, a systematic review analysing the benefit of qSOFA combined with CRP is warranted. This paper aimed to systematically evaluate the prognostic value of CRP combined with qSOFA, compared to qSOFA alone, in predicting mortality among adult hospital patients.

## Methods

### 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.[20] The study protocol was developed and registered with PROSPERO (Registration No. CRD42020190973).

#### Literature search and study selection

A comprehensive electronic search of eight databases (Figure 1), including PubMed, Embase, MEDLINE, Scopus, CINAHL, Web of Science, Science Direct, Clinical Trials Registry, Open Grey and the Grey Literature Report was performed (see Appendix for the search strategies). Reference lists were also hand searched for any additional relevant studies.

No restrictions were placed on publication date, allowing complete coverage of included databases. Publications were restricted to original research. The search was completed on the 8th of August 2020. Following deduplication of the search results, two review authors (AZ, KA) independently performed title, abstract and keyword screening, whereby pre-decided eligibility criteria (see next section) were applied to all results.

References that were relevant to the topic after title, abstract and key word screening had full text articles retrieved. Subsequently, they 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) to reach consensus.

### Eligibility criteria

Studies had to meet all of the inclusion criteria and none of the exclusion criteria to be included in this review. The inclusion criteria were: (i) study population aged  $\geq 18$  years or adult patients as defined in the papers, (ii) a comparison between qSOFA (reference test) to qSOFA combined with CRP (index test), (iii) study set in a hospital environment, (iv) original research performed regardless of study design, and (v) published in English or with a readily available English translation. We accepted any combination of CRP and qSOFA used by the study authors. We defined hospital setting as either emergency department, intensive care unit or ward environment. We only accepted papers in English or with English translations readily available due to time and resource constraints.

The exclusion criteria were: (i) study population younger than 18 years old and (ii) papers based on opinions or expert views. The study population was confined to patients 18 years or older, as paediatric and neonatal populations have unique responses to sepsis at the cellular, organ, and whole organism level.[21]

### Outcomes

Our primary outcome is the accuracy of patient mortality risk stratification.

### Data extraction

All relevant study characteristics and design information were extracted into a pre-designed excel template, which included: country of study, study design, sample size, clinical context of study, setting of study, and study population demographics (sex, age,

comorbidities). Similarly, all relevant outcome information were extracted, where possible, into a pre-designed Excel template, which included: overall mortality rates, 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)). Data extraction was performed independently by two reviewers (AZ, KA), with any disagreements being settled through discussion or by consultation with a third team member (LL). For any missing data, the relevant author was contacted via email, and in one case this was successful.[22]

## Quality assessment

Two authors (AZ, KA) independently assessed the quality of each full text article via the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, which is recommended by the Cochrane Collaboration for the quality assessment of diagnostic studies. [23] Any disagreements were resolved by discussion and consultation with a third reviewer (LL). The QUADAS-2 tool consists of four domains, including: patient selection, index test, reference standard, and flow and timing.[23] It aims to assist systematic review authors to rate the risk of bias and applicability in studies investigating diagnostic test accuracy. Each domain has a grade of low, high or unclear for its risk of bias and its concerns regarding applicability.

## Data synthesis

Data synthesis was limited to narrative synthesis and summary statistics. Data regarding study characteristics (country of study, study design, sample size, clinical context of study, setting of study) and participant characteristics (sex, age, comorbidities) were synthesised into tables, which enabled comparison across the studies. For papers with available data, 2x2 tables comparing the number of patients with qSOFA  $\geq 2$ , qSOFA  $< 2$ , qSOFA+CRP  $\geq 2$ , and qSOFA+CRP  $< 2$  in survivors and non-survivors was designed. The sensitivity, specificity, negative predictive value and positive predictive value of the test for mortality risk prediction were calculated if not provided in the original papers. For papers with data not available to complete the table, Yu et al[24] and Kim et al[22], study authors were contacted via email. Kim et al[22] provided the requested raw data for us. To create the appropriate 2x2 tables from this raw data, we defined qSOFA combined with CRP as a four-point scoring system with one point attributed for: altered mental status, increased respiratory rate, decreased systolic blood pressure, and elevated CRP.

## Results

### Search results

Database searching retrieved 179 studies. After duplicates were removed, 83 articles underwent title, abstract and keyword screening (Figure 1). The full texts of 17 studies were screened, and subsequently, three papers met the inclusion criteria and were included in the final analysis.[19, 22, 24] Reasons for exclusion at this stage were recorded (Figure 1).

### Characteristics of studies

The characteristics of included studies and the characteristics of survivors and non-survivors are presented in Tables 1 and 2 respectively. Evaluating qSOFA combined with CRP was the primary aim for only one study.[19] The remaining two studies included qSOFA combined with CRP as a secondary aim.[22, 24] All studies were retrospective cohort studies with two performed at single centres, and one conducted across three hospital sites (Table 1).[19, 22, 24] Studies varied in their CRP cut off value. Yu et al[24] had the lowest CRP cut off value ( $>60$  mg/L) and Kim et al[22] had the greatest CRP cut off value ( $>128.8$  mg/L). All studies involved patients presenting to emergency departments with or without subsequent admission. Differences between survivors and non-survivors were apparent in age, presence of malignancy and presence of chronic renal failure (Table 2). However, all three studies had similar age and comorbidity distributions in their study populations, with diabetes and malignancy being present across all three studies.[19, 22, 24]

Table 1  
Characteristics of included studies

Study	Country	Study design	Number of participants	Clinical context	Setting	CRP cut off for qSOFA+CRP score (mg/L) (point)	Cut off score for qSOFA+CRP	Patient outcome
<b>Dimitrov et al (2019)</b> [19]	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
<b>Yu et al (2019)</b> [24]	China and Taiwan	Retrospective multi-centre cohort study	1318	Patients presenting to ED or who were admitted to hospital with symptoms that indicated systemic infection	3 hospitals	60-120 (1 point); >120 (2 points)	≥2	In-hospital mortality
<b>Kim et al (2017)</b> [22]	Korea	Retrospective chart review	125	Patients admitted to ED with discharge diagnosis of community acquired pneumonia	Hospital	>128.8 (1 point)	≥2	28-day mortality

Table 2  
Survivor vs non-survivor patient characteristics

		Dimitrov et al (2019) [19]	Yu et al (2019) [24]	Kim et al (2017) [22]
Age, years; Mean ± SD	Survivors	54.21 ± 18.29	62 (47–74) (median, IQR)	67.2 ± 18.0
	Non-survivors	73.25 ± 12.18	71 (55–81) (median, IQR)	76.4 ± 9.5
Male; n (%)	Survivors	33 (76.7)	708 (62.2)	70 (62.5)
	Non-survivors	10 (50)	118 (66.3)	8 (61.5)
Diabetes mellitus; n (%)	Survivors	6 (10.3%)	253 (22.2)	30 (26.8)
	Non-survivors	3 (15.0)	118 (66.3)	8 (61.5)
Hypertension; n (%)	Survivors	20 (30.4)	NR	46 (41.1)
	Non-survivors	10 (50.0)	NR	9 (69.2)
Malignancy; n (%)	Survivors	7 (12.1)	76 (6.7)	25 (22.3)
	Non-survivors	8 (40.0)	26 (14.6)	2 (15.4)
Chronic renal failure; n (%)	Survivors	1 (1.7)	NR	11 (9.8)
	Non-survivors	5 (25.0)	NR	4 (30.8)
Chronic liver disease; n (%)	Survivors	NR	84 (6.4)	3 (2.7)
	Non-survivors	NR	67 (5.9)	0

NR = Not reported

## AUROC values

The AUROC values were able to be extracted from each paper without any data synthesis and are illustrated in Table 3.[19, 22, 24] Across all studies there is a universal increase in AUROC values with the addition of CRP to qSOFA.[19, 22, 24]

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

Study	Test	AUROC (95% CI)	Sensitivity	Specificity	PPV	NPV
Dimitrov et al (2019)[19]	qSOFA	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
Yu et al (2019)[24]	qSOFA	0.670 (0.620 - 0.710)	NR	NR	NR	NR
	qSOFA+CRP	0.690 (0.640 - 0.730)	NR	NR	NR	NR
Kim et al (2017)[22]	qSOFA	0.810 (0.730 - 0.87)	0.538*	0.892*	0.368*	0.943*
	qSOFA+CRP	0.870 (0.790 - 0.920)	0.769*	0.785*	0.294*	0.967*

NR = not reported; \* Supplemental data supplied by study authors via email.

## Sensitivity and specificity: mortality prediction

Using 2x2 tables (see Appendix), it was possible to determine the sensitivity and specificity for two studies, Dimitrov et al[19] and Kim et al[22], with the results shown in Table 3. The sensitivity of qSOFA was poor across both studies at 0.350 and 0.538, respectively. However, with the addition of CRP scoring, the sensitivity increased in both studies to 0.600 and 0.769.[19, 22] This indicates addition of CRP to qSOFA increased sensitivity by 71.43% and 42.94%.[19, 22] Conversely, the addition of CRP scoring decreased the specificity compared to qSOFA alone. Using qSOFA alone the specificity was 0.983 and 0.892 in Dimitrov et al[19] and Kim et al[22] respectively. When using qSOFA combined with CRP the specificity decreased to 0.914 and 0.785.[19, 22] This indicates the addition

of CRP to qSOFA decreased the specificity by 7.02% and 12.00%.[19, 22] Ultimately, increasing the sensitivity of qSOFA through the addition of a CRP score, resulted in a subsequent decrease in specificity.

## **Negative predictive value and positive predictive value: mortality prediction**

Similarly, the 2x2 tables were used to calculate the positive predictive value (PPV) and negative predictive value (NPV) for both qSOFA alone and qSOFA combined with CRP, with results illustrated in Table 3. The PPV for qSOFA was 0.875 and 0.368 in studies conducted by Dimitrov et al[19] and Kim et al[22], respectively. The PPV for qSOFA combined with CRP was 0.706 and 0.294.[19, 22] This indicates the addition of CRP to qSOFA decreased PPV by 19.31% and 20.11%.[19, 22] The NPV for qSOFA was 0.814 and 0.943 across the two studies, Dimitrov et al[19] and Kim et al[22]. Conversely, the NPV for qSOFA combined with CRP was 0.869 and 0.967, respectively.[19, 22] This indicates addition of CRP to qSOFA resulted in an increase in NPV by 6.76% and 2.55%.[19, 22]

## **Risk of Bias results**

Upon assessment of QUADAS-2, there were no concerns regarding risk of bias or applicability for any paper, with only one unclear point in regards to the reference standard used for Kim et al[22] (Figure 2).[23]

## **Discussion**

Sepsis remains a global challenge, with an estimated 50 million people suffering from sepsis worldwide in 2017 alone.[1] This comprehensive review presents evidence demonstrating that a combined qSOFA and CRP score improved the prognostic performance of qSOFA alone for mortality prediction, which has previously been shown to be suboptimal.[25] In all three included studies, the addition of a CRP score resulted in improved AUROC values for mortality prediction compared to qSOFA alone.[19, 22, 24] Furthermore, in the two studies with available data, adding CRP to the qSOFA tool increased the sensitivity and NPV compared to qSOFA.[19, 22] In contrast, the addition of CRP to qSOFA resulted in a reduced specificity and PPV for mortality prediction.[19, 22] This is expected as sensitivity and specificity are inversely related, and therefore an increase in a test's sensitivity will cause a decrease in its specificity.[26] As sepsis is a highly-fatal and time-critical condition having a higher sensitivity results in a greater likelihood of identifying septic patients earlier in the disease course, and consequently, offers improved chances of better outcomes.[27] Therefore, it is acceptable to have a lower specificity in favour of a higher sensitivity for the early identification of sepsis.

Our findings present an opportunity for improved early detection of patients with a higher risk of poor outcomes from sepsis, especially in the emergency setting. qSOFA combined with CRP is most suited to fast paced, high patient flow-through settings where the emphasis is on rapid and sensitive risk stratification assessments. Furthermore, as CRP is one of the earliest biomarkers to rise in response to infection, it is well placed to be implemented in a clinical environment where patients are initially presenting.[12] Use of qSOFA combined with CRP is less beneficial in ward and intensive care environments as there is more time, patient history and resources to inform clinical decision making. Moreover, a CRP value is easily obtainable via venous collection and is a relatively inexpensive test with results obtainable quickly.[28] Due to its early rise in infection, ease of access, cost-effectiveness, and broad applicability, CRP is an ideal biomarker to combine with qSOFA for use in the emergency setting.

The patient populations of the included papers presented with a spectrum of conditions, including complicated abdominal infections, community acquired pneumonia, and symptoms suggesting systemic infection.[19, 22, 24] This reflects the variation in sepsis presentations and impacted patient populations. In addition, the patient populations in these studies had comorbidities widely present in the community including diabetes, hypertension, malignancy, and chronic renal and liver disease. Therefore, this review presents initial evidence showing qSOFA combined with CRP is useful in a spectrum of patient populations, including those with common comorbidities.

Implications of this novel research are particularly prominent for developing countries. Research has shown the need for a test to facilitate early septic patient detection in low resource settings, as they carry the majority of sepsis incidence and mortality globally.[1, 29] We defined low resource setting according to a recent systematic review that thematically approaches the term.[30] We applied the themes: financial pressure, geographical and environmental factors, to define low resource settings.[30] Importantly, CRP measurement can be achieved through inexpensive and rapid PoC testing, which can be performed at the bedside.[31, 32] Similarly, the qSOFA score components are simple and inexpensive bedside measurements.[33] Thus, the combined qSOFA and CRP score offers a low-cost prognostic and risk stratification tool that incorporates clinical and biochemical scores to improve the timely identification of patients with a high risk of sepsis-related poor outcomes.[15, 16] Earlier recognition of such patients can improve time to antibiotics initiation, and hence could improve mortality and morbidity rates of sepsis.[16, 17] Therefore, the combined qSOFA

and CRP score shows promise as a tool for early sepsis identification in low resource settings and is a valuable area for further research.

The studies included in this systematic review implemented a wide spectrum of CRP cut-off values, ranging from 60mg/L to 128.8mg/L.[19, 22, 24] One study included two cut-off values for the combined qSOFA and CRP score[24] and all three studies used similar CRP thresholds of 100-128.8mg/L. The CRP threshold chosen will influence the risk stratification of patients. Some previous studies have indicated that the optimal CRP cut-off value for sepsis identification in adults is 61 to 84mg/L.[7, 12] However, the optimal CRP threshold could be influenced heavily by age.[34–36] In addition, studies included in this review involved patients with community acquired pneumonia, complicated abdominal infections, and a range of comorbidities.[19, 22, 24] As sepsis impacts a diverse range of patients with varying and often complex medical histories, future research should investigate the role of age, comorbidities, and common concurrent conditions on the reliability of CRP cut-off values for the diagnosis of sepsis. Furthermore, future studies investigating CRP in combination with qSOFA should endeavour to use an evidence-based and consistent threshold as a cut off, to improve validity and reliability between studies.

Other biomarkers, such as procalcitonin (PCT), can be added to the combination of CRP and qSOFA to further increase the sensitivity or specificity of the score. Recent studies have shown merit of using a combination of PCT and CRP in diagnosing sepsis in both neonatal and adult populations.[37, 38] Further research should investigate the role of other biomarkers in combination with CRP and qSOFA.

The quality of evidence presented in this review is of an acceptable standard, evaluated using the QUADAS-2 tool.[23] All studies were recently published, using the most up to date definition of sepsis, sepsis-3.[2] A key methodological limitation across all studies is that it is unclear if the reference standard results, qSOFA, were interpreted without knowledge of results of the index test, qSOFA combined with CRP. However, as all studies were retrospective analyses, there is a low possibility for the introduction of bias, as the data has already been collated. Overall, as evidenced in the QUADAS-2 risk of bias assessment, the three studies included in this review were of low risk of bias with low concerns regarding applicability of studies.

A strength of this review is the systematic and comprehensive literature search with a robust search strategy that included multiple databases, grey literature and hand searching. Thereby, obtaining the best likelihood that all relevant papers were included. A limitation of this review is it was restricted to papers written in English or those with an English translation readily available. This was done 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 standardised effect sizes. Study authors were contacted via email to seek additional information, however, only one replied and supplied additional data.[22] Secondly, the limited number of studies included (n=3) displayed substantial heterogeneity in the clinical setting, CRP cut-off values and included patient populations.

## Conclusion

Sepsis remains a global challenge, with best outcomes yielded from rapid identification and risk stratification of septic patients. Our comprehensive review demonstrates that inclusion of CRP to qSOFA confers improved prognostic performance of identifying patients at risk of poor outcomes, compared to qSOFA alone. Critically, the addition of CRP to qSOFA improved the sensitivity of qSOFA. This review yields new evidence for an improved tool to identify the septic patient in both high and low resource settings. We have shown that the combination of qSOFA and CRP could be beneficial for an ED setting as it is a rapid PoC test and CRP is one of the earliest biomarkers to rise in sepsis patients. Further research into the combined CRP and qSOFA score is encouraged to confirm these promising preliminary findings, with a focus to investigate the performance of CRP combined with qSOFA in larger patient cohorts. This would contribute to determining the optimal cut-off level for CRP when combined with qSOFA, and the role of other biomarkers in combination with qSOFA.

## Declarations

### Ethics approval and consent to participate

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

### Consent for publication

Not applicable

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

### **Authors' contributions**

AZ planned the study objectives, designed, and executed the search across all databases, performed title, abstract, keyword, and full text screening, extracted data, performed risk of bias analysis, and drafted the final manuscript. KA performed title, abstract, keyword, and full text screening, extracted data, performed risk of bias analysis, and reviewed the manuscript. CH & VL assisted with project design and manuscript review. LL was responsible for overall project, study design, being consulted on issues during screening, extraction, and risk of bias, and manuscript review. All authors read and approved the final manuscript.

### **ACKNOWLEDGEMENTS**

The authors would like to thank our librarian, Ms Mary Simons, for her expertise in refining the search strategy and translating it for other databases.

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## Figures

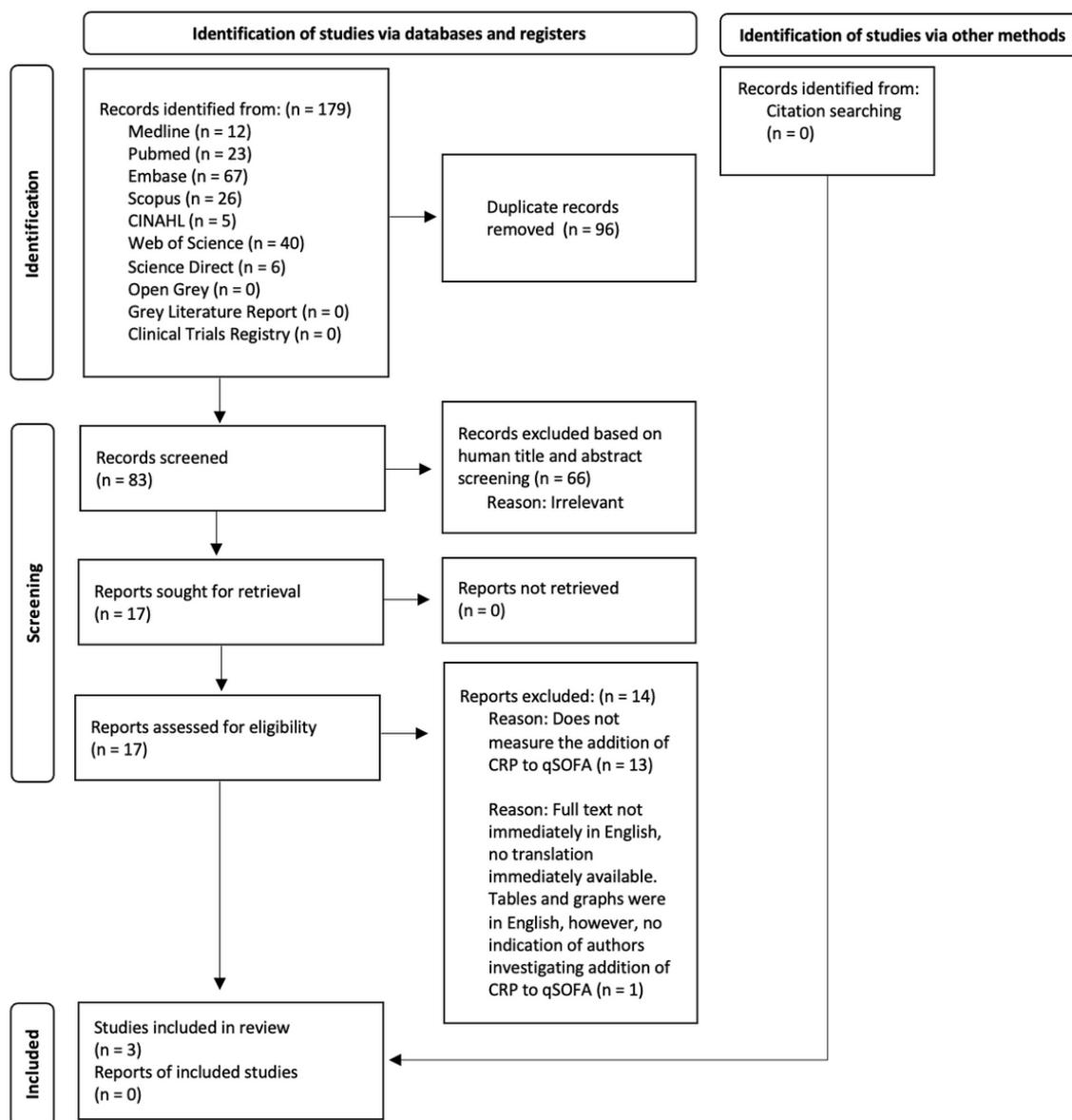


Figure 1

PRISMA flowchart



**Figure 2**

QUADAS-2 risk of bias summary of assessment

## Supplementary Files

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- [Appendix.docx](#)
- [PRISMAchecklist.docx](#)