Diagnostic test accuracy of procalcitonin and C-reactive protein for predicting invasive and serious bacterial infections in young febrile infants: a systematic review and meta-analysis

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Summary

Background Febrile infants presenting in the first 90 days of life are at higher risk of invasive and serious bacterial infections than older children. Modern clinical practice guidelines, mostly using procalcitonin as a diagnostic biomarker, can identify infants who are at low risk and therefore suitable for tailored management. C-reactive protein, by comparison, is widely available, but whether C-reactive protein and procalcitonin have similar diagnostic accuracy is unclear. We aimed to compare the test accuracy of procalcitonin and C-reactive protein in the prediction of invasive or serious bacterial infections in febrile infants.

Methods For this systematic review and meta-analysis, we searched MEDLINE, EMBASE, Web of Science, and The Cochrane Library for diagnostic test accuracy studies up to June 19, 2023, using MeSH terms "procalcitonin", and "bacterial infection" or "fever" and keywords "invasive bacterial infection*" and "serious bacterial infection*", without language or date restrictions. Studies were selected by independent authors against eligibility criteria. Eligible studies included participants aged 90 days or younger presenting to hospital with a fever (≥38°C) or history of fever within the preceding 48 h. The primary index test was procalcitonin, and the secondary index test was C-reactive protein. Test kits had to be commercially available, and test samples had to be collected upon presentation to hospital. Invasive bacterial infection was defined as the presence of a bacterial pathogen in blood or cerebrospinal fluid, as detected by culture or quantitative PCR; authors' definitions of serious bacterial infection were used. Data were extracted from selected studies, and the detection of invasive or serious bacterial infections was analysed with two models for each biomarker. Diagnostic accuracy was determined against internationally recognised cutoff values (0·5 ng/mL for procalcitonin, 20 mg/L for C-reactive protein) and pooled to calculate partial area under the curve (pAUC) values for each biomarker. Optimum cutoff values were identified for each biomarker. This study is registered with PROSPERO, CRD42022293284.

Findings Of 734 studies derived from the literature search, 14 studies (n=7755) were included in the meta-analysis. For the detection of invasive bacterial infections, pAUC values were greater for procalcitonin (0·72, 95% CI 0·56–0·79) than C-reactive protein (0·28, 0·17–0·61; p=0·016). Optimal cutoffs for detecting invasive bacterial infections were 0·49 ng/mL for procalcitonin and 13·12 mg/L for C-reactive protein. For the detection of serious bacterial infections, procalcitonin and C-reactive protein had similar pAUC values (0·55, 0·44–0·69 *vs* 0·54, 0·40–0·61; p=0·92). For serious bacterial infections, the optimal cutoffs for procalcitonin and C-reactive protein were 0·17 ng/mL and 16·18 mg/L, respectively. Heterogeneity was low for studies investigating the test accuracy of procalcitonin in detecting invasive bacterial infection (I^2=23·5%), high for studies investigating procalcitonin for serious bacterial infection (I^2=75·5%), and moderate for studies investigating C-reactive protein for invasive bacterial infection (I^2=49·5%) and serious bacterial infection (I^2=28·3%). The absence of a single definition of serious bacterial infection across studies was the greatest source of interstudy variability and potential bias.

Interpretation Within a large cohort of febrile infants, a procalcitonin cutoff of 0·5 ng/mL had a superior pAUC value to a C-reactive protein cutoff of 20 mg/L for identifying invasive bacterial infections. In settings without access to procalcitonin, C-reactive protein should therefore be used cautiously for the identification of invasive bacterial infections, and a cutoff value below 20 mg/L should be considered. C-reactive protein and procalcitonin showed similar test accuracy for the identification of serious bacterial infection with internationally recognised cutoff values. This might reflect the challenges involved in confirming serious bacterial infection and the absence of a universally accepted definition of serious bacterial infection.

Funding None.

Research in context

Evidence before this study

The evaluation of febrile infants younger than 90 days for invasive or serious bacterial infections is challenging. International practice is evolving from a treat-all approach towards safely identifying a lower-risk population who do not require as many invasive tests, parenteral antibiotics, or hospital admission. Biomarkers, namely procalcitonin and C-reactive protein, are used to aid decision making as part of a sequential assessment. The evidence thus far from observational studies suggests that procalcitonin outperforms C-reactive protein in this cohort.

Procalcitonin is not universally available, however, and whether C-reactive protein has the necessary diagnostic test accuracy to be substituted for procalcitonin in the sequential assessment of febrile infants remains unclear. This uncertainty is a barrier to the adoption of CPGs based on sequential assessment in settings in which procalcitonin is unavailable.

The only previous systematic review and meta-analysis reporting the test accuracy of procalcitonin was published in 2014 and included 2317 infants from seven studies. In that review, the authors reported that procalcitonin at a concentration of more than 0·3 ng/mL was associated with a relative risk for serious bacterial infection of 3·97 (95% CI 3·41–4·62). No comparison was made with C-reactive protein, data were limited to serious bacterial infection only, and the authors did not report sensitivity, specificity, or area under the curve values. These considerations, in combination with an increased number of relevant publications since 2014, warrant an updated systematic review and meta-analysis of biomarker accuracy.

Added value of this study

This study represents the only systematic review and meta-analysis to directly compare the diagnostic test accuracy of procalcitonin and C-reactive protein in febrile infants younger than 90 days presenting to emergency care. The results show that, among 7755 febrile infants presenting in the first 90 days of life, procalcitonin has superior test accuracy characteristics to C-reactive protein when compared at the internationally used cutoffs for identifying invasive bacterial infection. The optimum cutoff value for procalcitonin is approximately 0·5 ng/mL and the optimum cutoff value for C-reactive protein is approximately 15 mg/L.

Implications of all the available evidence

Several clinical practice guidelines recommend use of procalcitonin in the sequential assessment of febrile infants presenting to emergency care. In settings without procalcitonin testing, there is concern that C-reactive protein lacks the necessary diagnostic test accuracy to be used instead of procalcitonin. The findings from this systematic review and meta-analysis indicate that procalcitonin has a significantly better diagnostic test accuracy for the identification of invasive bacterial infection in febrile infants than C-reactive protein. Considering the importance and risk associated with missing invasive bacterial infection in febrile infants, these findings suggest that, without access to procalcitonin, C-reactive protein should be used cautiously in this population. When C-reactive protein is the only available biomarker, a lower cutoff value of (15 mg/L) should be considered rather than the 20 mg/L cutoff currently recommended.

Introduction

Young febrile infants, defined as infants aged 90 days or younger with a fever of 38°C or higher, are at increased risk of invasive bacterial infection (ie, bacterial meningitis or bacteriaemia) than older children. Studies from the UK, Europe, and the USA have consistently reported rates of 1–3% among cohorts of febrile infants attending emergency care.[1–3] Younger infants have a less developed immune system than older children, are typically undervaccinated, and have subtle clinical features when unwell.[4] About 15% of febrile infants acquire other serious bacterial infections, mainly urinary tract infections (UTIs), which (together with invasive bacterial infections) must be identified promptly.[1–3,5] Combined, the high risk of invasive bacterial infection, challenging nature of clinical assessment, and poor outcomes associated with sepsis and meningitis have resulted in a necessarily cautious approach to assessing and managing young febrile infants.

Traditionally, all young febrile infants were assumed to have invasive bacterial infection until proven otherwise. Their assessment would typically include clinical examination, blood testing, urinalysis, and lumbar puncture, and their treatment would be parenteral antibiotics.[6,7] However, the epidemiology of bacterial infections in febrile infants has changed, owing to improved vaccination schedules, perinatal care, and safer food hygiene standards. Consequently, the prevalence of invasive and serious bacterial infection and the risks posed by causative pathogens have changed in the past few decades.[8,9] A conservative approach is still advocated in several countries including the UK, where the National Institute for Health and Care Excellence advises a low threshold for parenteral antibiotics.[10] 90% of febrile infants in the UK are admitted to hospital for a median of 2 days, and more than 80% receive parenteral antibiotics.[1] Among patients hospitalised with fever, young febrile infants use more clinical resources than any other age group (£1000·28 per child).[11]

Internationally, however, approaches vary, and national clinical practice guidelines (CPGs) are increasingly advocating for the sequential assessment of febrile infants (figure 1). Sequential assessment aims to identify low-risk infants for whom community management without parenteral antibiotics is suitable. Typically,

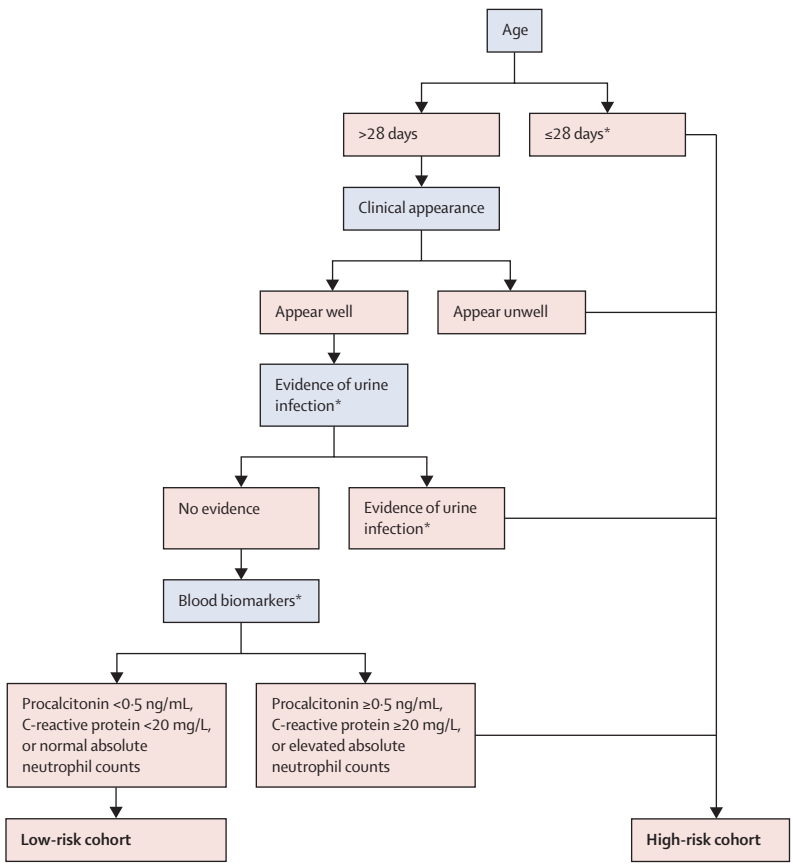


Figure 1: **Summary of the sequential approach used by CPGs**
CPGs include the Step by Step model, the PECARN rule, and the American Academy of Pediatrics guidance for the assessment of a febrile infant younger than 90 days. CPGs=clinical practice guidelines. *Threshold varies between CPGs.[2,3,5]

sequential assessment considers the infant's age, clinical appearance, urinalysis, and blood biomarkers to determine risk of bacterial infection (figure 1). This approach has several potential advantages, including reduced admission rates and treatment costs and strengthened antimicrobial stewardship. The three most widely recognised CPGs, the European Step-by-Step CPG, the Paediatric Emergency Care Applied Research Network (PECARN) CPG, and the American Academy of Pediatrics (AAP) CPG,[2,3,5] all advise procalcitonin testing, although the AAP guidance does allow for the use of either procalcitonin or C-reactive protein.

Procalcitonin is a peptide prehormone secreted by C-cells in the thyroid gland and by neuroendocrine cells in the lungs. Ordinarily, procalcitonin maintains calcium-phosphate homoeostasis,[12,13] but it also acts as an acute phase reactant to inflammation in a variety of tissues. C-reactive protein is another acute phase reactant that is synthesised and released from the liver in response to inflammation. Procalcitonin is released within 4 h of exposure to endotoxins, peaking at 8 h and remaining elevated for 24 h,[14] whereas C-reactive protein is released within 10 h of an inflammatory signal, peaking around 36 h later.[13] These differences in kinetics are often cited when arguing in favour of procalcitonin testing over C-reactive protein. However, procalcitonin tests are not accessible in all settings. Whether C-reactive protein has the necessary diagnostic test accuracy to be used in such settings remains unclear. Comparative data are needed to overcome concerns with test kinetics before CPGs can advise C-reactive protein-based sequential assessment in settings that do not have access to procalcitonin testing.

The most rigorous assessment of procalcitonin test accuracy to date is a 2014 systematic review and meta-analysis of seven studies (2317 patients), which reported procalcitonin test accuracy for serious bacterial infection in febrile infants younger than 3 months.[15] However, this review did not include a comparison with C-reactive protein, did not account for a variety of cutoff values, and did not use invasive bacterial infection as the reference standard.[15] These considerations, combined with an increased number of relevant reports since 2014, warrant an updated systematic review and meta-analysis.

The objective of this systematic review and meta-analysis was to determine the diagnostic test accuracies and optimum cutoff values of procalcitonin and C-reactive protein for detecting invasive bacterial infection and serious bacterial infection in young febrile infants no older than 90 days.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis adhered to PRISMA-DTA standards, and the study protocol has been published.[16,17] Eligible studies included participants aged 90 days or younger presenting to a hospital with fever (38°C or higher) or history of fever within 48 h of presentation. Studies conducted exclusively in neonatal units were excluded. The primary index test was procalcitonin, and the secondary index test was C-reactive protein. Both tests had to be commercially available laboratory or point-of-care tests, that used serum or plasma samples, and were sampled on presentation to hospital. The reference standard, invasive bacterial infection, was defined as the presence of a bacterial pathogen in blood or cerebrospinal fluid (CSF), detected either by culture or by quantitative PCR (qPCR). Clinical diagnosis of sepsis or invasive bacterial infection without isolation of pathogen was deemed an inacceptable definition of invasive bacterial infection. The secondary reference standard, serious bacterial infection, is often defined as the presence of a bacterial pathogen in urine, blood, or CSF, detected by culture or qPCR. However, many studies have taken a broader definition and included other localised bacterial infections such as gastroenteritis or pneumonia; we therefore accepted the authors' definitions of serious

bacterial infection. Studies examining procalcitonin testing alongside other biomarkers were included if procalcitonin performance data could be extracted. Similarly, studies of procalcitonin testing for infants older than 90 days were included if data relevant to younger infants could be extracted. No language or publication date restrictions were applied.

We searched MEDLINE, EMBASE, Web of Science, and The Cochrane Library in collaboration with a specialist librarian on March 7, 2022. The key MeSH terms "procalcitonin", and "bacterial infection" or "fever" were used, and terms were exploded when available. The keywords "invasive bacterial infection*" and "serious bacterial infection*" were added to the search to find additional studies. The relevant age group was achieved with limits in the MEDLINE and EMBASE databases and with keywords in in all other databases. Clinical trial registries were searched to identify further literature including clinical trial protocols, conference abstracts, and unpublished data. An identical search was rerun on June 19, 2023, to update the search results. Database search examples are available in the appendix (p 1).

Screening was conducted by three authors independently (HN-B, CM, and EU) using the Rayyan online management programme.[18] Following initial screening of titles and abstracts, and removal of duplicates, those studies meeting eligibility criteria underwent full-text reviews by at least two authors (HN-B, CM, or EU), with any discrepancies resolved by a fourth author (TW). All studies were examined for duplicate cohorts before confirming the final list of studies for meta-analysis.

A minimum of two authors (HN-B, CM, or DMC) independently extracted data from each of the selected studies with a standardised data extraction tool that had been piloted by two authors (CM and HN-B). Modifications were agreed on and shared with the other authors, and a third author (EU or TW) resolved discrepancies in data extraction. The data extraction tool included an assessment of each study according to STARD criteria,[19] a checklist of 30 essential reporting items for diagnostic accuracy studies. If a publication did not offer sufficient data for our meta-analysis, the respective corresponding author was contacted by email (up to three times over a 3-month period) and invited to submit the necessary data. Studies with insufficient data were excluded. As per protocol,[17] interstudy variables were defined to categorise studies by inclusion criteria: premature infants younger than 36 weeks' gestation; infants with a fever without apparent source; infants who were previously well; and infants who presented appearing unwell.

A modified quality assessment of diagnostic accuracy studies (QUADAS-2) tool[20] was used to independently assess all included studies for applicability to the review question and risk of bias by at least two authors (HN-B, CM, EU, or DMcC).

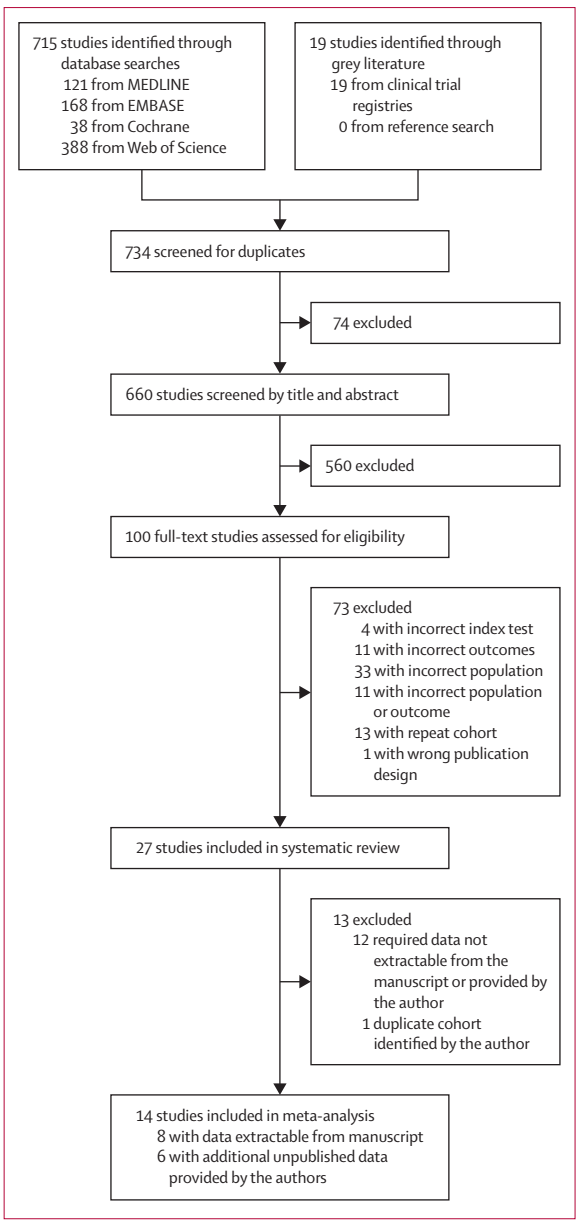


Figure 2: **Study selection**

See **Online** for appendix

Data analysis

Extracted data were used to create multiple 2×2 tables to calculate pooled sensitivity, specificity, and 95% CIs of procalcitonin and C-reactive protein for identifying invasive bacterial infection. This process was repeated for the detection of serious bacterial infection.

Cutoff values of 0·5 ng/mL for procalcitonin and 20 mg/L for C-reactive protein were compared to reflect the key international guidance in Europe and the USA and the literature.[2,5] For the purposes of this study, these cutoff values are referred to as the primary cutoff values. If diagnostic accuracy for alternative or additional cutoff values was given, the data were extracted at the respective

	Country	Prevalence of reference standard		Study patients (N)		Baseline interstudy variables according to inclusion criteria					Cutoff value of index tests			
		Invasive bacterial infection	Serious bacterial infection	With procalcitonin data	With C-reactive protein data	Age of participants	Preterm (<36 weeks of gestation)	FWAS	Previously well	Appear unwell	Procalcitonin 1, ng/mL	Procalcitonin 2, ng/mL	C-reactive protein 1, mg/L	C-reactive protein 2, mg/L
Díaz et al (2016)[4]	Spain	11 (3·5%)	..	318	318	0–90 days	No	Yes	Yes	Yes	0·5*	2	30	..
Gomez et al (2012)†[29]	Spain and Italy	23 (2·1%)	290 (26·0%)	1112	1110	0–90 days	Yes	Yes	No	No	0·5*	2	20*	40
Han et al (2019)[34]	Korea	..	68 (34·2%)	199	199	29–90 days	No	No	Yes	Yes	0·5*	1	20*	40
Lee et al (2018)[33]	Korea	..	38 (11·0%)	336	336	1–3 months	Yes	Yes	Unclear	Yes	0·5*	..	50	..
Maniaci et al (2008)‡[30]	USA	..	30 (12·8%)	234	0	0–90 days	Yes	Yes	Yes	Yes	0·13	..	..	..
Milcent et al (2016)[24]	France	21 (1·0%)	139 (6·8%)	2047	2037	7–91 days	Unclear	No	Yes	Yes	0·5*	0·3	20*	40
Park et al (2021)‡[25]	Korea	..	61 (19·2%)	317	0	0–90 days	Unclear	No	Unclear	Yes	0·3	..	20*	..
Waterfield et al (2018)†[35]	UK	4 (3·2%)	14 (11·1%)	126	121	0–90 days	Yes	No	No	Yes	0·5*	..	20*	..
Woelker et al (2012)‡[32]	USA	..	13 (8·4%)	155	0	2–60 days	Yes	No	No	Unclear	0·2	0·3	..	..
Gomez et al (2016)†[2]	Spain, Italy, and Switzerland	87 (3·9%)	515 (23·5%)	2185	2185	0–90 days	Yes	Yes	No	Yes	0·5*	2	20*	40
Markic et al (2015)†[28]	Croatia	4 (5·6%)	28 (39·4%)	71	71	0–180 days	No	Yes	Yes	Yes	0·5*	..	20*	40
Nijman et al (2014)†[27]	Netherlands	2 (2·6%)	15 (19·5%)	77	137	1 month to 16 years	Yes	No	Yes	Yes	0·5*	..	20*	..
Olaciregui et al (2009)[31]	Spain	..	82 (25·6%)	320	339	4–90 days	Yes	Yes	Yes	Yes	0·5*	..	20*	30
Sutiman et al (2022)†[26]	Singapore	9 (3·5%)	94 (36·5%)	258	258	0–90 days	No	No	Yes	Yes	0·5*	1·7	20*	..

Prevalence data are n (% of participants with procalcitonin data). FWAS=fever without apparent source. *Primary cutoff values in this study. †Included unpublished data. ‡Studied procalcitonin only.

Table 1: **Summary of the 14 studies included in the meta-analysis**

authors' given cutoff values (maximum two values per biomarker per study) and incorporated into the meta-analysis models. If data for more than two cutoff values were presented, the two values closest to the primary cutoff values were chosen.

Two statistical models, with functions in R software (version 4.2.2; packages mada_0·5.10, meta_5·5–0, dmetar_0·0.9000, and diagmeta_0·5–0), were used in combination for each analysis. The analysis was performed in duplicate by two experienced medical statisticians (HM and LM), and results were checked against each other for accuracy.

First, a bivariate model was applied with the primary cutoff values 0·5 ng/mL for procalcitonin and 20 mg/L for C-reactive protein to calculate the pooled sensitivity and specificity. This model uses an equivalent hierarchal summary receiver operating characteristic (ROC) curve to produce an area under the curve (AUC) value for each biomarker. To minimise comparison of AUC values corresponding to data from outside the available data range, a post-hoc decision was made to use partial AUC (pAUC) analysis. The pAUC is the calculation of the AUC within defined ranges of the false positive rate (FPR), which is covered by the data extracted. The difference between the pAUC for each biomarker was tested with a validated method in the bivariate model, and significance assessed with a p value.[21] This method uses bootstrapping and restricted maximum likelihood estimates to ensure interpretation is of patient-derived data. To compare the pAUC values of procalcitonin and C-reactive protein, a common range of FPR was used. The confidence intervals and the bootstrapping samples mirror the constricted FPR ranges used in each analysis. This model was also used for sensitivity analyses.

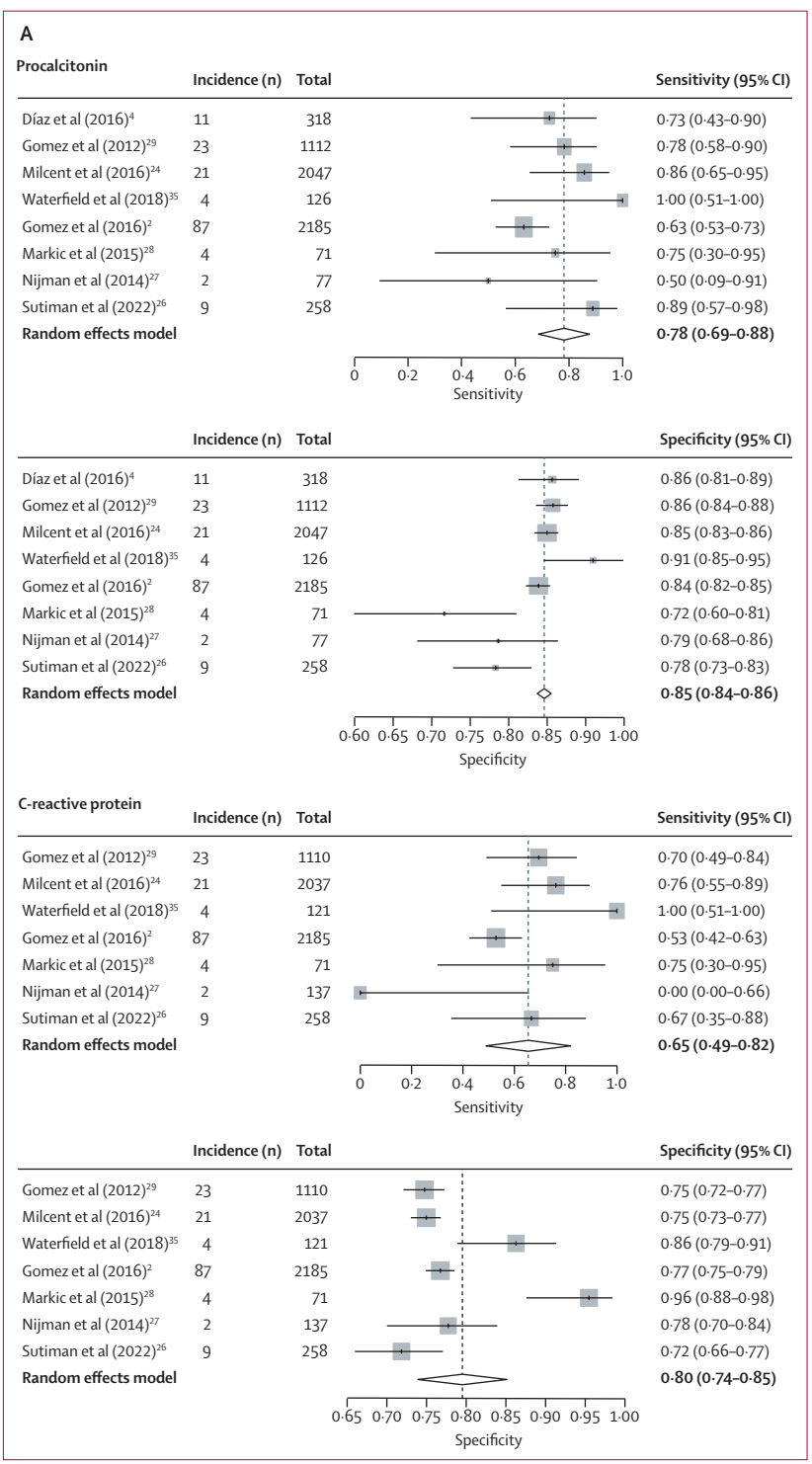
Second, a multiple cutoffs model, in which more than one cutoff value for the same outcome could be incorporated per study, was used to identify optimal cutoff values. The optimal cutoff value reflects the maximal combined sensitivity and specificity with the estimated parameters in the multiple cutoffs model. The model assumes equal weighting for sensitivity and specificity, and the resultant optimal cutoff value maximises the Youden index. A series of cutoff values were tested within the multiple cutoffs model and the sensitivity and specificity were reported for multiple cutoff values.

To investigate the influence of individual studies on the pAUC results derived from the bivariate model, a further post-hoc sensitivity analysis applied the leave-one-out method. Here the range of the FPR was not constricted to the common ranges but used the full observed FPRs for each biomarker. Heterogeneity between studies was quantified with the Cochran's Q test statistic and I^2 statistic. Funnel plots of the diagnostic odds ratios are presented, and Egger's test was used to assess funnel plot asymmetry.[22,23]

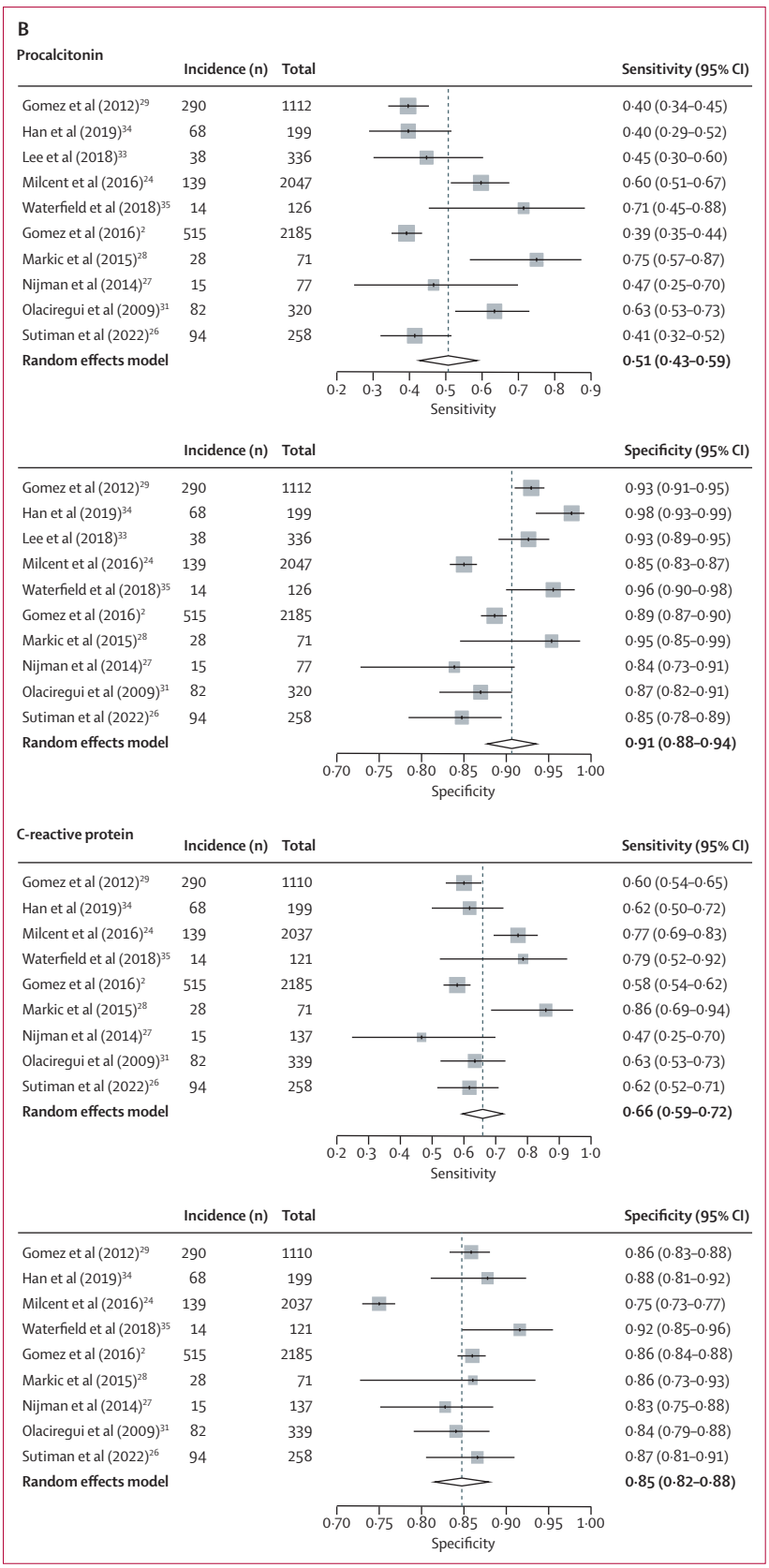
This systematic review and meta-analysis was registered with PROSPERO, CRD42022293284.

Role of the funding source

This study had no funding source.



(Figure 3 continues on next page)



Results

The electronic database searches rendered 734 results. The results of the two searches (from March, 2022, and June, 2023) were combined and are displayed in figure 2. 74 studies were excluded as duplicates and a further 550 studies were excluded during screening of titles and abstracts. The remaining 100 texts were reviewed in full, and a further 73 titles were excluded (figure 2; appendix pp 2–8). Corresponding authors of 27 studies were contacted for further unpublished data. Of these, 12 were excluded because additional data could not be obtained. One further study was excluded because the author identified duplication of participants from a larger study that was already included in the meta-analysis. In total, datasets from 14 studies, involving 7755 participants and published between 2008 and 2022, were included in this meta-analysis.[2,4,24–35] Baseline study characteristics are summarised in table 1.

For the detection of invasive bacterial infection, procalcitonin (with a cutoff value of 0·5 ng/mL) had a sensitivity of 0·50–1·00 and specificity of 0·72–0·91. C-reactive protein (with a cutoff value of 20 mg/L) had a sensitivity of 0·00–1·00 and specificity of 0·72–0·96. The pooled sensitivity and specificity of procalcitonin (0·5 ng/mL) was 0·78 (95% CI 0·69–0·88) and 0·85 (0·84–0·86), respectively, and the pooled sensitivity and specificity of C-reactive protein (20 mg/L) was 0·65 (0·49–0·82) and 0·80 (0·74–0·85), respectively (figure 3A). The pAUC for invasive bacterial infection was 0·72 (95% CI 0·56–0·79) for procalcitonin (0·5 ng/mL) and 0·28 (0·17–0·61) for C-reactive protein (20 mg/L; p=0·016; figure 4A).

For the detection of serious bacterial infection, procalcitonin (with a cutoff value of 0·5 ng/mL) had a sensitivity of 0·39–0·75 and specificity of 0·84–0·98. C-reactive protein (with a cutoff value of 20 mg/L) had a sensitivity of 0·47–0·86 and specificity of 0·75–0·92. The pooled sensitivity and specificity of procalcitonin (0·5 ng/mL) was 0·51 (95% CI 0·43–0·59) and 0·91 (0·88–0·94), respectively, and the pooled sensitivity and specificity of C-reactive protein (20 mg/L) was 0·66 (95% CI 0·59–0·72) and 0·85 (0·82–0·88), respectively (figure 3B). No difference was found between the pAUCs for detection of serious bacterial infection with procalcitonin (0·5 ng/mL) and C-reactive protein (20 mg/L; 0·55 [95% CI 0·44–0·69] *vs* 0·54 [0·40–0·61]; p=0·92; figure 4B).

The MCM identified optimum procalcitonin cutoffs of 0·49 ng/mL for detecting invasive bacterial infection and 0·17 ng/mL for detecting serious bacterial infection. The

Figure 3: **Paired forest plots for the pooled sensitivity and specificity of each biomarker for the detection of (A) invasive bacterial infection and (B) serious bacterial infection**

Generated with primary cutoff values (0·5 ng/mL for procalcitonin and 20 mg/L for C-reactive protein) in the bivariate model.

optimal C-reactive protein cutoff was 13·12 mg/L for detecting invasive bacterial infection and 16·18 mg/L detecting serious bacterial infection. Details of the diagnostic performance of each biomarker at various cutoff values are shown in table 2.

The QUADAS-2 results suggested the quality of included studies was high (appendix p 9). Data from the 14 included studies provided adequate descriptions of the index tests, timing of sampling, population characteristics, sample type, and detection method for confirmation of invasive bacterial infection. None of the studies shared a single definition for the diagnosis of serious bacterial infection, which was the greatest source of interstudy variability and potential bias or compromised applicability. Patient selection was another source of variability (table 1). Heterogeneity assessments were performed in the bivariate model with the primary cutoff values for each biomarker. Heterogeneity was low among studies of procalcitonin to detect invasive bacterial infection (I^2=23·5%). In contrast, heterogeneity was high among studies of procalcitonin to detect serious bacterial infection (I^2=75·5%). The corresponding I^2 values for C-reactive protein were 49·5% for studies of invasive bacterial infection and 28·3% and serious bacterial infection. Full details of the heterogeneity assessments, including Egger's test, are reported in the appendix (p 10).

Further sensitivity analysis with the bivariate model did not identify differences between studies that included a population with fever without an apparent source and those that did not, or between studies that included premature infants and those that did not (p>0·11 in all analyses; appendix p 11). Sensitivity analysis of other selection criteria were not possible due to insufficient data, and subgroup analysis by age was limited by a shortage of unpublished data. Sensitivity analysis to examine the effect of removing individual studies showed that no single study considerably affected the pAUC values obtained from the bivariate model (appendix pp 12–13).

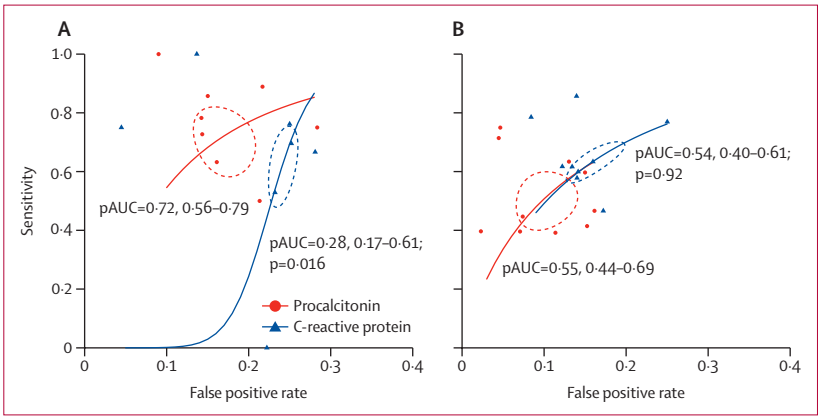


Figure 4: **ROC curves to produce pAUC values for each biomarker for the detection of (A) invasive bacterial infection and (B) serious bacterial infection**
Generated with primary cutoff values (0·5 ng/mL for procalcitonin and 20 mg/L for C-reactive protein) in the bivariate model for the detection of (A) invasive bacterial infection (false positive rate range 0·090–0·281) and (B) serious bacterial infection (false positive rate range 0·084–0·161). Labelled with pAUC values and the corresponding p value for the test of significant difference. pAUCs for the ROC curves are shown with 95% CIs. AUC=area under the curve. pAUC=partial area under the curve. ROC=receiver operating characteristic.

	Invasive bacterial infection		Serious bacterial infection	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Procalcitonin, ng/mL				
0·1	0·87 (0·66–0·96)	0·60 (0·53–0·66)	0·81 (0·70–0·89)	0·64 (0·50–0·76)
0·2	0·82 (0·61–0·93)	0·72 (0·68–0·76)	0·71 (0·59–0·80)	0·76 (0·65–0·84)
0·3	0·78 (0·58–0·90)	0·78 (0·75–0·81)	0·63 (0·51–0·74)	0·81 (0·73–0·88)
0·5*	0·73 (0·53–0·86)	0·84 (0·82–0·86)	0·53 (0·41–0·64)	0·87 (0·80–0·91)
1	0·65 (0·45–0·81)	0·90 (0·88–0·92)	0·39 (0·28–0·51)	0·92 (0·87–0·95)
2	0·56 (0·34–0·76)	0·94 (0·93–0·95)	0·27 (0·17–0·39)	0·95 (0·92–0·97)
C-reactive protein, mg/L				
10	0·77 (0·50–0·92)	0·61 (0·55–0·66)	0·85 (0·72–0·92)	0·62 (0·42–0·79)
15	0·69 (0·45–0·85)	0·70 (0·66–0·74)	0·77 (0·62–0·88)	0·73 (0·54–0·86)
20*	0·61 (0·40–0·78)	0·76 (0·73–0·79)	0·71 (0·54–0·83)	0·79 (0·62–0·89)
30	0·50 (0·31–0·69)	0·83 (0·80–0·85)	0·60 (0·42–0·75)	0·86 (0·73–0·93)
40	0·42 (0·24–0·63)	0·86 (0·84–0·88)	0·51 (0·34–0·69)	0·89 (0·79–0·95)
50	0·36 (0·18–0·59)	0·89 (0·87–0·91)	0·45 (0·28–0·63)	0·91 (0·83–0·96)

The cutoff values include the internationally used and optimal values identified in the meta-analysis with the multiple cutoff model. *Primary cutoff values in this study.

Table 2: **Diagnostic performance of the two biomarkers at multiple cutoff values**

Discussion

This systematic review and meta-analysis is the largest and most robust assessment of the diagnostic test accuracy of procalcitonin and C-reactive protein in predicting invasive bacterial infection in young febrile infants. 14 studies included 7755 young febrile infants, 161 of whom had proven invasive bacterial infection. Procalcitonin (cutoff of 0·5 ng/mL) was superior to C-reactive protein (cutoff of 20 mg/L) in detecting invasive bacterial infection. This finding was reflected in the significantly different pAUC values for the two biomarkers in detecting invasive bacterial infection. These findings confirm that when applying internationally used cutoff values of procalcitonin and C-reactive protein, procalcitonin (0·5 ng/mL) has better diagnostic accuracy than C-reactive protein (20 mg/L) for the detection of invasive bacterial infection. This conclusion supports evidence from recent studies suggesting the superiority of procalcitonin, which led to its incorporation into the sequential assessment of modern CPGs.[2,5,29] Therefore, in settings where procalcitonin is unavailable, guidance advocating for the interchangeable application of these biomarkers should be followed with caution.[3,36]

Numerous diagnostic accuracy studies have attempted to define the optimal cutoff values for procalcitonin and C-reactive protein as part of the sequential assessment of febrile infants. Most validated CPGs (eg, StepByStep, PECARN, and AAP) recommend low cutoff values of 0·5 ng/mL for procalcitonin and 20 mg/L for C-reactive protein. Our analysis suggested 0·49 ng/mL as the

optimum procalcitonin cutoff value for invasive bacterial infection, which is similar to the international standard. By contrast, the analysis suggested that 13·12 mg/L C-reactive protein was a more optimum cutoff value for detecting invasive bacterial infection, which is lower than the current international standard. CPGs using C-reactive protein as the biomarker for sequential assessment might therefore consider lowering their recommended C-reactive protein cutoff. Ultimately, the optimum cutoff value depends on the level of acceptable risk of missing invasive bacterial infection balanced against the perceived benefits of avoiding admission and treatment with antibiotics within the context of the local prevalence of invasive bacterial infection. Indeed, the variable performance of the biomarkers suggested that lowering the cutoff value could improve sensitivity at the expense of a higher false positive rate. As reported by Pantell and colleagues,[3] when presenting the recently published AAP guidance, risk is not a number.

Unfortunately, limited data access limited our ability to compare pAUC values for the optimal cutoffs that we identified in this meta-analysis. Although the primary cutoff value for procalcitonin is similar to the optimum cutoff value identified in the multiple cutoffs model, the discrepancy between the international standard cutoff value and newly identified optimum cutoff value for C-reactive protein could affect the reported difference in pAUC. We were unable to test whether the difference between the performance of the biomarkers would remain significant when detecting invasive bacterial infection if a more pragmatic cut off value for C-reactive protein, such as 15 mg/L, was used. Nevertheless, comparison of the reported sensitivity and specificity from the multiple cutoffs model at these optimum cutoff values suggests that procalcitonin might remain superior, particularly in regard to specificity.

Febrile infants presenting in the first 90 days of life can have a serious bacterial infection that is not necessarily invasive. UTIs are the most common serious bacterial infection type, accounting for over 90% of cases.[2,3,24] C-reactive protein and procalcitonin performed similarly in the identification of serious bacterial infection in our meta-analysis. This finding might reflect challenges in confirming a serious bacterial infection: for example, radiographically confirmed pneumonia can be viral or bacterial; a localised skin infection might not elicit a systemic response; and a UTI might be falsely diagnosed due to contamination of urine during the collection process. The challenges associated with confirming a serious bacterial infection are reflected in the heterogeneity assessments. The greater heterogeneity observed for the serious bacterial infection analysis can probably be explained by the variability in definitions between selected studies and contributes to the funnel plot asymmetry seen in this diagnostic accuracy study.[23] There is no universally accepted definition of serious bacterial infection; as such, the reference standard of serious bacterial infection was probably more heterogeneous than the more widely accepted definition of invasive bacterial infection. This discrepancy highlights the importance of focusing on uniform identification of UTIs and clarifying the term serious bacterial infection in future studies of febrile infants. As suggested by the author committee of the AAP guidance who "strongly discourage[s] further use of the term" serious bacterial infection, researchers should move away from this term to allow the comparison of studies in the future.[3]

Other potential sources of heterogeneity could stem from differences in inclusion and exclusion criteria between studies. However, sensitivity analysis showed no influence of whether or not the apparent source of infection was known or if preterm infants were included.

This systematic review and meta-analysis has several limitations. We were unable to obtain the unpublished data needed to include all 27 eligible studies. The differences between included and excluded studies were that excluded studies were more likely to extend beyond 90 days of age and many were published more than 20 years ago, with their data no longer available for additional analysis. A move to routinely placing data in public repositories has the potential to improve future reviews, as more studies would be available for comparison. The studies selected for review reported data from infants presenting to emergency care and came entirely from high-resource settings. This limits the generalisability of the results beyond these settings. In particular, the kinetic profile of procalcitonin in the newborn period is different to that of older infants and newborn participants in the meta-analysis were not well represented.[37] As such, the findings of this systematic review should not be applied to neonatal units and newborns within the first 48 h of life. Finally, performing a sensitivity analysis to compare the test accuracy of procalcitonin and C-reactive protein for infants with a very short duration between onset of their fever and their presentation to a hospital was not possible, so the findings of this systematic review and meta-analysis should be applied cautiously to such infants.

The impact of a tailored approach to treating febrile infants presenting to hospital within the first 90 days of life cannot be underestimated. This cohort represents a challenge to clinicians. The risk of invasive bacterial infection is high, and clinical assessment can be difficult for even experienced paediatricians.[3,5] CPGs are therefore cautious, advocating a low threshold for admission to hospital and treatment with broad-spectrum parenteral antibiotics.[2,5,10] Admission to hospital and treatment just in case, however, is not without risks and harms. Admission early in life can interfere with maternal bonding and breastfeeding. The early use of broad-spectrum antibiotics can disturb the developing microbiome; has been associated with increased rates of autoimmune diseases, such as asthma, allergies, and

multiple sclerosis; and is associated with longer hospital stays and higher rates of adverse events.[3,38] Tailored care based on the principles of sequential assessment can be used to identify infants at lower risk who might be suitable for management without parenteral antibiotics. Most CPGs with sequential assessment advocate the use of procalcitonin over C-reactive protein, but procalcitonin is not universally available.

This systematic review and meta-analysis shows that, among 7755 febrile infants presenting in the first 90 days of life, a procalcitonin cutoff of 0·5 ng/mL has superior diagnostic accuracy to C-reactive protein with a cutoff value of 20 mg/L for identifying invasive bacterial infections. Given the priority to safely yet accurately detect invasive bacterial infection, these findings would suggest that, when procalcitonin is unavailable, C-reactive protein should be used cautiously as the alternative biomarker. When C-reactive protein is the only available biomarker, a lower cutoff value (15 mg/L) should be considered over the 20 mg/L cutoff currently recommended in CPGs.

Contributors

HN-B, TW, and EU conceptualised, designed, and oversaw the systematic review. CM and DMcC contributed to the process of screening, data extraction, and methodological assessment. HM and LMcF supported both the design and running of the statistical analysis. HN-B is the lead author and guarantor; they provided the first draft of the manuscript. HN-B, CM, HM, and LMcF accessed and verified the data. All authors had complete access to all the data in this Article, approved the final manuscript, and share final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

This meta-analysis did not require the collection of new data, but rather the analysis of previously published data. However, unpublished data were supplied from authors of other studies and these remain subject to their data sharing policies. Details of our meta-analysis process are available on request to the corresponding author.

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