Improving management of infectious diseases at the emergency department: from risk prediction to treatment strategies

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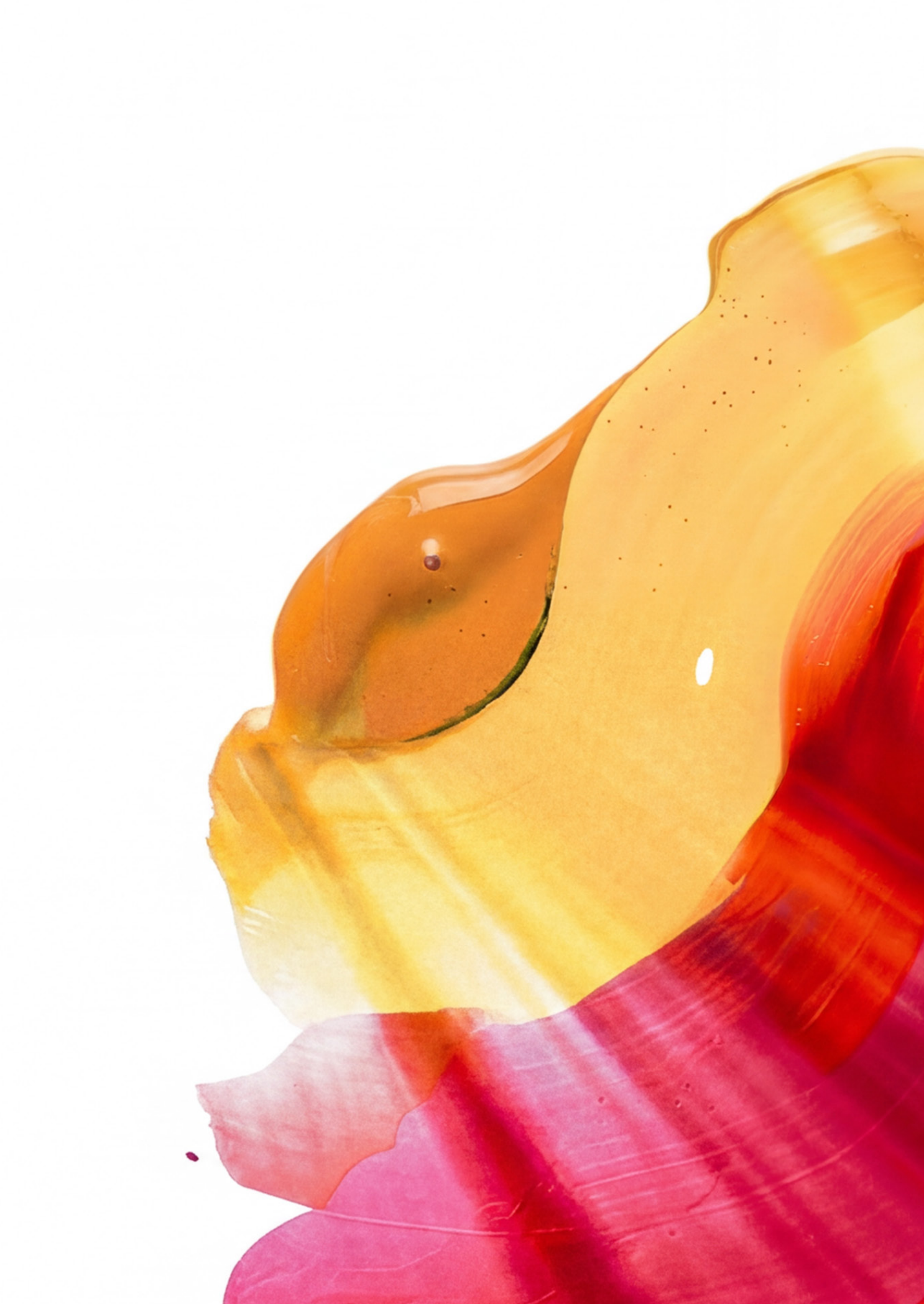

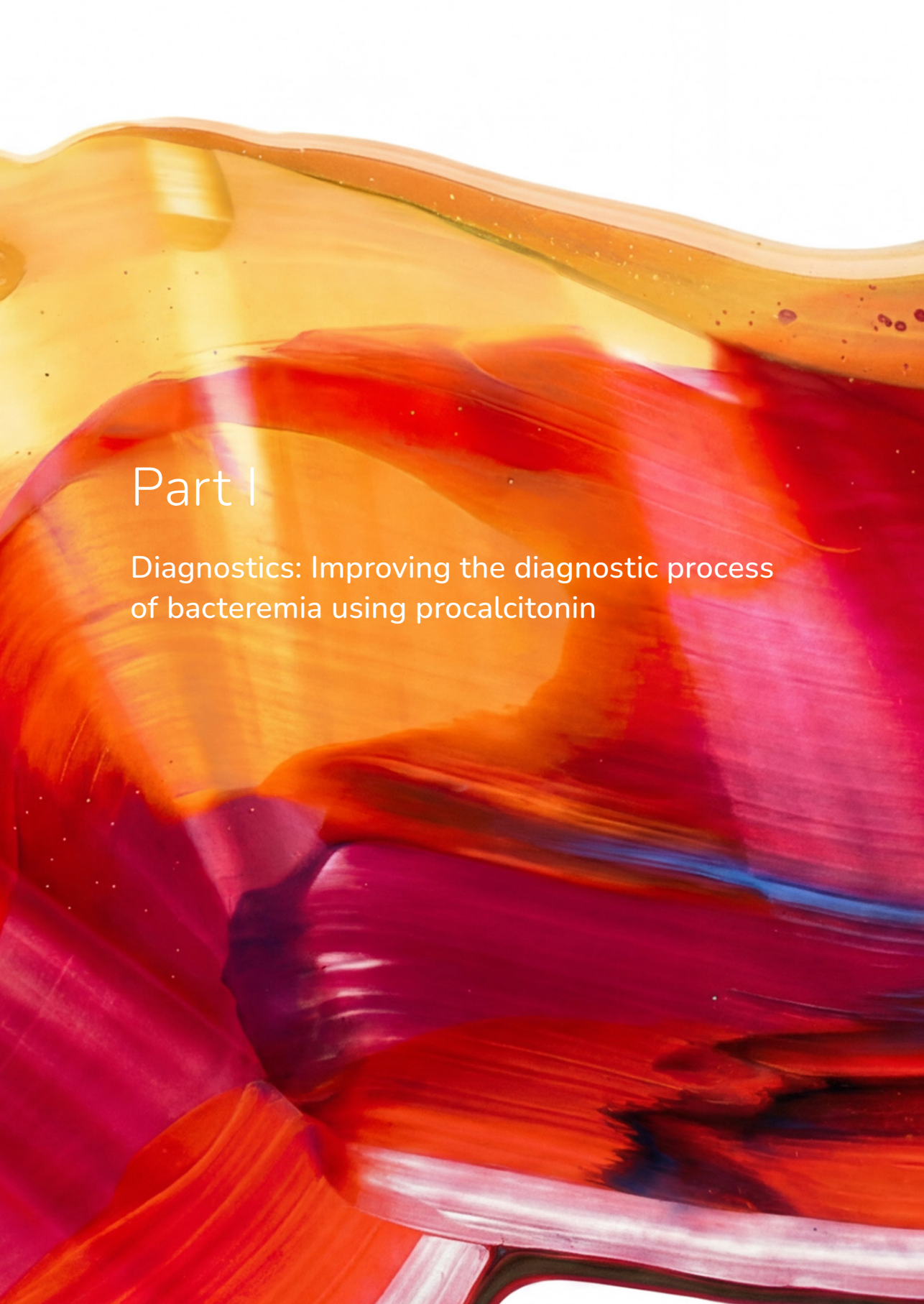

Part I

Diagnostics: Improving the diagnostic process of bacteremia using procalcitonin

Chapter 2

The diagnostic accuracy of procalcitonin for community-acquired bacteraemia: an updated systematic review and meta-analysis

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Clinical Microbiology and Infection, 2026; 32, 749-759

ABSTRACT

Background

Procalcitonin is known to have moderate diagnostic accuracy for bacteremia. A 2014 meta-analysis showed 76% sensitivity for a 0.50 ng/mL threshold. Lower thresholds might improve sensitivity.

Objectives

To determine the diagnostic accuracy of procalcitonin for community-acquired bacteraemia by conducting a systematic review and meta-analysis, focusing on the ability to exclude bacteraemia.

Methods

Data sources: We searched PUBMED, EMBASE and Web of Science from 1 January 2014 to 20 May 2025.

Study eligibility criteria and participants

Articles studying diagnostic accuracy of procalcitonin for community-acquired bacteraemia in adults.

Test and reference standard

Procalcitonin was compared with blood culture results.

Assessment of risk of bias

Risk of bias was assessed using the QUADAS-2 tool.

Methods of data synthesis

We pooled sensitivity/specificity with a bivariate random-effects model and created a summary receiver-operating curve. The main analysis focused on studies reporting on a procalcitonin threshold of 0.10 ng/mL. In addition, we analysed results for all studies, studies with a 0.25 ng/mL and studies with a 0.50 ng/mL threshold.

Results

We included 40 of 5450 identified articles, reflecting 192 529 patients of whom 31 480 (16%) had bacteraemia. Of 40 studies, 32 had high risk of bias. The pooled sensitivity for a 0.10 ng/mL threshold was 93% (95% CI: 85-97%) with a specificity of 36% (95% CI: 26-47%). The area under the summary receiver-operating curve for all studies was 0.80 (95% CI: 0.76-0.83%; prediction interval 0.57-0.91).

Discussion

A low cut-off value of procalcitonin can be useful to exclude community-acquired bacteraemia, depending on what the treating clinician considers to be an acceptable trade-off between sensitivity and specificity. Procalcitonin may require combination with clinical characteristics for accurate assessment of the risk of bacteraemia and safely reducing unnecessary blood cultures.

INTRODUCTION

Community-acquired bacteraemia (CAB) continues to lead to high morbidity and mortality if not treated timely and adequately.[1] Recognizing bacteraemia can be difficult because patients' symptoms are unspecific and most commonly used diagnostic tools either lack accuracy or do not lead to timely results to be used at an emergency department (ED). The fear of missing bacteraemia leads to overuse of diagnostic tests. Currently, the reference standard is blood cultures.[2] These only yield a true positive result in 4-11% of all blood cultures taken at the ED, whereas another 2-8% is contaminated with skin flora, and performing blood cultures is costly.[3-8] It would therefore be of great value to find a way to improve the diagnostic process for bacteraemia. Because most patients with suspected infection or sepsis at ED do not have bacteraemia, finding a way to immediate rule out bacteraemia would help avoid unnecessary blood cultures and negative consequences of false-positive results.[6-8] This is also in line with the increasing call for diagnostic stewardship aiming to minimize inappropriate diagnostic microbiology testing.[9,10]

Procalcitonin (PCT), a biomarker with growing relevance to identify bacterial infections, has been extensively researched to identify bacteraemia.[11-15] A systematic review and meta-analysis from 2007 concluded that PCT had a moderate performance for diagnosing bacteraemia with an area under the curve (AUC) value of 0.84, a pooled sensitivity of 76% (95% CI: 66-84%) and a pooled specificity of 70% (95% CI: 60-79%).[11] In 2015, Hoeboer et al.[12] conducted a meta-analysis that concluded that PCT had a fair diagnostic accuracy for bacteraemia with an AUC of 0.78, a pooled sensitivity of 76% (95% CI: 69-82%) and a pooled specificity of 69% (95% CI: 64-72%) in the ED population. Both meta-analyses used cut-offs closest to 0.5 ng/mL in their analysis, whereas especially low values of PCT (<0.10 ng/mL, <0.25 ng/mL) are reported to have high sensitivities.[12-14]

Since this last review, multiple studies have been published that evaluate the diagnostic accuracy of PCT for bacteraemia using lower thresholds. This could lead to a better understanding of the usability of PCT to safely withhold blood cultures. Therefore, we aim to provide an up-to-date overview of the diagnostic accuracy of PCT for bacteraemia in adult patients presenting to the hospital with suspected infection, with a particular focus on its ability to exclude CAB, by performing a systematic review and meta-analysis.

METHODS

Search strategy and study selection

A search strategy was set up in collaboration with an information specialist (PG), see the supplementary material. The search strategy was built on a combination of terms for PCT, bacteraemia and diagnostic properties. We searched PUBMED, EMBASE and Web of Science from 1 January 2014 to 20 May 2025. We used Rayyan to identify potential duplicates. This programme estimates the probability that an article is included in duplicate. We deleted articles with a certainty over 95%. Studies were screened by title and abstract by a minimum of two individual researchers (AGK, MN, KS, CvN), and final inclusion was done after full-text review. Any disagreement was resolved through discussion. Finally, the reference lists of included articles were searched for additional relevant articles.

We included studies that studied solely adult patients ≥18 years suspected of having an infection. Articles were eligible for inclusion if they compared the diagnostic accuracy for CAB for PCT compared with the reference standard: blood cultures. They had to report diagnostic properties needed to create a 2 × 2 table of PCT versus blood culture results. CAB had to be defined as growth of a bacterial pathogen from a blood culture, taken at ED and/or within 48 hours of hospital admission. PCT had to be tested within 24 hours of blood culture withdrawal. Finally, a minimum of one cut-off value for PCT had to be defined. We included possible articles from all languages, using the translation app DeepL for languages other than English, Dutch or Spanish. Exclusion criteria were animal studies, case report or case-control studies, studies studying catheter related bacteraemia, studies that included common skin contaminants in their definition for positive blood culture or studies in burn patients. For studies that seemed eligible but did not report all necessary information, we contacted the corresponding author per e-mail to request additional information. Authors of studies that only reported on part of the cut-offs of interest were also asked to provide additional results. This study is reported according to the preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA) standards.[16]

Study protocol

We registered the study protocol at Prospero, with registration number CRD42023426791.

Data collection

We used a predefined data collection form (see supplementary material) for data collection. All information was collected in duplicate. Any disagreement was resolved by discussion, and in case of persistent disagreement, one of the other authors was consulted. We collected data regarding study characteristics (study design, country, and study year), specific information regarding the patient population such as reported use of immunosuppressants or recent antibiotics, whether there was a clear definition of false-positive blood cultures and the method used to analyse PCT.

Quality assessment

We used the QUADAS-2 tool to evaluate risk of bias and concerns regarding applicability.[17] All evaluations were done in duplicate, with discrepancies resolved by discussion.

Statistical analysis

Because we aim to analyse the ability of low PCT values to exclude bacteraemia, our main analysis focused on the results reported for a PCT threshold of 0.10 ng/mL, including lower thresholds and up to 0.15 ng/mL. In addition, we analysed results for (1) thresholds of 0.25 ng/mL (including 0.15 ng/mL up to 0.35 ng/mL), (2) the more commonly suggested threshold of 0.50 ng/mL, including thresholds from 0.35 up to 0.65 ng/mL and (3) using the results of one PCT cut-off closest to 0.5 ng/mL for all included studies. For each analysis, only one cut-off per study was included.

We used the bivariate random-effects regression model to pool sensitivity and specificity. This was also used to create a summary receiver-operating curve for all included studies, using the results of the reported threshold closest to 0.5 ng/mL for comparability with previous studies. We included a prediction region to reflect the estimated sensitivity and specificity for a new study, taking between-study heterogeneity into account. We do not report quantitative measures of heterogeneity because these are not routinely used in DTA reviews because they do not account for heterogeneity explained by phenomena such as different positivity thresholds between studie.[18] Heterogeneity can be visually inspected by the degree to which the observed study results lie close to the summary ROC curve. We estimated the prediction interval for the AUC of the ROC curve by running a random-effect meta-analysis with the 'metafor' package on all studies that reported the AUC with CI, estimating the results on a logit scale.[19] In addition, we explored the influence of study and patient characteristics by performing multiple subanalyses in selected subgroups: prospective versus retrospective studies, according to setting (ED, ward, intensive care unit, or mix), studies with a clear definition of false-positive blood

cultures versus those without, studies including immunocompromised patients versus studies with immunocompetent patients only, according to whether studies included patients with recent use of antibiotics and, finally, according to specific site of infection. We used Deeks' funnel plot asymmetry test to evaluate publication bias, using the commonly used p value of <0.10 for the slope coefficient as a sign of significant asymmetry, indicating potential publication bias.[18] A sensitivity analysis was done by calculating the summary estimates for low and high risk of bias studies and low level of concern and high level of concern for applicability as assessed by the QUADAS-2 criteria. Unclear risk was reclassified as high risk for this comparison. All analyses were conducted using Rstudio version 2024.09.0.

RESULTS

Study selection

Our literature search retrieved 5450 unique articles, of which 5255 were excluded after screening of title and abstract. A total of 191 full-text articles were screened for eligibility, of which 151 were excluded. Reasons for exclusion are depicted in Fig. 1; 31 were excluded because of multiple reasons that are separately listed in the supplementary material. Finally, a total of 40 cohort studies were included (Fig. 1, Table 1) accounting 192 529 patients of whom 31 480 (16.3%) had bacteraemia. The reported PCT cut-offs ranged from 0.10 to 10.83 ng/mL. All studies used automatized PCT assays (see supplementary material).

Risk of bias and applicability

We evaluated all studies using the QUADAS-2 tool (Table 2). Overall, 32 of 40 studies had a high risk of bias on at least one domain. An important source of bias was the unclear handling of contaminated blood cultures, by either not using a clear definition or unclear handling of the contaminated cultures in the analysis. We found less applicability concerns, only in 9 of 40 studies, which were mostly caused by the selection of a very specific population.

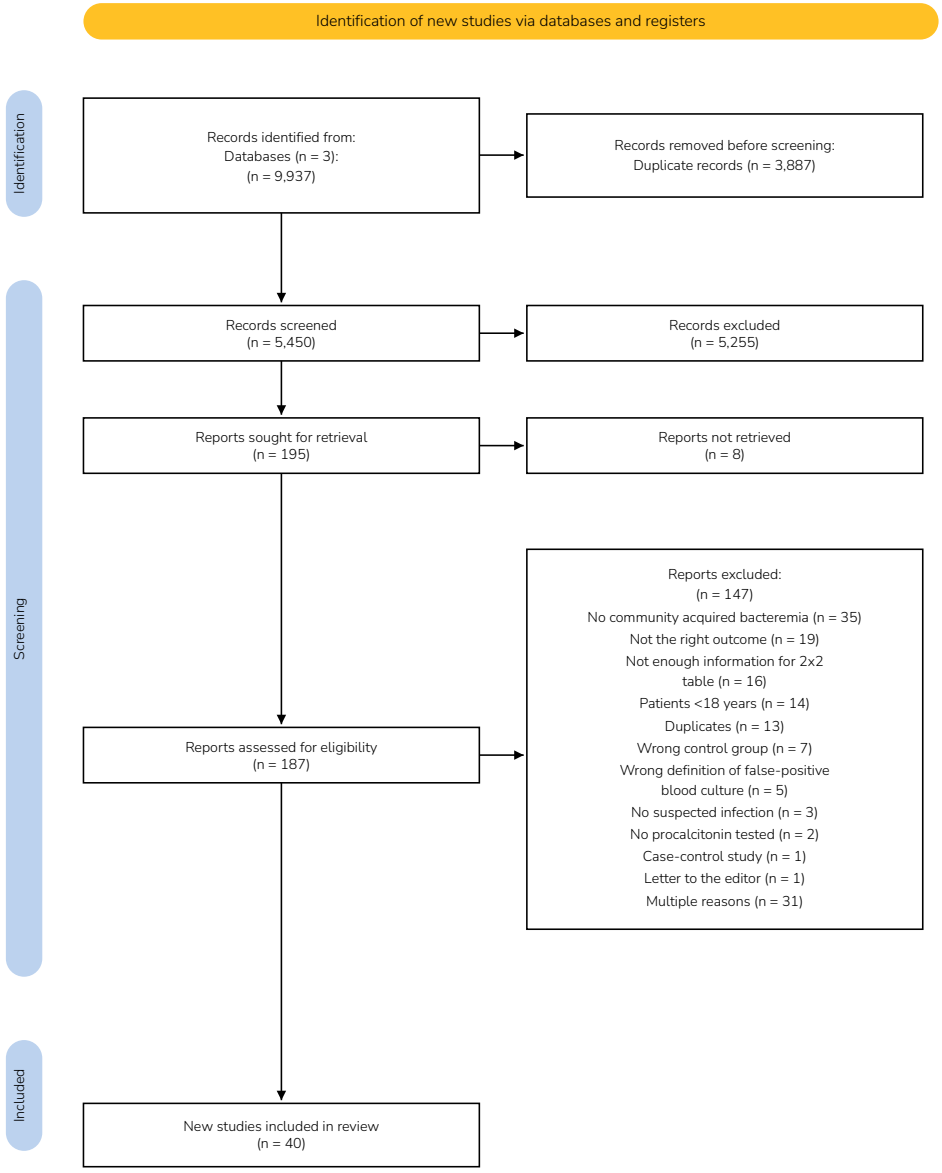

Figure 1. Flowchart of identification of new studies

Table 1. Characteristics of all included studies.

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Azijli et al., 2022 [20]	Netherlands	Pro-spective	Suspected infection with performing of blood cultures and influenza PCR test	ED	546	64 (17)	301 (55)	47 (9)	Clear	Viral	Yes	Yes	0.1, 0.25, 0.5
Choe et al., 2016 [21]	Korea	Retro-spective	Septic shock or severe sepsis with blood lactate ≥2.0 mmol/L	ED	1212	66 (55-74)	718 (59)	421 (35)	Unclear	Mixed	Yes	Unclear	0.25, 0.50
Ciotti et al., 2019 [22]	Italy	Pro-spective	Febrile outpatients with haematological malignancies	ED	70	Not specified	Not specified	11 (16)	Unclear	Mixed	Yes	Unclear	0.5
García de Guadiana-Romualdo et al., 2019 [23]	Spain	Pro-spective	Febrile neutropenia	ED	111	63 (21-85)	42 (38)	16 (14)	Clear	Mixed	Yes	Unclear	0.34
Julián-Jiménez et al., 2022 [24]	Spain	Pro-spective	Patients >65 y with clinically suspected infection	ED	2401	80 (8)	1489 (62)	579 (24)	Clear	Mixed	Unclear	Unclear	0.5
Harikrishna et al., 2020 [25]	India	Pro-spective	Acute fever	Mixed	450	51 (18)	312 (65)	44 (10)	Clear	Mixed	Unclear	Unclear	0.5
Hertz et al., 2024 [26]	Denmark	Pro-spective	Suspected urogenital tract infection	ED	173	75 (17)	102 (59)	39 (23)	Clear	Urogenital	Unclear	Unclear	0.15
Hoenigl et al., 2014 [27]	Austria	Pro-spective	Positive SIRS criteria	Mixed	515	BC-: 68, BC+: 66a	519 (58)a	282 (55)	Clear	Mixed	Unclear	No	0.1, 0.25, 0.5

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Inoue et al., 2020 [28]	Japan	Unclear	Diagnoses of infection and hospitalisation after performing blood cultures	ED	5064	77 (68-83)	3217 (64)	365 (7)	Unclear	Mixed	Unclear	Unclear	0.45
Iqbal et al., 2020 [29]	Spain	Retro-spective	Suspected infection	ED	1425	53 (19)	666 (47)	179 (13)	Clear	Mixed	Yes	Yes	0.51
Jimenez-Santos et al., 2014 [30]	Spain	Pro-spective	Oncology patients with fever	ED	152	63 (22)	71 (53)	22 (14)	Clear	Mixed	Yes	Unclear	0.11, 0.2, 0.5
Julián-Jiménez et al., 2022 [31]	Spain	Pro-spective	Clinical suspicion and diagnosis of infectious processes	ED	4436	67 (19)	2648 (60)	899 (20)	Clear	Mixed	Yes	Yes	0.1, 0.25, 0.51
Kaal et al., 2024 [32]	Netherlands	Pro-spective	Performing blood cultures	ED	2111	63 (NA)	1147 (54)	273 (13)	Clear	Mixed	Yes	Yes	0.1, 0.25, 0.5
Kim et al., 2015 [33]	Korea	Retro-spective	Testing of ANC, CRP, PCT and body temperature	ED	3305	Not specified	1855 (56)	564 (17)	Clear	Mixed	Unclear	Unclear	0.1
Laukemann et al., 2015 [14]	Switzerland	Pro-spective	Suspected infection	ED	1083	67 (53-78)	623 (58)	104 (10)	Clear	Mixed	Yes	Yes	0.1, 0.25, 0.5
Lawandi et al., 2023 [34]	USA	Retro-spective	Blood cultures and PCT testing within 24 h of admission	Mixed	74958	Not specifiedb	36589 (50)	9865 (13)	Clear	Mixed	Unclear	Unclear	0.1, 0.25, 0.5
Lee et al., 2018 [35]	Zuid Korea	Retro-spective	Suspected acute cholangitis	ED	204	76 (17-102)	118 (58)	65 (32)	Unclear	Abdominal	Unclear	Unclear	0.5

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Leroux et al., 2021 [36]	France	Retro-spective	PCT testing	ED	852	62 (23)	419 (49)	74 (9)	Clear	Mixed	Yes	Unclear	0.1, 0.25, 0.5
Lin et al., 2017 [37]	Taiwan	Retro-spective	Performing blood cultures	ED	886	Not specified	Not specified	197 (22)	Clear	Mixed	Unclear	Unclear	0.5
Ljungstrom et al., 2017 [38]	Sweden	Pro-spective	Suspected community-onset sepsis	ED	1572	71 (58-81)	875 (56)	197 (13)	Unclear	Mixed	Unclear	Unclear	0.1
Loonen et al., 2014 [39]	Netherlands	Retro-spective	Clinically suspected infection with >2 SIRS criteria and performing of blood cultures	ED	118	BC-: 60, BC+: 69	74 (59)	20 (17)	Clear	Mixed	Unclear	Unclear	2
Marik et al., 2020 [40]	USA	Retro-spective	Testing of PCT, lactate, CBC with differential and blood cultures for suspected bacteraemia	Mixed	1767	61 (49-71)	NA (52)	384 (22)	Clear	Mixed	Unclear	Unclear	0.5
Naffaa 2014 [41]	Israel	Pro-spective	Sepsis of any cause	Mixed	40	79 (68-84)	25 (63)	10 (25)	Clear	Mixed	Unclear	No	1.35
Nishino 2017 [42]	Japan	Pro-spective	Acute cholangitis	Mixed	62	75	46 (74)	29 (47)	Unclear	Abdominal	Unclear	Unclear	3
Oksuz et al., 2015 [43]	Turkey	Pro-spective	Febrile patients >37°C	Mixed	661	52 (18)	Not specified	77 (12)	Clear	Mixed	Unclear	Unclear	0.1, 0.25, 0.5
Oura et al., 2023 [44]	Japan	Retro-spective	Suspected acute cholangitis	Mixed	127	77 (71-85)	93 (67)c	71 (56)	Clear	Abdominal	Unclear	Yes	2.8

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Palma et al., 2024 [45]	Spain	Retro-spective	Patients ≥75 y with clinically suspected infection and performing of blood cultures	ED	109	83 (6)	64 (59)	22 (20)	Clear	Mixed	Yes	Unclear	0.76
Romualdo et al., 2014 [46]	Spain	Pro-spective	At least two SIRS criteria and clinical suspicion of bacteraemia with performing blood cultures	ED	226	67 (26)	132 (58)	37 (16)	Clear	Mixed	Unclear	Yes	0.45
Roy et al., 2018 [47]	USA	Retro-spective	Suspected bacterial infection, PCT and blood cultures tested within 24 h of admission	Mixed	339	66 (17)	33 (50)	25 (7)	Clear	Mixed	Unclear	Unclear	0.5
Seo et al., 2015 [48]	Japan	Pro-spective	Admission due to infection	Mixed	78	79	40 (51)	29 (37)	Unclear	Mixed	No	Unclear	0.1, 0.25, 0.5
Takahashi et al., 2024 [49]	Japan	Retro-spective	Admission due to DKA or HHS	Mixed	608	58 (19)	329 (54)	70 (12)	Clear	Mixed	Unclear	Yes	0.1, 0.25, 0.5
Timbrook et al., 2023 [50]	USA	Retro-spective	Performing of blood cultures and PCT on day one of admission	Mixed	71105	68 (56-79)	35713 (50)	14846 (21)	Clear	Mixed	Yes	Unclear	0.5

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Toreh et al., 2017 [51]	Indonesia	Unclear	Suspected urosepsis with performing of blood cultures	Mixed	141	Not specified	Not specified	69 (49)	Clear	Urogenital	Unclear	Unclear	0.5
Uyar et al., 2023 [52]	Turkey	Pro-spective	Suspected sepsis	ED	47	BC-: 61. BC+: 62	31 (66)	20 (43)	Clear	Mixed	No	Yes	0.55
Wiwatcharagoses and Kingnakom 2016 [53]	Thailand	Pro-spective	Symptoms of systemic infections such as sepsis, severe sepsis, or septic shock	ED	110	52 (21)	59 (54)	23 (21)	Clear	Mixed	No	No	2
Xiao et al., 2024 [54]	China	Retro-spective	Admission due to sepsis or septic shock with testing blood cultures, PCT, presepsin and CRP	Mixed	577	70 (59-81)	340 (59)	170 (29)	Unclear	Mixed	Yes	Unclear	4.31
Yamaguchi et al., 2023 [55]	Japan	Retro-spective	Suspected acute cholangitis with performing of blood cultures	Mixed	69	BC-: 75, BC+: 82	44 (47)d	35 (51)	Clear	Abdominal	No	No	0.5
Youkhana et al., 2017 [56]	USA	Retro-spective	PCT and blood cultures performed within 24 h	Mixed	14387	Not specified	Not specified	1160 (8)	Clear	Mixed	Yes	Unclear	0.5

Study	Country	Type	Inclusion criteria	Setting	Patients (n)	Age (y)	Male (%)	True positive BCs (%)	Contamination	Infection	Immuno-compromised	Antibiotic treatment	Cut-off values (ng/mL)
Zhang et al., 2021 [57]	China	Pro-spective	At least two SIRS criteria with clinical suspicion of bacteraemia and performing blood cultures	Mixed	149	BC-: 59, BC+: 57	93 (62)	59 (40)	Clear	Mixed	No	Unclear	1.29
Zhang et al., 2023 [58]	China	Pro-spective	Suspected acute cholangitis and performing of presepsin, acylcarnitines and blood cultures	Mixed	280	74 (66-84)	166 (59)	92 (33)	Unclear	Abdominal	Unclear	Unclear	10.83

Type = retrospective versus prospective cohort study. Contamination: was there a clear definition of contaminated blood cultures? Immunocompromised: were immunocompromised patients included? Antibiotic treatment: inclusion of patients with recent (<7 d) antibiotic treatment. ANC, absolute neutrophil count; BC, blood culture; CBC, complete blood count; CRP, C-reactive protein; DKA, diabetic keto-acidosis; ED, emergency department; HHS, hyperglycemic hyperosmolar state; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome.

a A total of 515 patients had a BC and PCT test; the mean age and gender were only given for the total number of patients: 898.

b Only age given for six subgroups, with medians ranging between 65 and 68 y.

c A total of 127 patients had a BC and PCT test; the mean age was only given for the total number of patients: 138.

d A total of 69 patients had a BC and PCT test; the mean age was only given for the total number of patients: 94.

Table 2. Risk of bias and applicability concerns per individual study as assessed by the QUADAS-2 tool

	Risk of bias				Applicability concerns		
	Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Referece standard**
Azijli et al., 2022 [20]	Low	Low	Low	Low	Low	Low	Low
Choe et al., 2016 [21]	High	Low	High	High	Low	Low	High
Ciotti et al., 2019 [22]	Unclear	Low	Unclear	Unclear	High	Low	Low
García de Guadiana-Romualdo et al., 2019 [23]	Low	High	Low	Low	Low	Low	Low
Julián-Jiménez et al., 2022 [24]	High	Low	Low	Low	Low	Low	Low
Harikrishna et al., 2020 [25]	Low	High	High	Low	Low	Low	Low
Hertz et al., 2024 [26]	Low	High	Low	High	Low	Low	Low
Hoenigl et al., 2014 [27]	High	Low	Low	Low	Low	Low	Low
Inoue et al., 2020 [28]	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear
Iqbal et al., 2020 [29]	High	Low	Low	Low	Low	Low	Low
Jimenez-Santos et al., 2014 [30]	Low	Unclear	Low	Low	Low	Low	Low
Julián-Jiménez et al., 2022 [31]	Low	Low	Low	High	Low	Low	Low
Kaal et al., 2024 [32]	Low	Low	Low	Low	Low	Low	Low
Kim et al., 2015 [33]	Low	Low	Low	Low	Low	Low	Low
Laukemann et al., 2015 [14]	Low	Low	Low	Low	Low	Low	Low
Lawandi et al., 2023 [34]	High	Low	Low	High	Low	Low	Low
Lee et al., 2018 [35]	Low	High	High	Low	Low	Low	Low
Leroux et al., 2021 [36]	Low	Low	High	High	Low	Low	Low
Lin et al., 2017 [37]	Low	Low	Low	Low	Low	Low	Low
Ljungstrom et al., 2017 [38]	Low	Low	High	High	Low	Low	Low
Loonen et al., 2014 [39]	Low	Unclear	Low	High	Low	Low	Low

	Risk of bias				Applicability concerns		
	Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Referece standard**
Marik et al., 2020 [40]	Low	Low	Low	High	Low	Low	Low
Naffaa 2014 [41]	Low	Low	High	Unclear	Low	Low	Low
Nishino 2017 [42]	Unclear	High	Unclear	Unclear	Low	Low	Unclear
Oksuz et al., 2015 [43]	Low	High	Low	Low	Low	Low	Unclear
Oura et al., 2023 [44]	Low	Low	Low	Low	Low	Low	Low
Palma et al., 2024 [45]	Low	High	Low	Low	Low	Low	Low
Romualdo et al., 2014 [46]	Low	High	Low	Low	Low	Low	Low
Roy et al., 2018 [47]	Unclear	Low	High	Unclear	Low	Low	Low
Seo et al., 2015 [48]	High	High	High	High	High	Low	High
Takahashi et al., 2024 [49]	Unclear	Low	Low	High	High	Low	Low
Timbrook et al., 2023 [50]	Low	Low	Low	High	Low	Low	Low
Toreh et al., 2017 [51]	Unclear	Low	Unclear	Unclear	Low	Low	Unclear
Uyar et al., 2023 [52]	Low	High	Low	High	Low	Low	Low
Wiwatcharagoses and Kingnakom 2016 [53]	High	Low	High	High	Low	Low	Low
Xiao et al., 2024 [54]	High	High	High	Unclear	Low	Low	Low
Yamaguchi et al., 2023 [55]	High	Low	Low	High	Low	Low	Low
Youkhana et al., 2017 [56]	Unclear	Unclear	Low	High	Unclear	Unclear	Unclear
Zhang et al., 2023 [58]	High	High	High	Unclear	Low	Low	Low
Zhang et al., 2021 [57]	Low	High	Low	High	Low	Low	Low

Results of individual studies

Of all studies reporting on the lowest threshold (up to 0.15 ng/mL), sensitivity ranged from 28% to 99.9% with corresponding specificity of 15-80%. Fig. 2 shows the forest plot of all included studies. The corresponding 2 × 2 table can be found in the supplementary material. Of 40 studies, 30 reported an AUC of the ROC curve, ranging from 0.56 to 0.96, with substantial uncertainty per study.

Pooled results

The pooled sensitivity for the 0.10 ng/mL threshold was 93% (95% CI: 85-97%) with a specificity of 36% (95% CI: 26-47%) and an AUC of 0.68 (95% CI: 0.53-0.80). At the average bacteraemia prevalence of 16.3%, this would lead to a negative predictive value of 97.1%. The sensitivity prediction interval for a 0.10 ng/mL cut-off was 24-99.8% with specificity ranging between 17% and 94%. See Table 3 for the results for the other thresholds. The pooled AUC for all studies was 0.80 (95% CI: 0.76-0.83) (Fig. 3). The prediction interval for the AUC was 0.57-0.91.

Table 3. Pooled sensitivity and specificity with corresponding prediction intervals for all four analyses.

PCT threshold	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Sensitivity prediction interval (%)	Specificity prediction interval (%)
0.10 ng/mL	92.8 (85.3-96.7)	35.7 (26.1-46.7)	24.0-99.8	17.0-94.0
0.25 ng/mL	85.1 (74.0-92.0)	55.4 (43.4-66.9)	20.0-99.0	8.0-88.0
0.50 ng/mL	78.6 (71.8-84.2)	68.9 (59.3-77.1)	27.0-97.0	3.0-87.0
Closest to 0.50 ng/mL	78.2 (72.8-82.7)	69.1 (62.0-75.7)	30.0-97.0	4.0-84.0

The first three analyses include only articles reporting on that threshold, whereas the fourth includes all articles using the threshold closest to a procalcitonin value of 0.50 ng/mL. The pooled sensitivity and specificity reflect the estimated average result. The prediction interval answers the question: 'If I would perform a new study, what will be my sensitivity and specificity with 95% certainty?

Subanalyses

In the subanalyses of all groups, pooled sensitivity was higher for an ED setting than a mixed setting (95% vs. 89% at a 0.10 ng/mL cut-off, prediction interval 42-99.8%). Studies using a clear definition of contaminated blood cultures also showed higher sensitivity than those without (80% vs. 69%, cut-off closest to 0.50 ng/mL). In the sensitivity analysis, we found higher pooled sensitivity for studies with low risk of bias, especially for the lower cut-offs (97% vs. 87% at a 0.10 ng/mL cut-off, specificity 34% vs. 37%, negative predictive value 98.3% vs. 93.6%, supplementary material). The prediction intervals for these low bias studies were 58-99.9% for sensitivity and 28-90% for specificity.

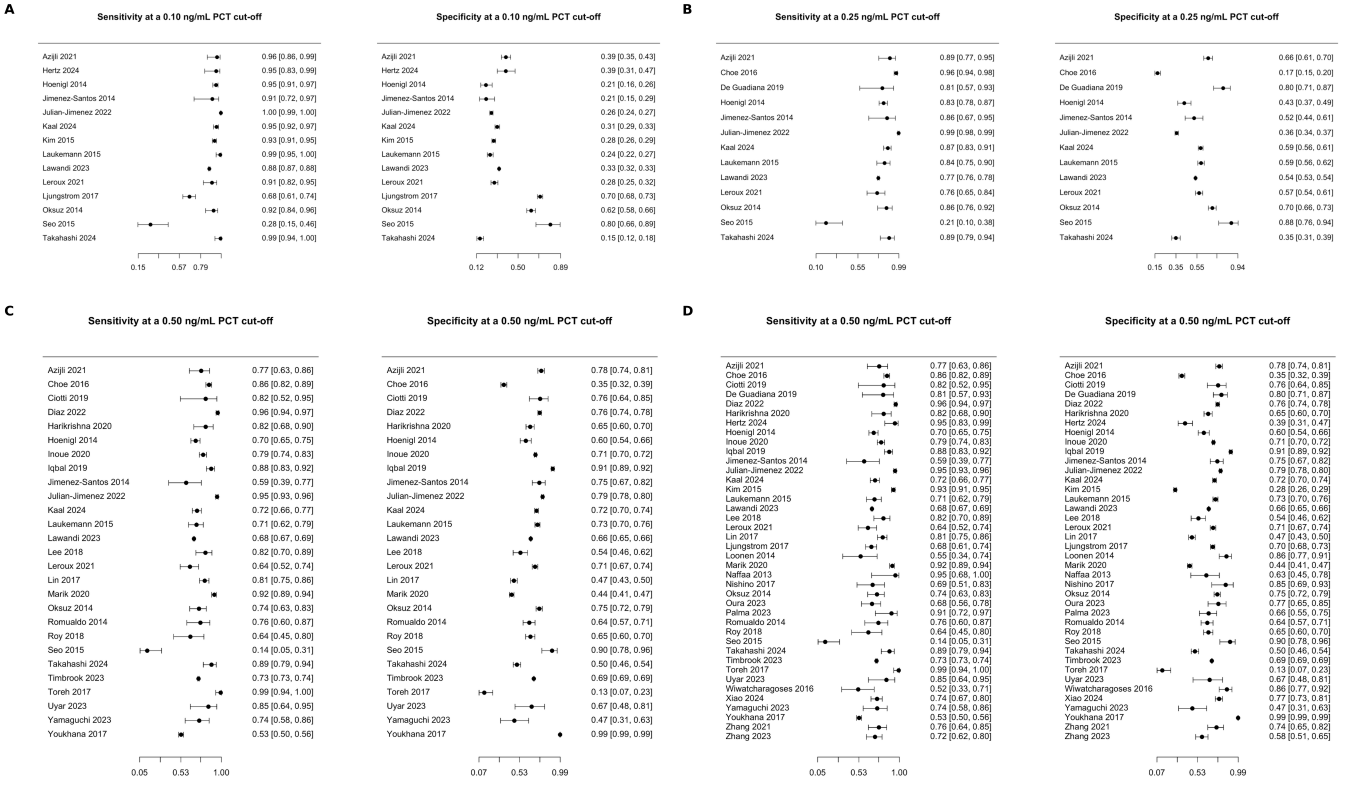

Fig. 2: Coupled forest plots of sensitivity and specificity of procalcitonin for the prediction of bacteraemia for all included studies. The four different panels A-D represent different cut-offs of procalcitonin. Panel (A) displays results for a cut-off of 0.10 ng/mL, (B) for 0.25 ng/mL, (C) for 0.50 ng/mL and (D) included all studies with the cut-off closest to 0.50 ng/mL.

Publication bias

There was no indication of publication bias based on Deeks' funnel plot (p 0.59) (see supplementary material).

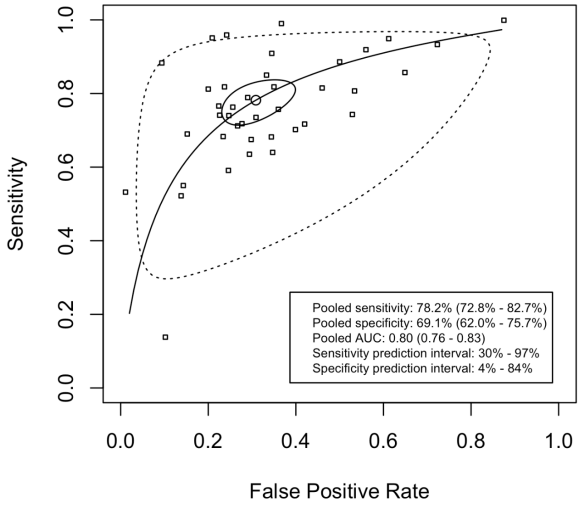

Fig. 3: Summary receiver operating characteristic (sROC) curve for the diagnostic accuracy of procalcitonin for bacteraemia, including the results at the reported threshold closest to 0.50 ng/mL. The small circle reflects the pooled sensitivity and specificity with the 95% CI shown as the larger solid circle, whereas the squares represent the results of the individual studies. The dotted line represents the prediction region, which illustrates the expected variability of sensitivity and specificity of a new study, accounting for between-study heterogeneity.

DISCUSSION

In this study, we updated a systematic review and meta-analysis of all studies published since the last meta-analysis regarding the diagnostic accuracy of PCT for CAB. We chose a new approach, focusing on the potential use of PCT to exclude CAB, to safely withhold unnecessary blood cultures. We found that with a low cut-off of 0.10 ng/mL, for a typical average study, the rate of missed bacteraemic episodes would be 7.2% (95% CI: 3.3-15%), while saving 36% (95% CI: 26-47%) of blood cultures. At the ED, the expected potential average savings are comparable (34% [95% CI: 25-44%]) with around 5% missed true positive blood cultures (95% CI: 2-11%).

Our findings are in line compared with one previous meta-analysis regarding a 0.50 ng/mL cut-off: a pooled sensitivity of 79% versus 76% and pooled specificity of

69% versus 69%, and an AUC of 0.81 versus 0.79 [12]. Another meta-analysis also showed a comparable AUC of 0.84 (0.75-0.90).[11]

It is important to recognize the difference between the estimated pooled parameters with their CIs and the prediction intervals. The first estimates an average value. However, the prediction interval answers the question: 'If I would perform a new study, what will be my sensitivity and specificity with 95% certainty?'. This might be more relevant for clinical practice, and our results show that there is substantial between-study variation. The sensitivity prediction interval for a 0.10 ng/mL cut-off was very large (24-99.8%), as was the prediction interval for the AUC, ranging from 0.57 to 0.91. However, it is known that large heterogeneity leads to irreducible uncertainty, even when more studies would be performed.[19] We did observe smaller intervals for studies with low risk of bias and ED studies. This underlines that the usability of PCT for excluding bacteraemia is highly dependent on the intended clinical setting.

On the basis of our findings, we believe that PCT can indeed be useful to rule out CAB in a typical setting, but we note that its value will largely depend on what risk of missing a true positive blood culture the treating clinician would find acceptable. It is known that clinicians require a high sensitivity, because this implies that we can safely exclude bacteraemia.[59] However, by decreasing the PCT threshold to increase sensitivity, specificity will inevitably decrease. This leads to less reduction of blood cultures, and will lead to more false-positive cultures. Some clinicians might argue that missing around 7% is unacceptable. The question remains whether this caution is justified because the vast majority of blood cultures do not impact treatment decisions; only 0.2-3% of all blood cultures taken at the ED do.[60,61] Meanwhile, it is known that false-positive blood cultures are common (2-8%) and associated with negative patient outcomes such as increased length of stay, increased costs and more exposure to antibiotics.[3-8] Therefore, we would argue that the local rate of false-positive cultures might be a good starting point when thinking about what rate of missed true positive blood cultures is acceptable.

In this meta-analysis, we choose to create four groups reflecting four thresholds. Each analysis was done using the bivariate model, including one threshold result per study. The Cochrane Handbook for diagnostic test accuracy reviews recommends using the hierarchical summary receiver operating characteristic (HSROC) model when studying multiple thresholds, because this model can include multiple thresholds per study in one analysis.[18] On the basis of this model, one could estimate the pooled sensitivity and specificity for a 0.10 ng/mL cut-off. However, given our primary interest in the results of this lower threshold, we elected to analyse studies that reported results for this threshold, as opposed to estimating results primarily

based on data from higher thresholds. In addition, we have opted for a similar approach to that employed in the 2014 meta-analysis. This might help to increase the comparability of results.[12]

PCT is not only used as a diagnostic test, but is also extensively studied as a biomarker to guide antibiotic treatment. A meta-analysis showed that PCT-based algorithms reduced antibiotic exposure without an increase in mortality.[62] Interestingly, although most of these PCT algorithms advice to withhold or to discontinue antibiotic treatment at a PCT level below 0.25 ng/mL, we showed that around 15% of true positive blood cultures did not have a PCT value over 0.25 ng/mL at presentation. This is a finding clinicians should be aware of when considering implementing such an algorithm.

It is impressive how many new articles in the past 10 years studied the diagnostic accuracy of PCT for CAB, whereas the results are comparable with previous meta-analysis. We believe that further studies regarding diagnostic accuracy of PCT for CAB will not lead to substantial reduction of uncertainty. Future studies should focus on either reporting even lower cut-offs of PCT that might lead to an acceptable trade-off between sensitivity and specificity, or on the interpretation of PCT in the clinical context. Prediction models that combine PCT with clinical predictors such as age and vital signs might help to safely withhold blood cultures.[32] Finally, studies focusing on the cost-effectiveness of PCT testing for CAB will also help to determine its use in clinical practice.[63]

We did not find an indication for publication bias using Deeks' funnel plot. However, detecting publication bias for diagnostic test accuracy studies is notoriously difficult, and cannot be excluded based on this test.[18] However, we performed a very extensive search across multiple databases to retrieve potential studies, including studies in all languages, and reached out to authors in cases of missing data or unclear data. These efforts have likely decreased the risk of publication bias in this meta-analysis.

Notably, we found that studies using a clear definition of contaminated blood cultures found higher sensitivities. This makes sense, because false-positive blood cultures do not represent an inflammatory process and PCT values will likely not be elevated. If these cultures are analysed as true positives, this would falsely lead to a lower sensitivity. We would argue that when conducting research regarding blood cultures, defining a false-positive blood culture and analysing them as negative cultures is essential to produce reliable results. In this analysis, 15 of 40 included articles failed to do so, leading to possible biased results.

A strength of this study is the rigorous literature search, in which we independently screened 5450 articles in duplicate. We were able to include 40 articles representing a very large number of patients from a wide range of counties, making the results very robust and broadly applicable. A limitation of the study is that we choose to include the studies with high risk of bias in our main analysis. Studies with a low risk of bias had a higher pooled sensitivity of 97% (95% CI: 92-99%) with a pooled specificity of 34% (95% CI: 26-44%) (please see supplementary material). Our general conclusion might therefore be an underestimation of the true diagnostic accuracy of PCT for CAB. Furthermore, the included studies used a variety of PCT assays. Although all of the assays had a detection range that should be adequate for this study, it cannot be excluded that differences in sensitivity of the used assays will have influenced our results. However, we do not expect this to have led to clinically relevant differences. Finally, we choose the bivariate model in a selection of studies rather than using the hierarchical summary receiver operating characteristic model. This approach leads to a loss of available information in the analysis. However, as explained previously, we consider our approach more appropriate to answer our primary research question focusing on ruling out CAB.

In conclusion, using lower cut-off values of PCT to exclude CAB might be useful, depending on what the treating clinician considers to be an acceptable trade-off between sensitivity and specificity. Studies reporting on the combination of PCT with clinical parameters are needed to increase our understanding of the possible use of PCT to safely withhold unnecessary blood cultures.

CRediT authorship contribution statement

Anna G. Kaal: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing—original draft, Writing—review and editing. **Margot Nieberg:** Investigation, Validation, Writing—review and editing. **Koen Stegmeijer:** Investigation, Validation, Writing—review and editing. **Ewout W. Steyerberg:** Conceptualization, Methodology, Supervision, Writing—review and editing. **Cees van Nieuwkoop:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing—review and editing. N/A: Funding acquisition, Resources.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

No external funding was used to support this study.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors made use of ChatGPT for the sole purpose of enhancing its readability and linguistic quality. After using this tool, the authors have reviewed and edited the content as needed and take full responsibility for the content of the publication.

Acknowledgements

We would like to thank Pema Gurung for her help with setting up the search strategy.

SUPPLEMENTARY MATERIAL

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