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Can procalcitonin be used to diagnose Gram-negative bloodstream infection? Evidence based on a meta-analysis

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Abstract. – OBJECTIVE: Procalcitonin (PCT) is a useful biomarker for systemic bacterial infection, and many studies have described the correlation between high serum PCT level and Gram-negative bloodstream infection (BSI), whereas the diagnostic accuracy of PCT for this kind of episode has not been summarized. This study aimed to estimate the overall accuracy of serum PCT for diagnosing Gram-negative BSI through a meta-analysis.

MATERIALS AND METHODS: We searched PubMed, EMBASE, Web of Science, and Scopus database for studies those met the inclusion criteria. The pooled sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), and diagnostic odds ratio (DOR) were calculated using bivariate random-effects models. Summary receiver operating characteristic (SROC) curve and area under the curve (AUC) were used to summarize overall diagnostic accuracy.

RESULTS: Our meta-analysis included 13 studies involving 4,513 subjects. Summary estimates for PCT in diagnosing Gram-negative BSI were as follows: sensitivity, 0.73 (95% CI 0.68 to 0.78); specificity, 0.74 (95% CI 0.64 to 0.81); PLR, 2.77 (95% CI 2.07 to 3.70); NLR, 0.37 (95% CI 0.31 to 0.42); DOR, 7.59 (95% CI 5.31 to 10.85); AUC, 0.79 (95% CI 0.75 to 0.82). The corresponding summary performance estimates for using PCT in differentiating Gram-negative BSI from gram-positive BSI were as follows: sensitivity, 0.73 (95% CI 0.66 to 0.78); specificity, 0.70 (95% CI 0.59 to 0.78); PLR, 2.40 (95% CI, 1.83 to 3.15); NLR, 0.39 (95% CI 0.33 to 0.46); DOR, 6.15 (95% CI 4.40 to 8.60); AUC, 0.77 (95% CI 0.73 to 0.81).

CONCLUSIONS: PCT may have a limited diagnostic value for Gram-negative BSI.

Key Words:
Procalcitonin, Bloodstream infection, Gram-negative bacteria, Diagnosis, Meta-analysis.

Introduction

Bloodstream infection (BSI) is a life-threatening situation resulting from the presence of organisms in the blood. Gram-negative bacteria have emerged as the prevalent pathogens causing BSI[1-4]. Gram-negative BSI is associated with longer length of hospital stay and high mortality (36.0%-47.9%)[5-8]. Moreover, ineffective initial antimicrobial therapy for such kind of episode was associated with poor outcome[7,9,10]. In practice, it is hard to diagnose BSI alone based on clinical manifestations. So, a reliable laboratory diagnostic method, which can guide early and accurate diagnosis of Gram-negative BSI, is crucial for patients.

Blood culture is regarded as the gold standard for laboratory diagnosis of bacterial BSI. Usually, 1-2 day is required to obtain Gram-stain result by direct smear from positive blood culture bottles. Sometimes, the result of direct smear method is not available because of its low sensitivity and specificity, and another 1-2 day is needed for obtaining the stain results from bacterial colony on the culture plate. Moreover, sensitivity of blood culture method for diagnosing BSI is relatively low[11] and sample contamination issue is also a challenge[12]. So biomarkers, which can help to early and accurately diagnose Gram-negative BSI, are useful for appropriate initial antibiotic therapy of the patients.

Procalcitonin (PCT) is a 116-amino-acid peptide synthesized by the C cells in the thyroid gland. Elevated serum levels of PCT are strongly associated with systemic bacterial infections[13]. Recently, higher serum PCT level was found to be associated with Gram-negative BSI, which

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suggested PCT may be a promising biomarker for diagnosing Gram-negative BSI[14-17]. Therefore, we conducted a meta-analysis to evaluate the overall diagnostic accuracy of serum PCT for Gram-negative BSI.

Materials and Methods

Study Selection

Two investigators (YCS and CH) conducted an independent literature search to identify relevant studies among the articles published up to January 2017 in PubMed, EMBASE, Web of Science, and Scopus database. The following search syntax was used as Medical Headings and/or text words: ''procalcitonin or PCT'' and ''bacteremia or bloodstream infection or sepsis" and "sensitivity or specificity or accuracy". Reference lists of the included studies or related review articles were also checked to identify potentially eligible studies. The following inclusion criteria were applied: (1) studies were original research articles and published in English; (2) studies evaluated the accuracy of serum PCT level for diagnosing Gram-negative BSI in adults (>18 years old); (3) studies reported sufficient data for calculating the value of true positive (TP), false positive (FP), false negative (FN) and true negative (TN). Conference proceedings and studies published only as abstracts and studies involving fewer than 20 patients were excluded. Discrepancies between these two investigators were resolved by consultation with a third researcher (BW).

Data Extraction and Quality Assessment of the Studies

Two investigators (BW and YFW) independently extracted data from the eligible studies and conducted 2 × 2 tables for calculating TP, FP, FN and TN values. The following data were also extracted: name of first author, publication year, country, study setting, study design, PCT assay method, and cut-off value. The quality of these studies was assessed using Quality Assessment of Diagnostic Accuracy Studies (QUADAS)[18].

Statistical Analysis

Using bivariate regression model, we calculated pooled estimates of sensitivity and specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), diagnostic odds ratios (DOR) and constructed summary receiver operating characteristic (SROC) curves[18]. The area under the curve (AUC) was calculated to assess the overall diagnostic performance. Heterogeneity was assessed using the I^2 inconsistency test. Possible causes of heterogeneity among studies were explored through subgroup analyses: study site (European *vs.* Asian), sample size (< 100 subjects *vs.* ≥ 100 subjects), study population/setting (multi-departments *vs.* other), study design (prospective *vs.* other), assay method (immunofluorescent assay *vs*. other), serum PCT cut-off value (< 1 ng/mL *vs.* ≥ 1 ng/mL), and QUADAS score (< 10 *vs.* ≥ 10). Deeks's funnel plot was used to detect publication bias[19].

Statistical Analysis

Statistical analysis was conducted by software STATA 12.0 (Stata Corporation, Lakeway Drive College Station, TX, USA) and Meta-Disc XI for Windows (Cochrane Colloquium, Barcelona, Spain). All statistical tests were two-sided, with $p < 0.05$ as the threshold for statistical significance.

Results

Characteristics of Included Studies

In our present meta-analysis, we included 13 studies[20-32], involving 4,513 subjects (2,298 BSI cases and 2,215 controls), according to the inclusion and exclusion criteria. The process of selecting studies was shown in Figure 1. All the

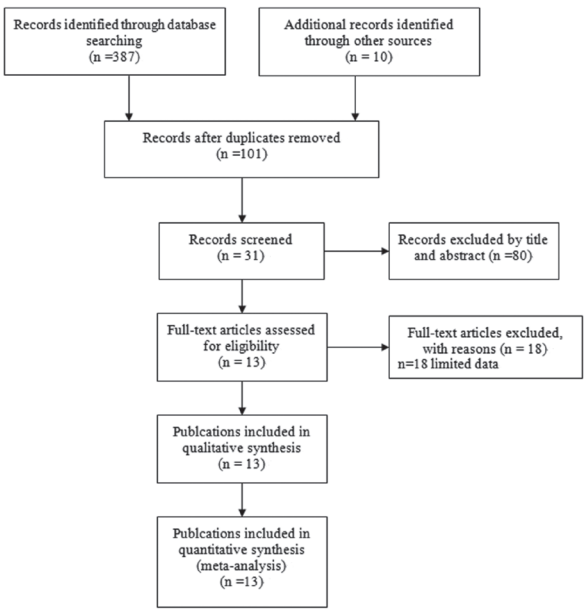

Figure 1. Flow diagram of study selection.

included studies have examined the ability of serum PCT to diagnose Gram-negative BSI[20-32], and 8 of them determined the ability of serum PCT to differentiate Gram-negative BSI from Gram-positive BSI[20,22,25-27,29,30,32]. The diagnosis of Gram-negative BSI was all based on the results of blood culture. The characteristics of included studies were summarized in Tables I-II.

Diagnostic Accuracy of Serum PCT

The overall sensitivity and specificity of PCT to diagnose Gram-negative BSI were 0.73 and 0.74, respectively (Figure 2a), and AUC of SROC curve was 0.79 (95% CI: 0.75-0.82) (Figure 3a). The corresponding values of PCT to differentiate Gram-negative BSI from Gram-positive BSI were 0.73, 0.70 and 0.77, respectively (Figure 2b, 3b). The pooled parameters calculated over studies examining serum PCT to diagnose Gram-negative BSI were listed in Table III.

Heterogeneity Examination and Publication Bias of the Studies

High I^2 values of sensitivity and specificity suggest substantial heterogeneity among included studies (Figure 2, all $p < 0.05$), so we performed a meta-regression to investigate the possible sources of heterogeneity. The results of meta-regression based on 7 covariates were summarized in Table IV, which indicated none of them was the source of heterogeneity (all $p > 0.05$). The slope coefficient of Deeks' funnel plot asymmetry test was associated with p-values of 0.07 and 0.53, suggesting symmetry in the data and low likelihood of such bias (Figure 4).

Discussion

The early and accurate diagnosis of Gram-negative BSI was associated with better clinical outcome[33-35]. Serum PCT is biomarker for diagnosing systematic bacterial infection[36], while its overall accuracy in differential diagnosis of Gram-negative BSI remains unclear. In our study, we summarized the overall diagnostic performance of PCT for Gram-negative BSI through a meta-analysis, and our results suggested that the value of PCT in diagnosing Gram-negative BSI may be limited.

The sensitivity and specificity of PCT in diagnosing Gram-negative BSI were 0.73 and 0.74, respectively, suggesting a relatively high rate of missed diagnoses (27%) and misdiagnoses

Table I. Characteristics of included studies using procalcitonin to diagnose Gram-negative bloodstream infection.

Author (Ref)	Year	Country	Episodes	Study population/ Setting	Study design	Assay	Cutoff (ng/mL)	Cases	Controls	TP	FP	FN	TN	QUADAS
Engel[20]	1999	Germany	103	Oncology	Prospective	IFA	1.1	12	91	7	5	5	86	10
Prat[21]	2008	Spain	57	Hematologic malignancy	Prospective	IFA	0.3	6	51	6	25	0	26	10
Charles[22]	2008	France	97	ICU	Retrospective	IFA	16	52	45	39	8	13	37	10
Koivula[23]	2011	Finland	90	Hematology	Prospective	ICA	0.5	10	80	7	18	3	62	11
Brodska[24]	2013	Czech Republic	166	ICU	Retrospective	ECLIA	0.015	78	88	59	11	19	77	9
Oussalah[25]	2015	France	2042	Multi-departments	Cross-sectional	IFA	0.6	1067	975	820	363	247	612	12
Guo[26]	2015	China	262	Multi-departments	Retrospective	CLEI	3.39	65	197	52	57	13	140	10
Leli[27]	2015	Italy	562	Multi-departments	Prospective	IFA	10.8	345	217	207	39	138	178	12
Vincenzi[28]	2016	Italy	181	Medical Oncology	Retrospective	IFA	1.52	130	51	94	15	36	36	10
Yan[29]	2016	China	456	ICU, ED	Retrospective	IFA	0.495	254	202	184	99	70	103	9
Li[30]	2016	China	298	Multi-departments	Retrospective	IFA	2.44	158	140	122	44	36	96	9
Stoma[31]	2017	Belarus	52	BMT and ICU	Prospective	IFA	1.5	30	22	19	3	11	19	11
Liu[32]	2017	China	147	Multi-departments	Retrospective	ECLIA	2.1	91	56	79	30	12	26	9

ICU: intensive care unit; ED: Emergency Department; BMT: Bone Marrow Transplantation; IFA: immunofluorescent assay; ICA, immunochromatographic assay; ECLIA: electrochemiluminescence immunoassay; CLEI, chemiluminescent enzyme immunoassay; NA: not available; TP: True positive; FP: False positive; FN: False negative; TN: true negative; QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

Table II. Characteristics of included studies using procalcitonin to differentiate gram-negative bloodstream infection from Gram-positive bloodstream infection.

Author (Ref)	Year	Country	Episodes	Study population/ Setting	Study design	Assay	Cutoff (ng/mL)	Cases	Controls	TP	FP	FN	TN	QUADAS
Engel[20]	1999	Germany	33	Oncology	Prospective	IFA	10	12	21	6	4	6	17	10
Charles[22]	2008	France	97	ICU	Retrospective	IFA	16	52	45	39	8	13	37	10
Oussalah[25]	2015	France	2042	Multi-departments	Cross-sectional	IFA	0.6	1067	975	821	363	246	612	12
Guo[26]	2015	China	122	Multi-departments	Retrospective	CLEI	6.47	65	57	48	11	17	46	10
Lel[27]	2015	Italy	562	Multi-departments	Prospective	IFA	10.8	345	217	207	39	138	178	12
Yan[29]	2016	China	456	ICU, ED	Retrospective	IFA	0.495	254	202	184	99	70	103	9
Li[30]	2016	China	298	Multi-departments	Retrospective	IFA	2.44	158	140	122	44	36	96	9
Liu[32]	2017	China	147	Multi-departments	Retrospective	ECLIA	2.1	91	56	79	30	12	26	9

ICU: intensive care unit; ED: Emergency Department; IFA: immunofluorescent assay; CLEI, chemiluminescent enzyme immunoassay; NA: not available; ECLIA: electrochemiluminescence immunoassay; TP: True positive; FP: False positive; FN: False negative; TN: true negative; QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

(26%). PLR > 10 and NLR < 0.1 are considered as strong indicators to rule in or rule out a diagnostic test, respectively. In our meta-analysis, PLR was 2.77 and NLR was 0.37, suggesting relatively low ability to diagnose Gram-negative BSI, consistent with the AUC in SROC analysis was 0.79. Additionally, it appears the PCT is not robust enough on its own to diagnose Gram-negative BSI with a low pooled DOR of 7.59, suggesting that the diagnostic accuracy of PCT combination with other biomarkers, such as CRP[37,38], presepsin[37,38], interleukin-1 receptor 2[15], should be evaluated. It is reported that serial evaluations of PCT seem to be more accurate to diagnose BSI in cancer patients[39], which suggested that further work might aim to determine whether continuously monitoring serum PCT level increases the sensitivity and specificity of diagnosing Gram-negative BSI or not. Also, diagnostic performance of PCT for BSI in immunocompromised/neutropenic patients was lower than that in patients without immunosuppression[31,36]. Studies in different populations (such as patients in intensive care unit, cancer patients, and transplant patients, etc.) should be performed to get a definite conclusion.

It is reported that Gram-negative bacteria and Gram-positive bacteria may activate different Toll-like receptor signaling pathways, resulting in the production of distinct pro-inflammatory cytokines that stimulate PCT release. Gram-negative bacteria can produce endotoxins that can also be released upon cell death, leading to persistently high levels of PCT[40]. Our meta-analysis found that the diagnostic performance of PCT in discriminating Gram-negative BSI from Gram-positive BSI is also not so good, with pooled sensitivity of 0.73, specificity of 0.70, and AUC of 0.77.

Our study has identified significant heterogeneity among included studies, while we didn't find the source of heterogeneity through a meta-regression analysis regarding the study site, sample size, study population/setting, study design, assay method, serum PCT cut-off value, and QUADAS score. Whereas, it is needed to pay attention to that cut-off value of PCT in diagnosing Gram-negative BSI ranged from 0.015 ng/mL to 10.8 ng/mL, such variation in cut-off value partly reflects differences in study context: assay method[41], study populations[31], bacterial species[29], etc. Although we didn't identify cut-off value of PCT as a source of heterogeneity in the meta-regression analysis,

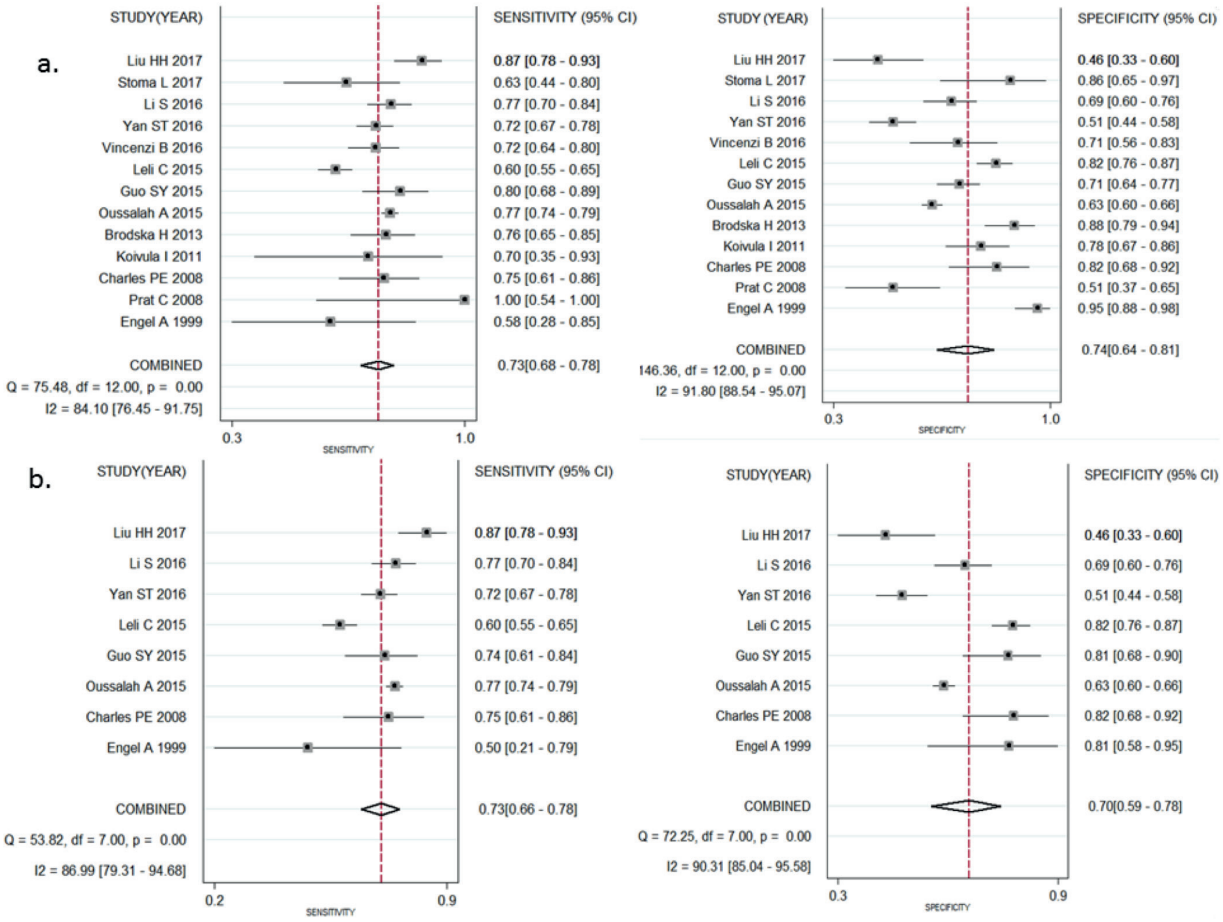

Figure 2. Forest plots of sensitivity and specificity for diagnosing Gram-negative bloodstream infection (BSI) using procalcitonin. ***A,*** Diagnosing Gram-negative BSI; ***B,*** Differentiating Gram-negative BSI from Gram-positive BSI.

specific cut-off values for different populations and bacterial species might give more useful information for clinical practice.

The findings of this meta-analysis should be interpreted with caution due to a few limitations. First, with our strict inclusion criteria, the number of included studies is limited. Second, we omitted unpublished studies and studies not indexed in our set of databases, which may bias for our results.

Conclusions

Our present meta-analysis suggests that PCT may play a limited role in diagnosing Gram-negative BSI. Further prospective work related on PCT combination with other biomarkers, dynamic evaluation of PCT, and PCT variation in different populations and species, might obtain a more definite conclusion.

Table III. Accuracy of procalcitonin for diagnosing Gram-negative bloodstream infection (BSI).

Aims	No. of studies	Cases	Controls	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
1	13	2298	2215	0.79 (0.75-0.82)	0.73 (0.68-0.78)	0.74 (0.64-0.81)	2.77 (2.07-3.70)	0.37 (0.31-0.42)	7.59 (5.31-10.85)
2	8	2044	1713	0.77 (0.73-0.81)	0.73 (0.66-0.78)	0.70 (0.59-0.78)	2.40 (1.83-3.15)	0.39 (0.33-0.46)	6.15 (4.40-8.60)

Aim 1: diagnosing Gram-negative BSI; Aim 2: differentiating Gram-negative BSI from Gram-positive BSI; AUC, Area under the curve; CI: Confidential interval; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic odds ratio.

Table IV. Meta-regression of potential heterogeneity among the included studies.

Covariates	No. of studies	Coefficient	SE	RDOR (95% CI)	*p*-value
Country					
European	9	0.48	0.37	1.61 (0.57-4.54)	0.27
Asian	4				
Sample size					
< 100	4	-0.63	0.44	0.53 (0.16-1.81)	0.23
≥ 100	9				
Study population/setting					
Multi-departments	5	0.35	0.25	1.42 (0.71-2.83)	0.23
Other	8				
Study design					
Prospective	5	-0.79	0.35	0.45 (0.17-1.21)	0.09
Other	8				
Assay					
IFA	9	-0.65	0.24	0.52 (0.27-1.03)	0.06
Other	4				
Cut-off					
< 1.0 ng/mL	5	0.26	0.25	1.29 (0.65-2.56)	0.36
≥ 1 ng/mL	8				
QUADAS score					
< 10	4	-0.29	0.33	0.75 (0.30-1.87)	0.43
≥ 10	9				

SE: Standard error; RDOR: Relative diagnostic odds ratio; CI: Confidential interval; QUADAS: Quality assessment for diagnostic accuracy studies.

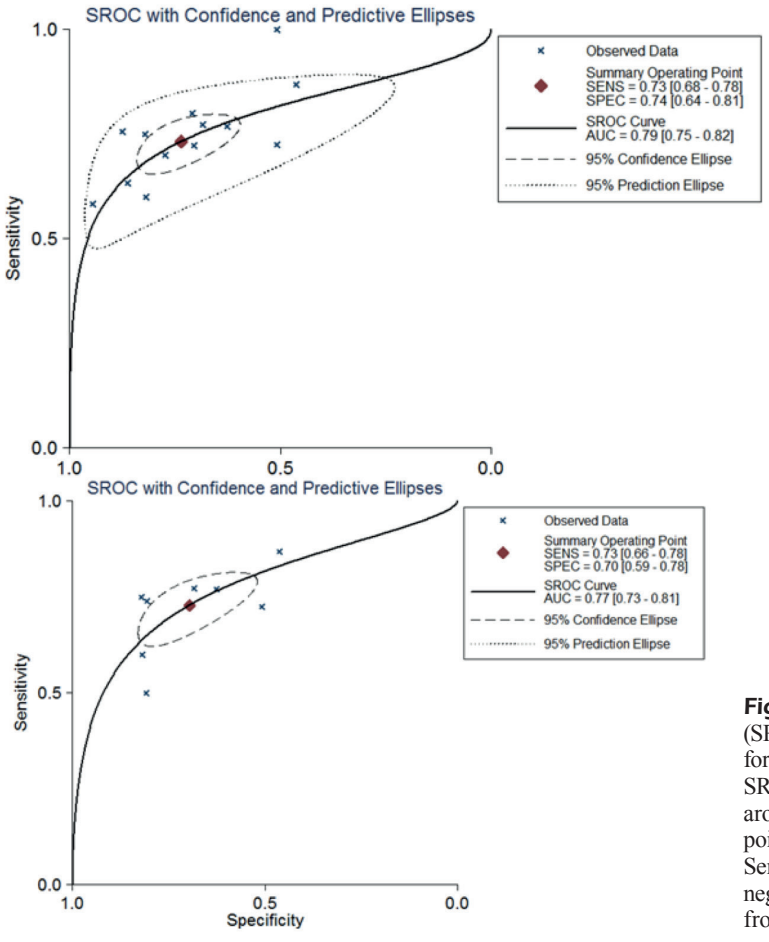

Figure 3. Summary receiver operating characteristic (SROC) curve for procalcitonin as a diagnostic test for Gram-negative bloodstream infection (BSI). The SROC curves with confidence and prediction regions around mean operating sensitivity and specificity point analyses. AUC, area under the curve; SENS, Sensitivity; SPEC, Specificity. ***A,*** Diagnosing Gram-negative BSI; ***B,*** Differentiating Gram-negative BSI from Gram-positive BSI.

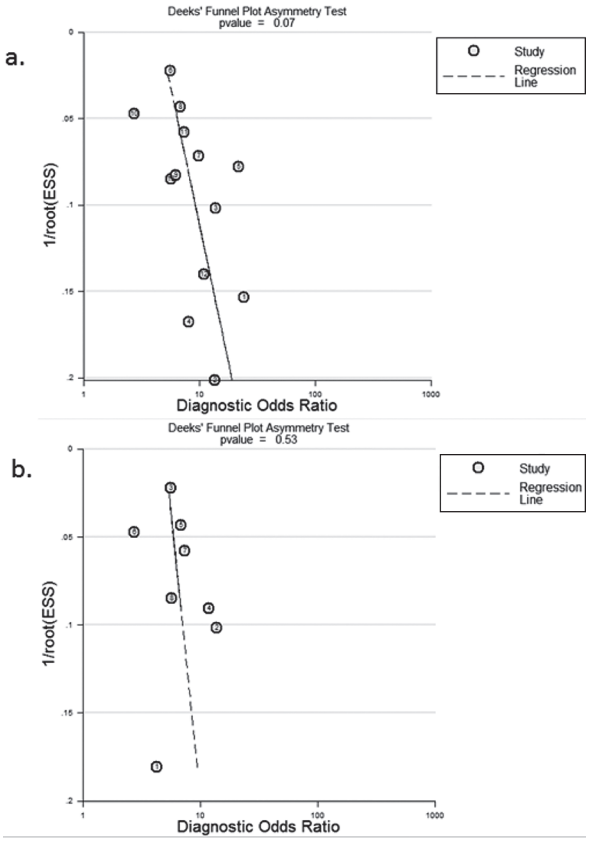

Figure 4. Deek's funnel plot to assess the likelihood of publication bias. The statistically non-significant *p*-value > 0.05 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias. ***A,*** Diagnosing Gram-negative BSI; ***B,*** Differentiating Gram-negative BSI from Gram-positive BSI.

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Conflict of Interest

No conflict of interests to disclose.

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