Original Contribution

The neutrophil-lymphocyte count ratio as a diagnostic marker for bacteraemia: A systematic review and meta-analysis

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ARTICLE INFO

ABSTRACT

Background: Bacteraemia is a common cause of increased morbidity and mortality in critically ill patients, but its early diagnosis and identification are complicated. The neutrophil-lymphocyte count ratio (NLCR) has been suggested as a useful indicator for the diagnosis of bacteraemia. We performed this meta-analysis to investigate the diagnostic accuracy of the NLCR for bacteraemia.
Methods: We searched the PubMed, Embase, Web of Science, and Cochrane Library databases for this meta-analysis. We calculated individual and pooled sensitivities and specificities. I^2 statistics and Cochran's Q test were used to evaluate heterogeneity, and the cause of heterogeneity was explored with sensitivity analyses.
Results: In total, 8 of 1086 eligible articles were included in the present meta-analysis. The pooled analyses revealed that the diagnostic accuracy of the NLCR in terms of its bacteraemia sensitivity was 0.723 [95% CI: 0.660, 0.777], and its specificity was 0.596 [95% CI: 0.556, 0.634]. The area under the summary receiver operating characteristic curve was 0.69 [95% CI 0.65–0.73].
Conclusion: The NLCR is an easy-to-collect marker for bacteraemia. However, the NLCR is inadequate, and only a combination of multiple biomarkers will improve its diagnostic accuracy for bacteraemia.

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1. Introduction

Bacteraemia is a life-threatening disease with high morbidity and mortality that requires early rapid identification and prompt antibiotic treatment [1-3]. Biomarkers can play an important role in this process, because they can indicate the presence, absence, or severity of the disease. Conventional inflammatory markers, including the white blood cell (WBC) count, neutrophil count, neutrophilic granulocyte percentage, C-reactive protein (CRP) level, and procalcitonin (PCT) level have limited evaluation potential and are expensive options for the assessment of bacteraemia [4-6]. Blood culture, which is considered the "gold standard", is the traditional approach for the detection of bacteraemia, but this method is time consuming [7]. In addition, the sensitivity of blood culture decreases significantly if fastidious or slow-growing pathogens are cultured or if antibiotic therapy has been instituted prior to blood sampling [7,8]. Therefore, other biochemical

markers are needed in addition to blood culture to evaluate bacteraemia.

Neutrophils and lymphocytes are the two major inflammatory cell types in the body. Currently, the neutrophil-lymphocyte count ratio (NLCR) is used in a wide range of applications for the diagnosis, treatment, and prognostic evaluation of inflammation-related diseases, such as malignant tumors, cardiovascular diseases, renal diseases, and inflammatory bowel diseases. Recently, several studies have assessed the value of the NLCR for the diagnosis of bacteraemia. The NLCR was also recently described a marker for the diagnosis of bacterial infections in young infants [9]. Some studies have described increased neutrophil production and lymphocyte apoptosis, which are the causes of the elevated NLCR during inflammatory stress [10]. Neutrophils and lymphopenias have been detected in patients with systemic inflammatory response syndrome. Additionally, the inflammatory response results in the destruction of cells at the site of inflammation, and thus, apoptosis may promote lymphopenia [11]. Therefore, the NLCR was proven to be a simple infection marker for predicting bacteraemia upon hospital admission [12]. A previous study considered the NLCR a rapid indicator of the inflammatory response in critically ill patients [13]. We conducted this meta-analysis to assess the diagnostic accuracy

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of the NLCR for bacteraemia and to assist physicians with clinical decision-making.

2. Methods

This meta-analysis followed the relevant guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA). An ethics statement was not required.

2.1. Literature search

We prepared a protocol before undertaking this systematic review and meta-analysis. A systemic overall search was conducted in the PubMed, Web of Science, Embase, and Cochrane Library databases to identify studies evaluating the diagnostic accuracy of the NLCR for sepsis published until March 2018 without any language restrictions. The following search terms were used ("bacteraemia"OR "infection" OR "sepsis" OR "critically ill patients") AND ("neutrophil-to-lymphocyte" OR "neutrophil/lymphocyte ratio" OR "neutrophil-lymphocyte count ratio" OR "neutrophil-lymphocyte ratio" OR "NLCR"). The references of the included articles were also checked to identify additional studies.

2.2. Study selection

The original data were independently collected from the retrieved studies by two investigators (JWJ and RL) using the same standards. Any disagreement was resolved through discussion, and if no agreement was reached, then a third reviewer (YQW) made the final decision. The studies were included if they met all of the following

criteria: the study evaluated the diagnostic accuracy of the NLCR for bacteraemia in adult patients (≥18 years old); blood culture was performed as a diagnostic criterion or control measure; and the sensitivity and specificity of the data were provided or could be calculated. Reviews, meetings, abstracts, letters, duplicated studies, studies without a 2 × 2 table, studies not related to the diagnostic value, and studies with pediatric patients were excluded.

2.3. Procedures

Two investigators independently extracted data from the retrieved studies using a standard form. Differences were resolved by a third author. The data included the year of publication, study design, population setting, cut-off values used, and details of the NLCR assays, including true positives (TP), true negatives (TN), false positives (FP), false negatives (FN), sensitivity (SEN), specificity (SPE), and area under the summary receiver operating characteristic (SROC) curve (AUC) for an early bacteraemia diagnosis.

The retrieved studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist [14]. We used the guidelines to score each item of the checklist in this meta-analysis.

2.4. Statistical analysis

Review Manager, version 5.1.3 (RevMan; the Cochrane Collaboration, Oxford, UK), and STATA, version 14.0 (Stata Corporation, College Station, TX, USA) were used to perform the statistical analyses. A bivariate random effects regression model was used to determine the SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio
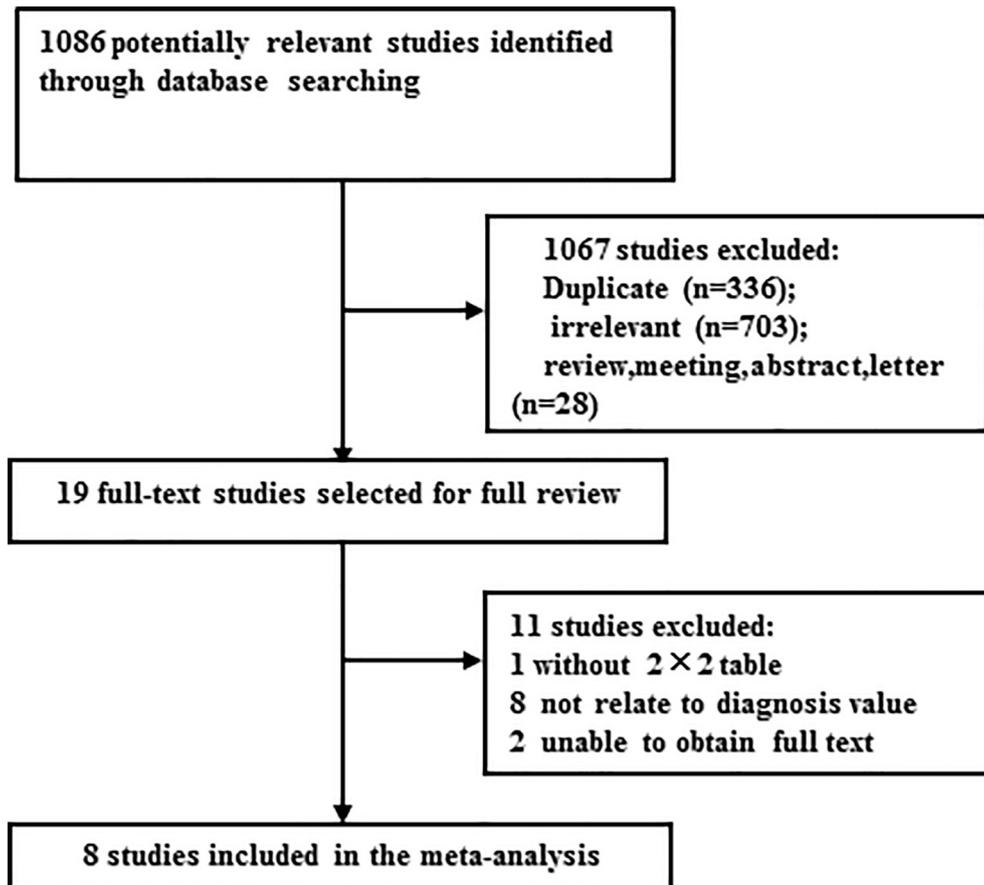

Fig. 1. Flow chart depicting the study selection procedure.

(NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (95% CIs). Then, we constructed an SROC curve by plotting individual and summary points for SEN and SPE to assess the diagnostic accuracy of the NLCR [15,16]. All statistical tests were bilateral, with statistical significance considered for differences with $p < 0.05$. Heterogeneity was calculated using Cochran's Q test and the I^2 inconsistency test. Cochran's Q test indicated heterogeneity at $p < 0.10$, and an $I^2 > 50\%$ was considered to indicate significant heterogeneity. A random effects method (Der Simonian-Laird method) was used to generate the pooled mean differences and 95% CIs. In addition, sensitivity analyses were conducted to investigate potential sources of heterogeneity. Publication bias was evaluated using a Deek funnel plot, and a Fagan nomogram was used to calculate the post-test probability (PTP).

3. Results

3.1. Literature search and study characteristics

The literature search found a total of 1086 articles, 8 of which [12,17-23] satisfied the inclusion criteria. After examining their titles and abstracts, we excluded 1067 studies. After reviewing the full contents, we excluded another 11 studies, resulting in the inclusion of 8 eligible studies (Fig. 1). The main reasons for excluding studies were that their sensitivity and specificity data could not be retrieved, a 2 × 2 table was not reconstructed, or they were not diagnostic studies. All studies were published between 2010 and 2018, and a total of 7095 patients were included in this meta-analysis. Six studies [12,17-19,21,23] were performed in the Emergency Department, and the other two studies [20,22] had unspecified patient sources. The cut-off values for the NLCR differed between studies. The study characteristics are shown in Table 1.

3.2. Study quality and publication bias

The QUADAS-2 tool was used to assess the risk of bias in the 8 [12,17-23] included studies (Fig. 2). The results revealed that 1 study [21] had a high risk of bias according to the reference standard. The Deek funnel plot is shown in Fig. 3. Significant publication bias was observed (p < 0.001).

3.3. Diagnostic value of the NLCR for the diagnosis of bacteraemia

The following pooled parameters were calculated for all 8 studies that examined the value of the NLCR for the diagnosis of bacteraemia. The overall I^2 value for the bivariate model was 91.51% (95% CI 83.52–99.51), indicating significant heterogeneity. The pooled SEN and SPE values were 0.723 (95% CI 0.660, 0.777) and 0.596 (95% CI 0.556, 0.634), respectively (Fig. 4). The AUC was 0.69 (95% CI 0.65, 0.73). (Fig. 5). Fagan's nomogram for the likelihood ratios indicated that utilizing the NLCR to diagnose bacteraemia increased the post-probability to 64% when the results were positive and reduced the post-probability to 32% when the results were negative (Fig. 6).

We concluded that the proportion of heterogeneity was most likely due to a threshold effect at 0.84 (tested with the STATA MIDAS module). However, no evidence of a threshold effect was found. Substantial heterogeneity was observed in both the SEN (Cochran's Q = 22.98, p < 0.001, $I^2 = 69.54\%$) and SPE (Cochran's Q = 50.84, p < 0.001, $I^2 = 86.23\%$) assessments among all included studies [24]. A proportion of the heterogeneity probably was caused by population differences, small sample size bias, and different cut-off values. Therefore, we performed sensitivity analysis to explore the sources of potential heterogeneity in SEN and SPE (Table 2). Due to the use of different cut-off values in the studies, we calculated the SEN and SPE of 6 studies with a cut-off value of 10.0. However the subsequently pooled performance indices were not significantly different; the SEN, SPE, PLR, NLR, and DOR were

Table 1
Characteristics of the included studies.

Author	Year	Population	Definition of bacteraemia	No. of patients/female/no. of patients with bacteremia	Mean age (years)	Time of markers detection	Setting	Cut off	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
De Jager	2010	Suspected community-acquired bacteremia	BCP	746/96/85	66 (18–96)	During the observation period	ED	10	71	34	21	58	0.77[0.67,0.85]	0.63[0.52,0.73]
Loonen	2014	With 2 SIRS criteria	BCP	140/NR/27	68.9 (51.6–86.2)	During the observation period	ED	10	23	65	4	68	0.85[0.66,0.96]	0.51[0.42,0.60]
Laukemann	2015	Suspected infection	BCP	1083/460/104	67 (53–78)	At enrollment	ED	10	73	374	28	596	0.72[0.62,0.81]	0.61[0.58,0.65]
Lowsby	2015	Suspected infection	BCP	2002/1001/270	66	during the study period	ED	10	270	1080	116	1432	0.70[0.65,0.74]	0.57[0.55,0.59]
Zhang HB	2016	With SIRS criteria and suspected or documented infection	BCP	120/47/60	62.6 (47.7–77.5)	NR	NR	9.37	49	22	11	38	0.82[0.70,0.90]	0.63[0.50,0.75]
Pan	2017	Suspicion of infection	BCP	1807/916/230	61 (47–72)	NR	NR	10	141	529	89	1031	0.61[0.55,0.68]	0.66[0.64,0.68]
Ljungstorm	2017	Suspicion of a community-onset sepsis	BCP	1572/697/197	71 (58–81)	At enrollment	ED	10	61	281	16	352	0.79[0.68,0.88]	0.56[0.52,0.60]
Camilo Vallejo	2017	BCP and BCN	BCP	162/65/81	68(50.9–85.1)	NR	ED	13.2	51	23	30	58	0.63[0.52,0.73]	0.72[0.60,0.81]

NR not report, BCP blood culture positive, BCN blood culture negative, TP true positive, FP false positive, FN false negative, TN true negative, ED Emergency department,
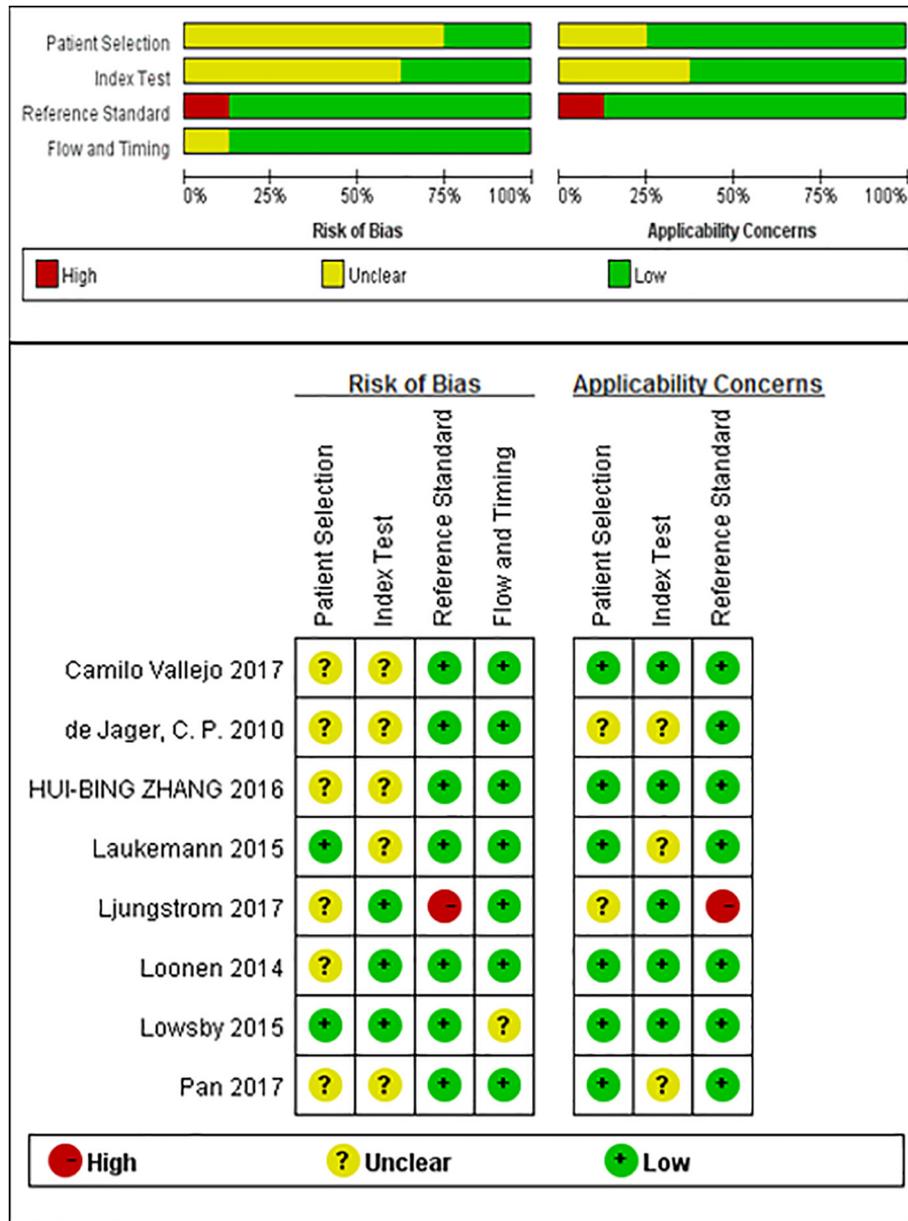
Fig. 2. Summary of the methodological quality of the studies according to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria.

0.721 (95% CI 0.652, 0.780), 0.586 (95% CI 0.545, 0.626), 1.741 (95% CI 1.594, 1.902), 0.476 (95% CI 0.390, 0.582), and 3.654 (95% CI 2.804, 4.763), respectively. Six of the included studies comprising 5168 patients were performed in the emergency care unit, and 2 studies did not specify patient sources. After omitting the latter two studies, the heterogeneity of the pooled DOR decreased from high to low, and the I^2 index decreased from 91.54% to 15.84%. The pooled SEN, SPE PLR, NLR, and DOR were 0.727 (95% CI 0.666, 0.781), 0.585 (95% CI 0.544, 0.626), 1.753 (95% CI 1.593, 1.929), 0.466 (95% CI 0.385, 0.565), and 3.760 (95% CI 2.886, 4.899), respectively. The estimated AUC was 0.69 (95% CI 0.65, 0.73). A subsequent evaluation should possibly be conducted using subgroup analyses to rule out the possibility of small sample size bias. We excluded three small-sized studies (<200 patients) [17,20,23] and calculated the SEN and SPE of the five remaining studies with relatively large numbers of patients (≥200) [12,18,19,21,22]. The SEN, SPE, PLR, NLR, and DOR were 0.702 (95% CI 0.642, 0.755), 0.597 (95% CI 0.559, 0.635), 1.742 (95% CI 1.604, 1.892), 0.499 (95% CI 0.424, 0.588), and 3.490 (95% CI 2.793, 4.464), respectively.

4. Discussion

Bacteraemia is a common cause of increased morbidity and mortality in critically ill patients, but early diagnosis and accurate identification are difficult. A series of studies explored the association between the NLCR and the diagnosis of bacteraemia. However, based on their results, the current value of the NLCR for the diagnosis of bacteraemia is uncertain. The NLCR is a relative bacteraemia biomarker with no prior meta-analysis of its value. Our meta-analysis assessed its diagnostic accuracy for bacteraemia in 8 studies including 7095 cases, which is the first systematic study on this topic. The results indicated that the NLCR was not superior at predicting bacteraemia over a single biological marker (AUC = 0.69, SEN = 0.723, and SPE = 0.59).

An ideal biological marker should be able to distinguish among bacterial, viral, and fungal infections as well as between systemic sepsis and local infection. Currently, approximately 150 biomarkers have been used to evaluate sepsis in the clinic [29]. In a meta-analysis from 2015, including 58 studies published between 1999 and 2014, Hoeboer and
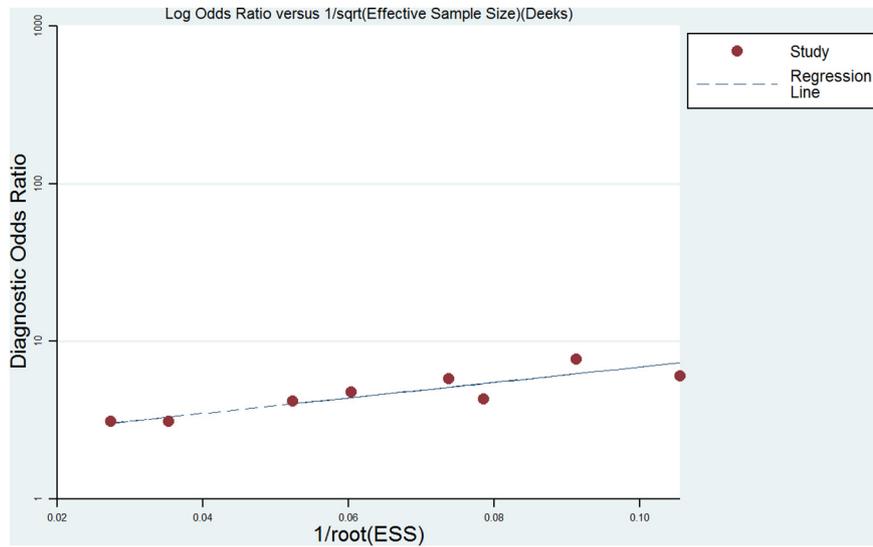
Fig. 3. Deek funnel plot asymmetry test to detect publication bias.

colleagues concluded that PCT is able to diagnosis bacteraemia, and the SROC curve was 0.79. He considered that low PCT levels can be used to exclude the presence of bacteraemia [30]. Qu and colleagues assessed the diagnostic value of PCT, CRP, interleukin-6 (IL-6) and serum amyloid A (SAA) levels for bacterial infections in febrile patients. The AUC values

for PCT, CRP, IL-6 and SAA were 0.804, 0.693, 0.658 and 0.687, respectively [31]. While some biomarkers for bacteraemia showed moderate diagnostic value, the quality, methods and sample size limitations that may affect their judgment diagnostic value [32]. Sepsis or bacteraemia is a pathophysiological process and a nonspecific syndrome that is too
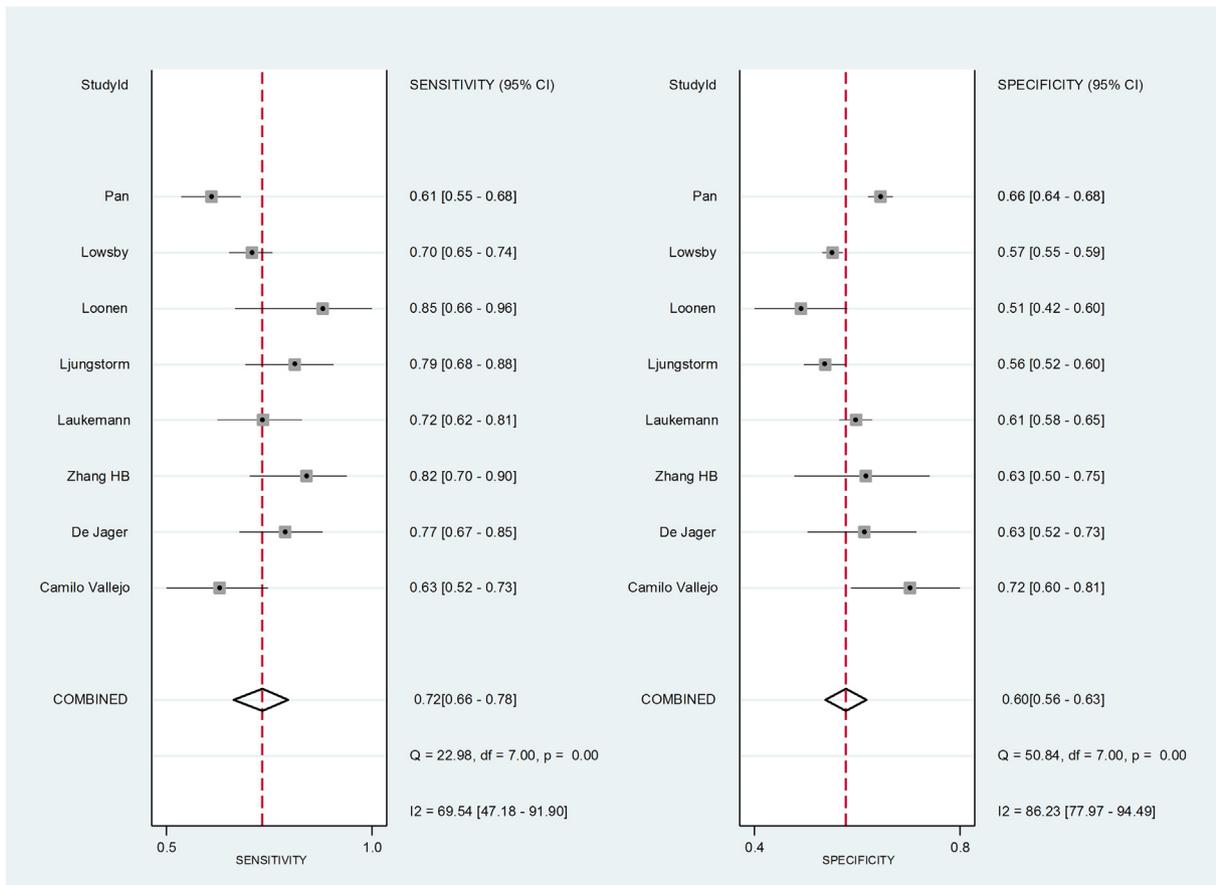

Fig. 4. Forest plot of the sensitivity and specificity of the NLCR for the diagnosis of bacteraemia.
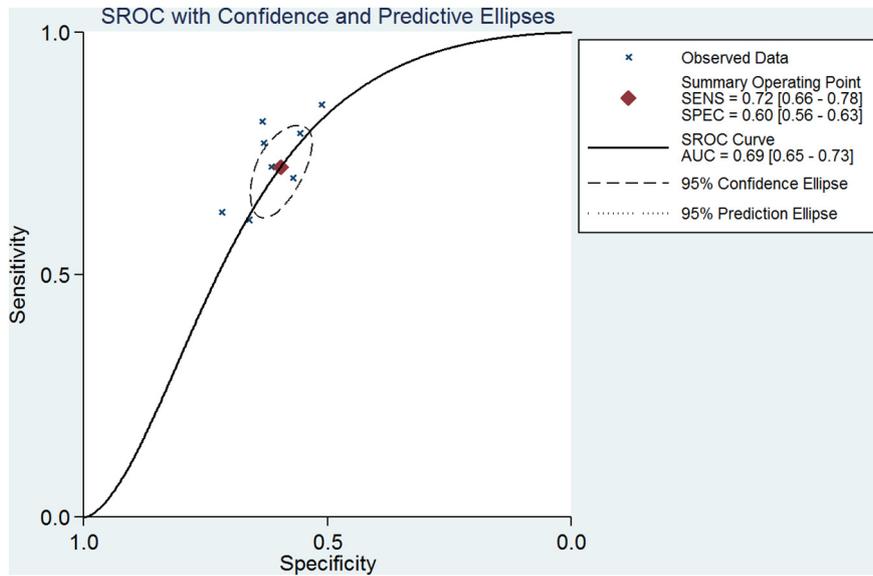
Fig. 5. Summary receiver operating characteristic graph for the included studies. AUC = area under curve, SEN = sensitivity, SPE = specificity.

complex to be explained by a single description, and thus, multiple combinations of biomarkers are needed to enhance clinical diagnosis in the ED. According to a previous study, the combination of lactate

Fig. 6. Fagan nomogram of NLCR for the diagnosis of bacteremia.

(Lac), PCT, The sequential organ failure assessment score (SOFA), and the NLCR is a useful tool for the early diagnosis of sepsis [34]. Studies showed that the NLCR and the currently available organ failure scoring systems, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) and SOFA, had weak but significant relationships, which could be useful for the assessment of severity in critical ill patients [35].

Positive blood cultures have been used as the gold standard to diagnosis bacteraemia. However, blood cultures are prone to errors. In particular, the relationship between the amount of blood cultured and the timing of blood collection and the start of antibiotic treatment are important factors [38]. When blood samples are collected after antibiotic treatment has begun, their sensitivity decreases significantly [7]. The NLCR is a potentially meaningful parameter for prediction of bacteraemia in patients suspected of having a community-acquired infection. A study showed that the NLCR measured after admission to the ICU was associated with short- and long-term mortality in critically ill patients [39]. Discussing the link between this marker and critical illness should be the focus of our future research.

Furthermore, this meta-analysis has limitations. First, this meta-analysis included only 8 studies and the number of included studies was small. Second, sensitivity analyses were not performed to reduce and interpret heterogeneity. Third, variations in the sampling times across studies may have affected the results, leading to bias in this analysis. Fourth, publication bias is the most common limitation of any systematic review. Unpublished data were not discovered or used. Fifth, we included some small sample studies, which may affect consistency of studies and cause bias. Finally, research addressing the diagnostic accuracy of the examined biomarker in patients of other ethnicities and from other regions may be required [28].

5. Conclusions

The NLCR is an easy-to-collect and inexpensive diagnostic marker for bacteraemia. However, the NLCR cannot be recommended as the only definitive test for the diagnosis of sepsis, due to its low sensitivity and specificity. It must be evaluated in the context of a detailed medical history, physical examination, and viable microbial assessment. In addition, reassessment should be continued during the disease course. Only the use of a combination of multiple biomarkers will improve the diagnostic accuracy of bacteraemia in a clinical setting.
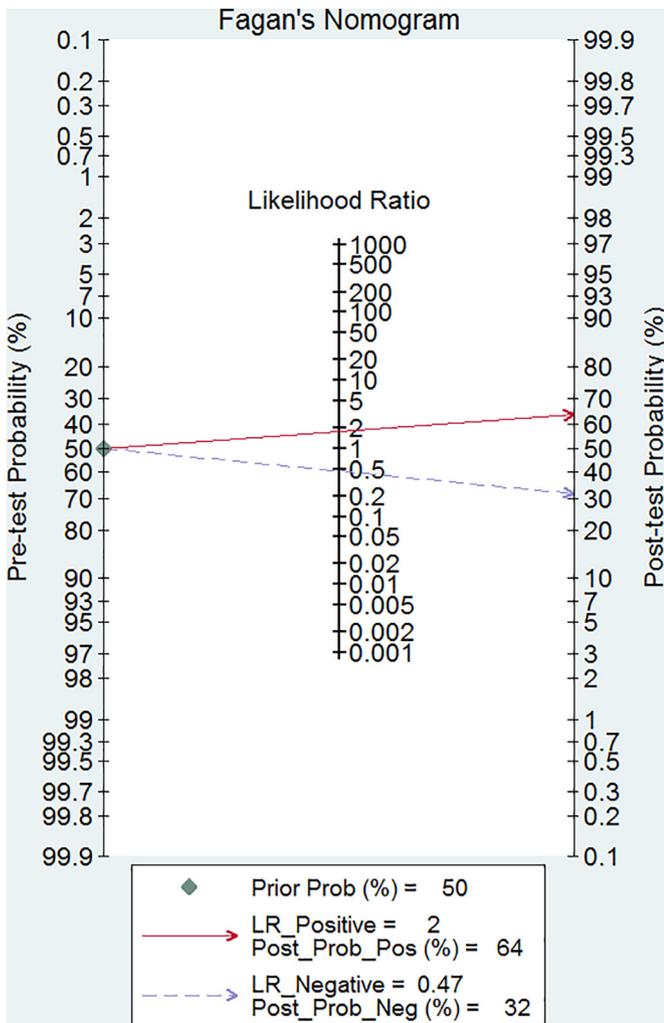
Table 2
Results of sensitivity analysis.

	Categories	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUC (95% CI)	DOR (95% CI)	Test for heterogeneity (I2)	Deek's funnel test (p value)
All studies		8	0.723[0.660,0.777]	0.596[0.556,0.634]	1788[1.642,1.946]	0.466[0.387,0.560]	0.69[0.65,0.73]	3.839[3.007,4.901]	91.51	<0.001
Sensitivity analysis	Patients admitted in ED	6	0.727[0.666,0.781]	0.585[0.544,0.626]	1.753[1.593,1.929]	0.466[0.385,0.565]	0.69[0.65,0.73]	3.760[2.886,4.899]	15.84	0.152
	Cut-off value of 10.0	6	0.721[0.652,0.780]	0.586[0.545,0.626]	1.741[1.594,1.902]	0.476[0.390,0.582]	0.68[0.64,0.72]	3.654[2.804,4.763]	90.65	<0.001
	Relatively large sample[a]	5	0.702 [0.642, 0.755]	0.597 [0.559, 0.635]	1.742 [1.604, 1.892]	0.499 [0.424, 0.588]	0.69 [0.65–0.73]	3.490 [2.791, 4.364]	88.53	<0.001

ED Emergency department, PLR Positive likelihood ratio, NLR Negative likelihood ratio, DOR Diagnostic odds ratio, AUC = area under curve,
[a] Number of patients ≥ 200.

Abbreviations

NLCR	Neutrophil-lymphocyte count ratio
SROC	the summary receiver-operating characteristic
WBC	white blood cell count
CRP	C-reactive protein
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TP	true positives
FP	false positives
FN	false negatives
TN	true negatives
PTP	post-test probability
SEN	sensitivity
SPE	specificity
PLR	positive likelihood ratio
NLR	negative likelihood ratio
DOR	diagnostic odds ratio

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available in the PubMed, Web of Science, EMBASE and the Cochrane Library databases.

Competing interests

The authors have no competing interests to declare.

Authors' contributions

JWJ and RL contributed equally to this work. JWJ participated in the study design, selected trials, extracted data, performed the statistical analyses, and drafted the manuscript. RL participated in the study design, selected trials, performed the statistical analyses, and drafted the manuscript. XY helped draft the manuscript and assessed the risk of bias of the trials. RY helped draft the manuscript and assisted with interpretation of the data. HX contributed to data collection. ZM participated in manuscript preparation. YQW collected the data, performed the statistical analyses, and supervised the study. All authors read and approved the final manuscript.

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