

BMJ Open Accuracy of the neutrophil-to-lymphocyte ratio for the diagnosis of neonatal sepsis: a systematic review and meta-analysis

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ABSTRACT

Objectives The purpose of this study was systematically and quantitatively to assess the value of the neutrophil-to-lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.

Design Systematic review and meta-analysis.

Methods Eight major databases, including The Cochrane, PubMed, Embase, Web of Science, CNKI, Wanfang, China Biomedical Literature Database and VIP Database, were systematically searched for NLR diagnoses of neonatal sepsis from inception to June 2022. Two investigators independently conducted the literature search, screening, data extraction and quality evaluation with the Quality Assessment of Diagnostic Accuracy Studies-2 checklist. Statistical analysis was performed using Review Manager V.5.3, Stata V.16.0, R (V.3.6.0) and Meta-DISC V.1.4.

Results A total of 14 studies comprising 1499 newborns were included in this meta-analysis. With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity of the NLR in the diagnosis of neonatal sepsis was 0.74 (95% CI: 0.61 to 0.83), the pooled specificity was 0.88 (95% CI: 0.73 to 0.95), the positive likelihood ratio (LR⁺) was 6.35 (95% CI: 2.6 to 15.47), the negative likelihood ratio (LR⁻) was 0.30 (95% CI: 0.19 to 0.46), the diagnostic OR (DOR) was 12.88 (95% CI: 4.47 to 37.08), area under the curve (AUC) was 0.87 (95% CI: 0.84 to 0.89). In the subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.75 (95% CI: 0.47 to 0.91), the pooled specificity was 0.99 (95% CI: 0.88 to 1.00), the LR⁺ was 63.3 (95% CI: 5.7 to 696.8), the LR⁻ was 0.26 (95% CI: 0.10 to 0.63), the DOR was 247 (95% CI: 16 to 3785) and the AUC was 0.97 (95% CI: 0.95 to 0.98).

Conclusions Our findings suggest that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined with other laboratory tests and specific clinical manifestations.

BACKGROUND

Neonatal sepsis is a systemic inflammatory response syndrome caused by a bacterial infection in the neonatal stage. The clinical manifestations gradually surface in the whole body of the inflammatory response and finally progress into organ failure, leading to death.¹ Studies have shown that the morbidity

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We conducted a comprehensive search of each literature database and formulated detailed inclusion and ranking criteria to ensure the quantity and quality of the included literature.
- ⇒ Subgroup analyses were performed according to sepsis type, study area and cut-off value as described in the methodology section of this study.
- ⇒ Our included articles lack more multicentre and large sample studies.
- ⇒ There may be other clinical and statistical heterogeneity in the included studies.

of neonatal sepsis is 1%–20% in newborns and is also the third highest after premature delivery and neonatal encephalopathy (perinatal asphyxia and trauma).² At present, neonatal sepsis is faced with insufficient diagnostic methods, resulting in the inability to guide clinical treatment in a timely manner, thereby affecting its therapeutic effect.

According to a survey, the global mortality rate of neonatal sepsis reached 1.0%–5.0%.³ Early and precise identification of neonatal sepsis is crucial for slowing the progression of the disease and decreasing mortality.⁴ Notwithstanding, there are many clinical biomarkers in the clinic for the diagnosis of neonatal sepsis, and due to the long time consumption, low diagnostic performance and the rapid progress of the disease, missed identification of neonatal sepsis delays diagnosis and treatment, increasing the risk of death.⁵

The accurate identification of neonatal sepsis is critical to provide sufficient treatment time and improve clinical outcomes. In contrast, the neutrophil-to-lymphocyte ratio (NLR) is an independent predictor in the clinic that has been widely used in various diseases, such as immune system diseases, tumours and cancers.⁶ Many studies have

shown that the NLR is more reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there is still a dispute about diagnosing the effectiveness of neonatal sepsis.^{7,8}

We assessed the accuracy as a biomarker for diagnosing neonatal sepsis in newborns by performing a systematic literature review and a meta-analysis, comparing the predictive value and providing a reference for the clinical diagnosis of neonatal sepsis.

METHODS

The present meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA). For details, see PRISMA-(diagnostic test accuracy) DTA for abstracts and PRISMA-DTA.

Patient and public involvement

No patients were involved.

Data source

We searched the Cochrane, PubMed, Embase, Web of Science, CNKI, Wanfang, China Biomedical Literature Database and VIP Database for studies on the diagnostic accuracy of neonatal sepsis published before June 2022. We used a combination of subject words and free words to search the study and the following keywords: 'Neutrophil and lymphocyte ratio', 'Infant', 'Newborn', 'Neonate', 'sepsis', 'septicemia', 'Neonatal Sepsis'. In addition, we checked the reference lists of each of the primary studies to identify additional publications. The retrieval format is shown in online supplemental additional file 1.

Study eligibility

Inclusion criteria: (1) The purpose of the study was to evaluate or explore the diagnostic value of the NLR in neonatal sepsis. (2) The case group included newborns with confirmed neonatal sepsis, and the control group included newborns with neonates without sepsis. (3) The diagnostic gold standard is blood culture. (4) It can directly or indirectly obtain the true positive, false positive, true negative and false negative values of the NLR in the diagnosis of neonatal sepsis. The language is English or Chinese.

Exclusion criteria: (1) Being able to be extracted from the full text. (2) Reviews, conference reports, individual cases and animal experiments. (3) A duplicated study.

Data extraction and quality assessment

Two authors (YX and YS) independently conducted the literature screening, data extraction and quality evaluation. In case of disagreement, the third author (WM) decided extracted data from the included literature, including the year of publication, country of origin, study design, author, publication year, newborn birth situation, study location, sample size, case and control numbers, cut-off value, true positive value, false positive value, false negative value, true negative value, sensitivity and

specificity. We assess the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist. We used Review Manager (V.5.3) for quality assessment.

Statistical analyses

Statistical heterogeneity was assessed using forest plots with 95% prediction interval, the tau-squared (τ^2) value and I^2 statistic. The 95% prediction interval was applied to estimate the effect size range in further studies.⁹ If there was heterogeneity between the studies, the source of the heterogeneity was further explored, and threshold effect and non-threshold effect analyses were carried out. Meta Disc V.1.4 software was used to analyse the threshold effect heterogeneity. For heterogeneity caused by non-threshold effects, we performed meta-regression analysis and sensitivity analysis to find the source of heterogeneity. At the same time, we performed subgroup analyses by cut-off value, neonatal birth status and type of sepsis to assess the stability of the results. The combined sensitivity, combined specificity, combined diagnostic OR (DOR), combined positive likelihood ratio (LR^+), combined negative likelihood ratio (LR^-) and its 95% CI were determined using Stata V.16.0. Simultaneously, summary receiver operating characteristic (SROC) curve analysis was performed. All studies are presented as a circle and plotted with the SROC curve. The summary point is represented by a dot which was surrounded by a 95% confidence region. The area under the SROC curve was calculated. At the same time, we assessed the bias of included studies by contour-enhanced funnel plots. If there was bias, we judged the stability of the results by the cut-and-fill method. We used Stata (V.16.0), R (V.3.6.0) and MetaDiSc (V.1.4) to perform the analyses.

RESULTS

Identification of studies

After checking duplicates and reading abstracts and excluding relevant literature according to the exclusion criteria, a final total of 14 studies were used for the current meta-analysis.^{10–23} The specific process is shown in figure 1. Of these, 783 neonates in the sepsis group and 716 neonates in the non-sepsis group were studied and evaluated. Online supplemental additional file 2 shows the significant characteristics of the selected studies. The baseline information included the following parameters: the number of patients, gestational age, regions, types of sepsis, disease diagnosis methods, study design and NLR cut-off value.

Quality of studies

We imported the literature into Review Manager V.5.3 and used the QUADAS-2 tool to evaluate the quality of the 14 included references. According to the methodological evaluation results, the gold standard for the diagnosis of all patients is blood culture. For patient selection, three references were considered high risk. Since most studies do not specify a threshold in advance, there may

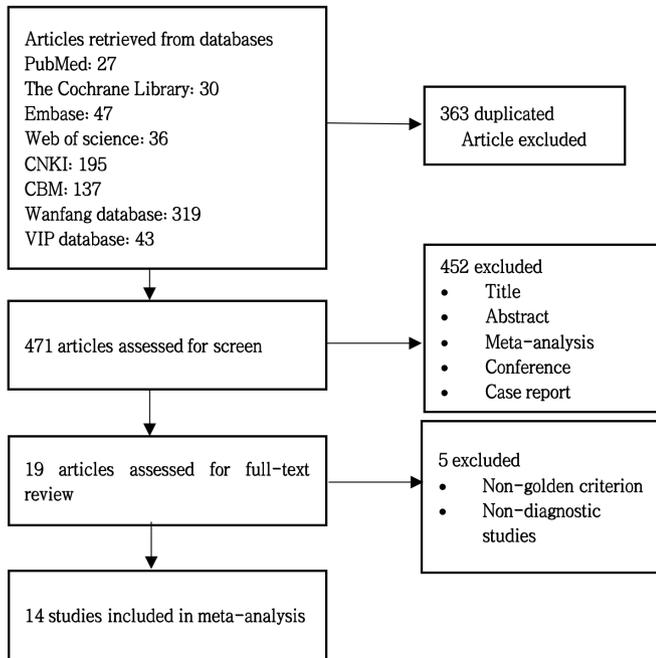


Figure 1 Flowchart of study selection, inclusion and exclusion for the meta-analysis.

be a risk of bias. Most articles did not mention whether the interpretation of the experimental results to be evaluated was performed without knowing the results of the

gold standard, indicating that it is not clear whether the interpretation of the results will produce a risk of bias (figures 2 and 3).

Heterogeneity exploration

Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly composed of threshold effect heterogeneity and non-threshold effect heterogeneity. Through the combination of data, by combining the data we found that the results were highly heterogeneous. We first conducted a threshold effect test. By using MetaDiSc V.1.4, we found that the Spearman correlation coefficient was -0.037 ($p=0.899$) ($p>0.05$). It shows no threshold effect heterogeneity, so to further find the source of heterogeneity, we carried out meta-regression and sensitivity analysis. In the meta-regression analysis, we used the publication year (with 2019 as the cut-off), region, study type and neonatal birth status as variables for analysis. The meta-regression results show that articles in prospective studies are the main source of heterogeneity ($p=0.01$) (online supplemental additional file 3). Sensitivity analysis removes non-Asian, preterm and late-onset sepsis research results and shows that the region is the main source of heterogeneity (online supplemental additional file 4).

Data synthesis and subgroup analysis

With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity and specificity of the NLR in the diagnosis of neonates were 0.74 (95% CI: 0.61 to 0.83) and 0.88 (95% CI: 0.73 to 0.95), respectively; LR^+ was 6.35 (95% CI: 2.5 to 15.47), LR^- was 0.30 (95% CI: 0.19 to 0.46), DOR was 12.88 (95% CI: 4.47 to 37.08) and area under the curve (AUC) was 0.87 (95% CI: 0.84 to 0.89) (figures 4–7).

The results of the (Early-onset sepsis)EOS subgroup analysis showed that the pooled sensitivity and specificity of the NLR in the diagnosis of neonatal sepsis were 0.75 (95% CI: 0.47 to 0.91) and 0.99 (95% CI: 0.88 to 1.00); LR^+ was 63.3 (95% CI: 5.7 to 696.8), LR^- was 0.26 (95% CI: 0.10 to 0.63), DOR was 247 (95% CI: 16 to 3785) and the AUC was 0.97 (95% CI: 0.95 to 0.98). The results of the LOS subgroup analysis showed that the pooled sensitivity and specificity of the NLR in the diagnosis of neonatal sepsis were 0.60 (95% CI: 0.53 to 0.67) and 0.85 (95% CI: 0.80 to 0.90); LR^+ was 3.71 (95% CI: 2.73 to 5.02), LR^- was 0.41 (95% CI: 0.08 to 1.94), DOR was 11.14 (95% CI: 6.54 to 18.98) and the AUC was 0.85. Cut-off value: 0–2, pooled sensitivity and specificity were 0.74 (95% CI: 0.69 to 0.78) and 0.90 (95% CI: 0.71 to 0.97), respectively; LR^+ was 7.1 (95% CI: 2.3 to 21.8), LR^- was 0.29 (95% CI: 0.23 to 0.36), DOR was 25 (95% CI: 7 to 88), the AUC was 0.77. Cut-off value: 2–4, pooled sensitivity and specificity were 0.79 (95% CI: 0.72 to 0.85) and 0.62 (95% CI: 0.54 to 0.70); LR^+ was 2.21 (95% CI: 1.24 to 3.92), LR^- was 0.33 (95% CI: 0.23 to 0.46), DOR was 6.73 (95% CI: 2.81 to 16.14) The AUC was 0.85. Cut-off value: >4, pooled sensitivity and specificity were 0.60 (95% CI: 0.53 to 0.67) and 0.91 (95% CI: 0.85 to 0.95); LR^+ was 9.0 (95% CI:

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Abdullah Kurt 2022	+	+	?	+	+	+	+
Emrah Can, MD2017	+	+	?	+	+	+	+
Heriyanto Lim2021	+	+	?	+	+	+	+
Ipek Guney Varal2020	+	+	+	+	+	+	+
Khadijah Rizky Sumitro2021	+	+	?	+	+	+	+
Nagwa Mohamed,SAM2020	+	+	+	+	+	+	+
Ori Goldberg2020	+	+	?	+	+	+	+
R H Ruslie2018	+	+	?	+	+	+	+
Rocky Wilar, MD2018	+	+	?	+	+	+	+
Santosh K. Panda2021	+	+	?	+	+	+	+
Sara Mohamed Mira2021	+	+	?	+	+	+	+
Senem Alkan Ozdemir2017	+	+	?	+	+	+	+
Shujian Zhang 2021	+	+	?	+	+	+	?
Xiaoyu Du2019	+	+	?	+	+	?	?

Figure 2 Risk of bias and applicability concerns summary.

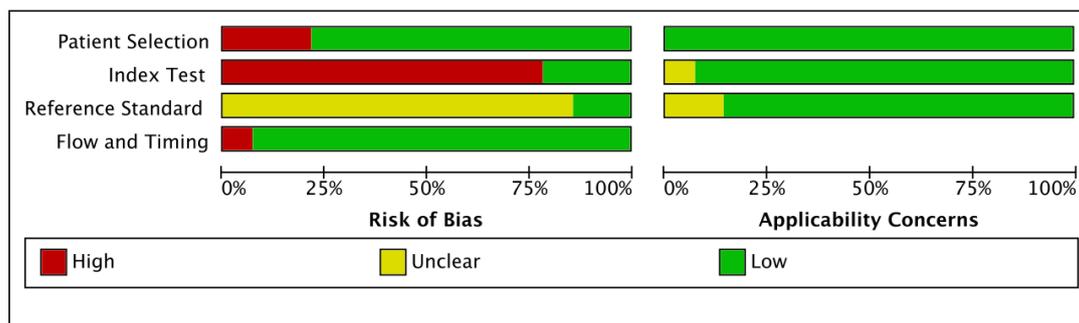


Figure 3 Risk of bias and applicability concerns graph.

0.3 to 270.24), LR^- was 0.29 (95% CI: 0.03 to 2.68), DOR was 31.51 (95% CI: 0.81 to 1229.29) The AUC was 0.95 (online supplemental additional file 5).

Publication bias exploration

The contour-enhanced funnel plot results suggested that there was publication bias, and after our cut-and-fill method, the results showed that the stability of our meta-analysis results was not affected (figure 8).

DISCUSSION

The early identification of neonatal sepsis remains challenging in the clinic, and the NLR is broadly used in diagnosing immune system diseases, tumours and cancers. However, the accurate diagnosis of neonatal sepsis is still questionable.²⁴⁻²⁶ For the first time, we conducted a meta-analysis and systematic review of the diagnostic performance of NLR in neonatal sepsis, which may provide a better reference value for the early diagnosis of neonatal

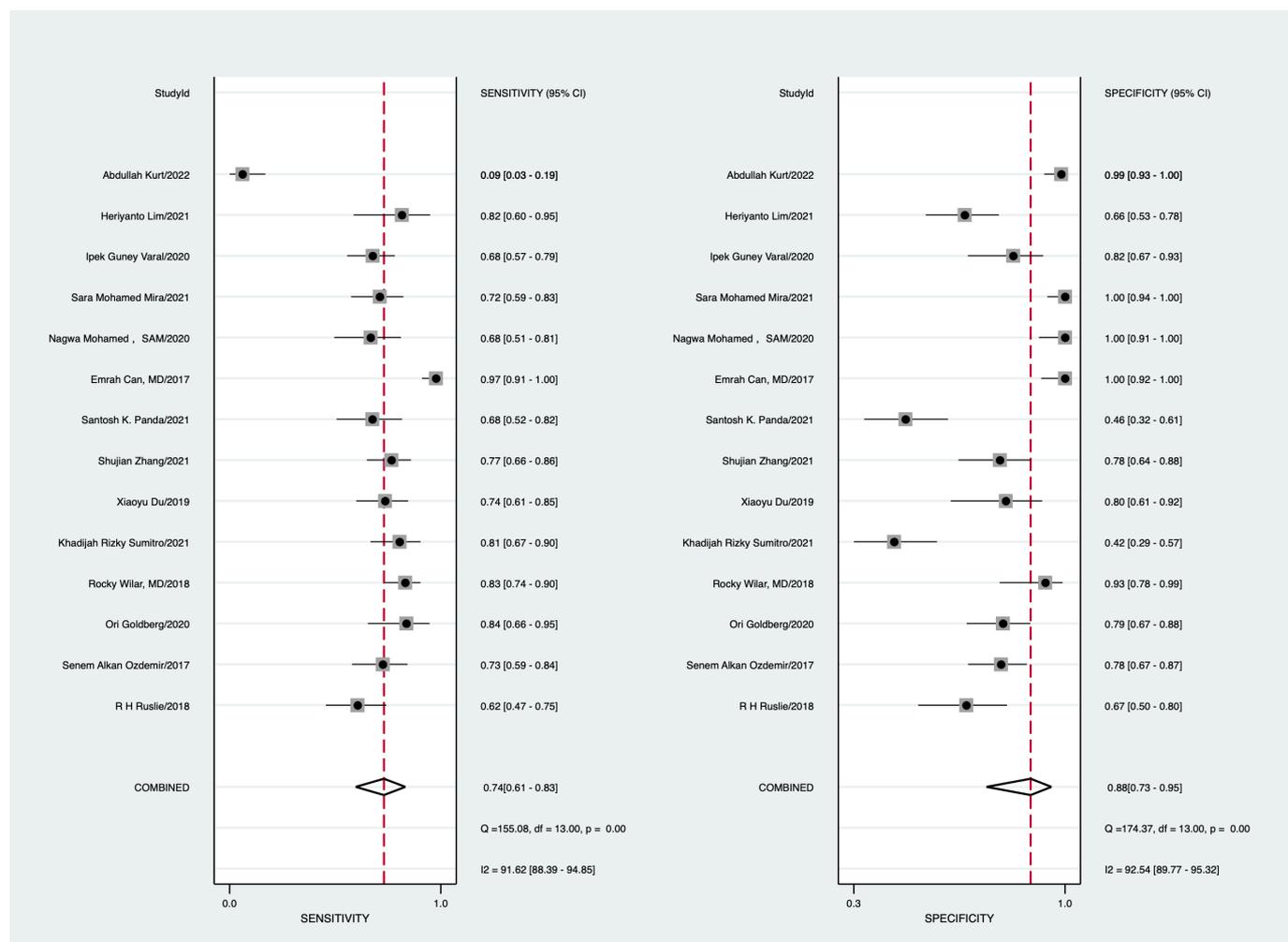


Figure 4 Forest plot of the pooled sensitivity and specificity.

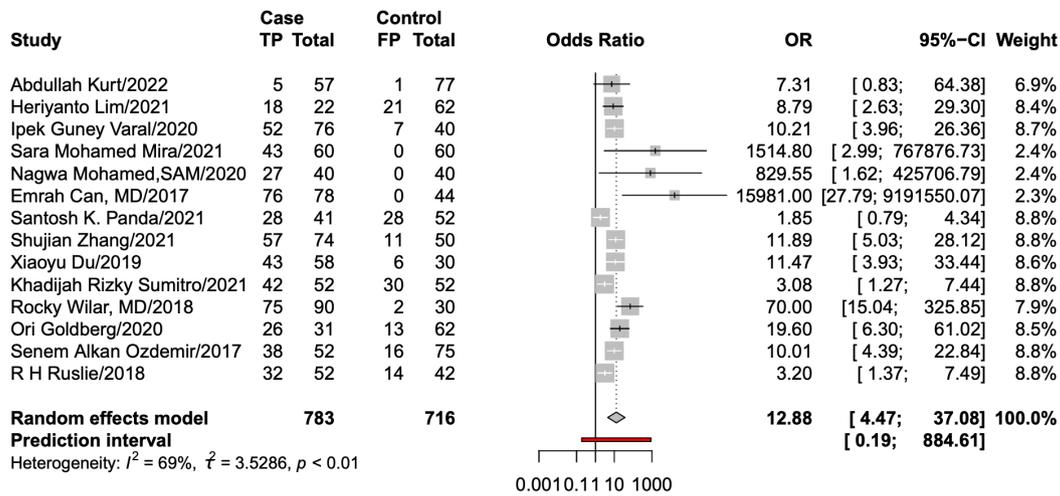


Figure 5 Forest plot of the pooled diagnostic OR. TP, True positive; FP, False positive.

sepsis and for NLR to diagnose neonatal sepsis, providing evidence-based evidence. The meta-analysis included all 14 studies from 7 nations, including 1499 patients with neonatal sepsis. Moreover, the results revealed that the combined AUC of the NLR in the diagnosis of neonatal

sepsis was 0.874 (95% CI: 0.84 to 0.89), showing that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis.

Omran *et al* found that NLR is closely related to neonatal sepsis. Within a few hours after neonatal sepsis, NLR can

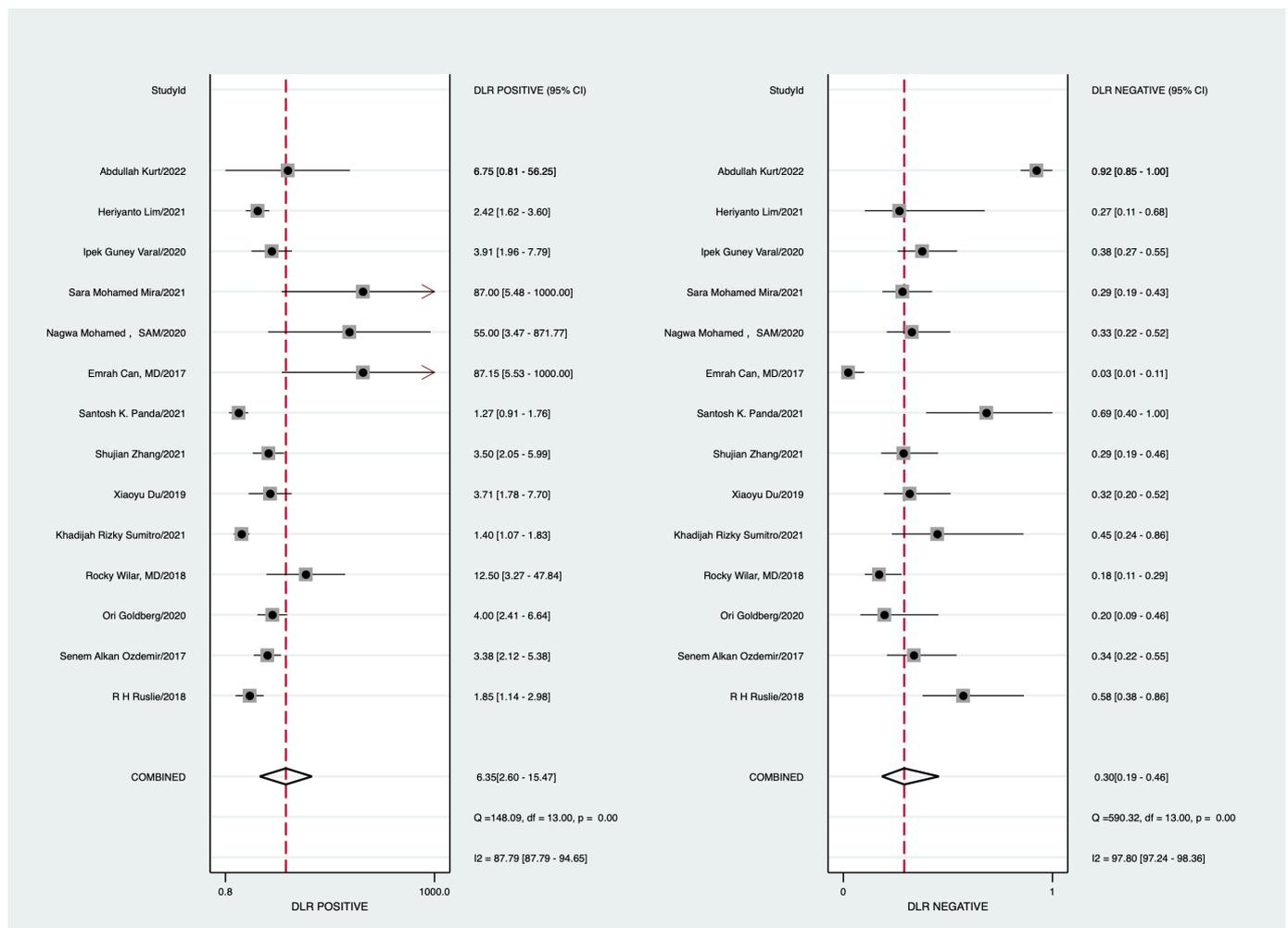


Figure 6 Forest plot of the pooled positive likelihood ratio (LR) and negative LR.

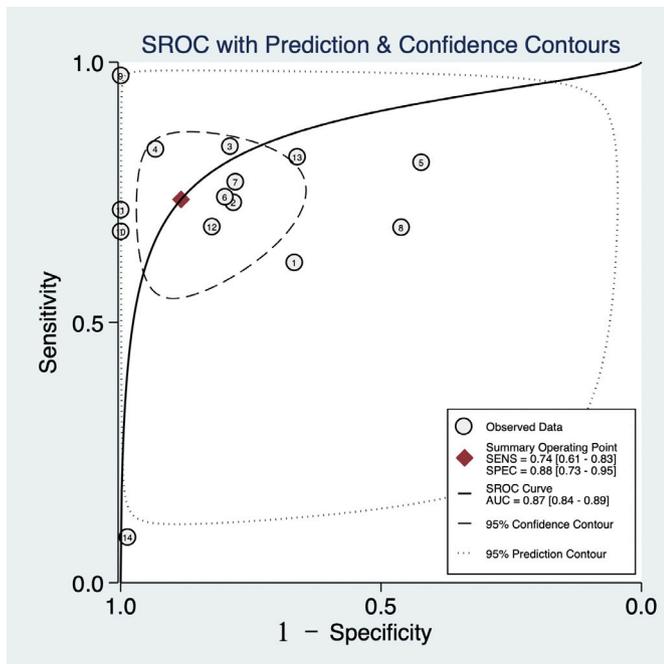


Figure 7 Summary receiver operating characteristic (SROC) of the neutrophil-to-lymphocyte ratio for the diagnosis of sepsis. AUC, area under the curve; SEN, Sensitivity; SROC, Summary Receiver Operating Characteristic.

rapidly increase in a short time compared with (C-reactive protein)CRP. The use of NLR makes it possible to identify neonatal sepsis early²⁷ can be used as an auxiliary diagnostic index for the diagnosis of neonatal sepsis,²⁸ timely diagnosis and early appropriate antibiotic treatment. Seymour *et al* showed that in the ROC curve analysis of bacterial sepsis according to the Sepsis-2 standard, NLR showed a moderate AUC (0.68), which was significantly higher than that of CRP, lactate and (procalcitonin)PCT,^{29 30} suggesting that NLR has better diagnostic performance. Mahmoud *et al* found that when the cut-off value was 0.1, NLR showed the best specificity and negative predictive value for neonatal sepsis ((specificity)SPE

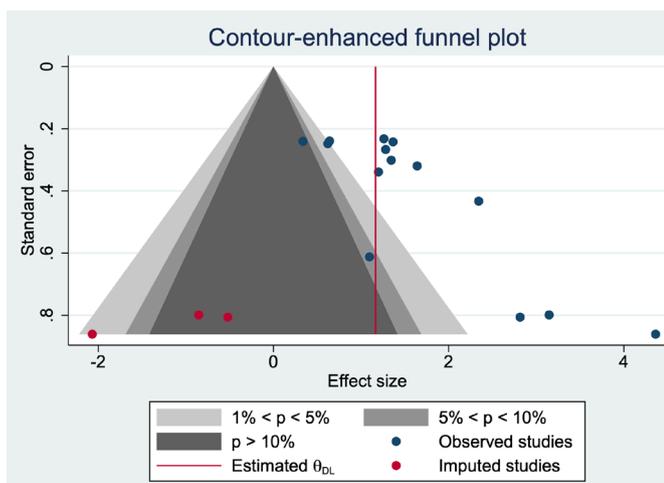


Figure 8 Contour-enhanced funnel plot of studies included in the meta-analysis.

was 99%, (Negative Predictive Value)NPV was 75%), compared with CRP and PCT, NLR showed higher specificity with better diagnostic power.¹⁹ A study by Alkan Ozdemir *et al* in the diagnosis of late-onset neonatal sepsis showed that NLR had a high sensitivity, specificity and accuracy of 0.73, 0.78, and 0.76, respectively, with an NLR cut-off value of 1.77.¹¹ In the study of Wilar, it was found that the cut-off value of NLR was 1.5, and NLR could be used as a single laboratory index to diagnose neonatal sepsis,¹³ indicating that NLR could be a valuable indicator to exclude neonatal sepsis.

Subgroup analysis indicated that pooled sensitivity and specificity were higher for detecting the NLR in a group of early-onset neonatal sepsis. The results express the stability of the results. Neonatal early-onset sepsis mainly emphasises that the bacteria originate from intrauterine tissue and during delivery, and the spectrum of pathogenic bacteria is relatively concentrated.^{31 32} *Streptococcus B* and *Escherichia coli* are the most common pathogens of early-onset neonatal sepsis. In the future, more research can be incorporated to further verify the accuracy of the NLR diagnosis of early-onset sepsis.

Our study included homogeneous research as much as possible, but the included studies still had heterogeneity in which non-threshold effects can be explained to partial heterogeneity. The results of the meta-regression analysis indicated that the study type may be the main sources of heterogeneity (online supplemental additional file 3). The sensitive analysis results also indicate that the non-Asian region is the primary source of heterogeneity (online supplemental additional file 4). However, after removing all non-Asian articles, heterogeneity still existed, indicating this study's heterogeneity is for other reasons.

In addition, several limitations of this study should be noted. (1) Although it is homogeneous to reduce the choice of bias applications, heterogeneity is still in the inclusive research. (2) The diagnosis of newborns will also have differences due to different researchers, resulting in false positive and false negative results for the diagnosis of neonatal sepsis, which leads to bias. (3) A part of the included research was a retrospective study, so there may be a selection of research objects. (4) The included research comes from different countries, and newborns have different immunity for different races and sexes. Therefore, it is necessary to carry out the same race, large sample, multicentre prospective clinical study to determine the value of the NLR in diagnosing neonatal sepsis in the future.

CONCLUSION

In summary, our findings suggest that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined with other laboratory tests and specific clinical manifestations. However, it is limited to the research site and research type. Further research is needed to carry out multicentre prospective studies with

multiple samples to verify the accuracy of NLR diagnosis and improve neonatal sepsis prognosis.

Contributors YX and YS were the guarantors for the study and affirm that this manuscript is an honest, accurate and transparent account of the study being reported. YX wrote the manuscript. HL, YZ and WM performed the literature review. YX and YS performed the statistical analysis. WM and CW revised the text. All authors read and approved the final manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Detailed retrieval strategy

Database	Pubmed
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Time	database building - 2022.06.28
Results	27
Search details	Search: (((nlr[Title/Abstract]) OR (Neutrophil to lymphocyte ratio[Title/Abstract])) OR ("Neutrophil and lymphocyte ratio"[Title/Abstract])) AND (((((Infant, Newborn[Title/Abstract]) OR (Newborn Infant[Title/Abstract])) OR (Newborn[Title/Abstract])) OR (Neonate[Title/Abstract])) OR ("Infant, Newborn"[Mesh])) AND (((((((Sepsis, Neonatal Late-Onset[Title/Abstract]) OR (Neonatal Sepsis[Title/Abstract])) OR (Neonatal Sepsis[Title/Abstract])) OR (Early Onset Sepsis[Title/Abstract])) OR (Sepsis, Neonatal Early-Onset[Title/Abstract])) OR (LOS[Title/Abstract])) OR (EOS[Title/Abstract])) OR ("Neonatal Sepsis"[Mesh])) OR (((((((sepsis[Title/Abstract]) OR (Bloodstream Infection[Title/Abstract])) OR (Pyohemia[Title/Abstract])) OR (Pyemia[Title/Abstract])) OR (Septicemia[Title/Abstract])) OR (Poisoning, Blood[Title/Abstract])) OR (Severe Sepsis[Title/Abstract])) OR ("Sepsis"[Mesh]))
Database	Embase
Website	https://www.embase.com
Time	database building - 2022.06.28
Results	47
Search details	No. Query #33: #10 AND #30 AND #32 #32: #1 OR #2 OR #3 OR #31 #31 : 'neutrophil lymphocyte ratio'/exp #30: 'neutrophil lymphocyte ratio'/exp #29 : #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 #28 : 'eos':ab,ti #27 : 'los':ab,ti #26 : 'sepsis, neonatal early-onset':ab,ti #25 : 'early onset sepsis':ab,ti #24 : 'sepsis, neonatal late-onset':ab,ti #23 : 'neonatal sepsis':ab,ti #22 : 'neonatal sepsis':ab,ti #21 : 'newborn sepsis':ab,ti #20 : 'newborn sepsis'/exp #19 : #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 #18 : 'severe sepsis':ab,ti #17 : 'poisoning, blood':ab,ti #16 : 'septicemia':ab,ti #15 : 'pyohemia':ab,ti #14 : 'pyohemia':ab,ti #13 : 'bloodstream infection':ab,ti #12 : 'sepsis':ab,ti

	<p>#11 : 'sepsis'/exp #10 : #5 OR #6 OR #7 OR #8 #9 : 'neonate':ab,ti #8 : 'newborn':ab,ti #7 : 'newborn infant':ab,ti #6 : 'newborn':ab,ti #5 : 'newborn'/exp #4 : #1 OR #2 OR #3 #3 : 'nlr':ab,ti #2 : 'neutrophil to lymphocyte ratio':ab,ti #1 : 'neutrophil and lymphocyte ratio':ab,ti</p>
Database	Web of science
Website	http://www.webofscience.com
Time	database building - 2022.06.28
Results	36
Search details	<p>#1 (((((((((((((TS=(Neonatal Sepsis)) OR TS=(Neonatal sepsis)) OR TS=(Sepsis, Neonatal Late-Onset)) OR TS=(Early Onset Sepsis)) OR TS=(Sepsis, Neonatal Early-Onset)) OR TS=(los)) OR TS=(eos)) OR TS=(sepsis)) OR TS=(Bloodstream Infection)) OR TS=(pyohemie)) OR TS=(pyaemic)) OR TS=(Septicemia)) OR TS=(Poisoning, Blood)) OR TS=(Severe Sepsis) #2 TS=(Neutrophil and lymphocyte ratio) or TS=(Neutrophil to lymphocyte ratio) or TS=(nlr) #3 ((TS=(Infant, Newborn)) OR TS=(Newborn Infant)) OR TS=(Newborn)) OR TS=(Neonate) #1 and #2 and #3</p>
Database	Cochrane
Website	https://www.cochrane.org
Time	database building - 2022.06.28
Results	30
Search details	<p>ID Search Hits</p> <p>#1 MeSH descriptor: [Neonatal Sepsis] explode all trees 86 #2 (Neonatal Sepsis):ti,ab,kw OR (Sepsis, Neonatal Late-Onset):ti,ab,kw OR (Neonatal Sepses):ti,ab,kw OR (Early Onset Sepsis):ti,ab,kw OR (Sepsis, Neonatal Early-Onset):ti,ab,kw (Word variations have been searched) 2151 #3 (LOS):ti,ab,kw OR (EOS):ti,ab,kw (Word variations have been searched) 15529 #4 #1 or #2 or #3 17494 #5 MeSH descriptor: [Sepsis] explode all trees 4918 #6 (sepsis):ti,ab,kw OR (Bloodstream Infection):ti,ab,kw OR (Pyohemia):ti,ab,kw OR (Pyaemia):ti,ab,kw OR (Septicemia):ti,ab,kw (Word variations have been searched) 13925 #7 (Poisoning, Blood):ti,ab,kw OR (Severe Sepsis):ti,ab,kw (Word variations have been searched) 4942 #8 #5 or #6 or #7 16646 #9 #4 or #8 31666 #10 MeSH descriptor: [Infant, Newborn] explode all trees 17498 #11 (Infant, Newborn):ti,ab,kw OR (Newborn Infant):ti,ab,kw OR (Newborn):ti,ab,kw OR (Neonate):ti,ab,kw (Word variations have been searched) 40837 #12 #10 or #11 40928</p>

	#13 (Neutrophil and lymphocyte ratio):ti,ab,kw OR (Neutrophil to lymphocyte ratio):ti,ab,kw OR (nlr):ti,ab,kw (Word variations have been searched) 915 #14 #9 or #12 68896 #15 #14 and #13 30
Database	CNKI (<i>Chinese database</i>)
Website	https://www.cnki.net
Time	database building - 2022.06.28
Results	195
Search detail	(主题=脓毒症 + 败血症 + 新生儿败血症 + 血流感染 + 早发性败血症 + 迟发性败血症 + 血液中毒 + 新生儿脓毒症) AND (主题=中性粒淋巴细胞比 + nlr)
Database	Wanfang (<i>Chinese database</i>)
Website	https://www.wanfangdata.com.cn/index.html
Time	database building - 2022.06.28
Results	319
Search details	检索表达式(中英文扩展&主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)
Database	China Biomedical Literature Database (<i>Chinese database</i>)
Website	http://www.sinomed.ac.cn/index.jsp
Time	database building - 2022.06.28
Results	137
Search details	(("中性粒淋巴细胞比值"[常用字段:智能] OR "nlr"[常用字段:智能])) AND (("脓毒症"[常用字段:智能] OR "败血症"[常用字段:智能] OR "新生儿脓毒症"[常用字段:智能] OR "新生儿败血症"[常用字段:智能] OR "早发性败血症"[常用字段:智能] OR "迟发性败血症"[常用字段:智能] or "血流感染"[常用字段:智能]))
Database	VIP Database (<i>Chinese database</i>)
Website	http://qikan.cqvip.com
Time	database building - 2022.06.28
Results	43
Search details	检索表达式(主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)

Table 1 characteristics of the included 14 studies.

Author	Year	Selected time	Study design	Sepsis diagnosis	Region	Early /Late	Case/C ontrol	T P	F P	F N	T N	SE	SP	Cut off	Neonates
R H Ruslie [1]	2018	2016-2017	Retrospective	Blood culture	USA	EOS、 LOS	52/42	32	14	20	28	61.5	66.7	9.4	A、 B、 C
Senem Alkan Ozdemir [2]	2017	2014-2015	Prospective	Blood culture	Turkey	LOS	52/75	38	16	14	58	73	78	1.77	A
Ori Goldberg [3]	2020	2016-2019	Retrospective	Blood culture	Israel	LOS	31/62	26	13	5	49	83.9	79	1.5	A、 B、 C
Rocky Wilar, MD [4]	2018	2017-2017	Cross-sectional study	Blood culture	Indonesia	EOS	90/30	75	2	15	28	83.3	93.3	1.24	A、 B、 C
Khadijah Rizky Sumitro [5]	2021	2019-2019	Cross-sectional study	Blood culture	Indonesia	EOS、 LOS	52/52	42	30	10	22	80.8	42.3	2.12	A、 B、 C
Xiaoyu Du [6]	2019	2015-2017	Retrospective	Blood culture	China	EOS、 LOS	58/30	43	6	15	24	73.3	81	0.7	NA
Shujian Zhang [7]	2021	2018-2020	Descriptive study	Blood culture	China	EOS	74/50	57	11	17	39	77	78	3.16	A、 B、 C
Santosh K. Panda [8]	2021	2018-2018	Retrospective	Blood culture	Philippines	EOS、 LOS	41/52	28	28	13	24	68.3	46.2	1.7	A、 B、 C
Emrah Can, MD [9]	2017	2015-2017	Prospective	Blood culture	Turkey	EOS	78/44	76	0	2	44	97.4	100	6.76	B
Nagwa Mohamed, SAM [10]	2020	2018-2019	Prospective	Blood culture	Egypt	EOS	40/40	27	0	13	40	67	99	0.1	B
Sara Mohamed Mira [11]	2021	2018-2019	Retrospective	Blood culture	Egypt	EOS	60/60	43	0	17	60	72	100	1	A、 B
Ipek Guney Varal [12]	2020	2016-2018	Retrospective	Blood culture	Turkey	LOS	76/40	52	7	24	33	68	82	1.57	A
Heriyanto Lim [13]	2021	2018-2018	Retrospective	Blood culture	Indonesia	EOS、 LOS	22/62	18	21	4	41	81.8	66.1	2.31	A、 B

Abdullah Kurt [14]	2022	2016-2018	Retrospective	Blood culture	Turkey	EOS、	57/77	5	1	52	76	8.8	98.7	4.79	NA
						LOS									
						EOS	20/77	3	1	17	76	15	98.7	4.79	
						LOS	37/77	2	1	35	76	5.4	98.7	4.94	

Note: EOS: Early-onset sepsis, LOS: Late-onset sepsis, A: Preterm, B: Term, C: Late term, NA:Not Available, TP: true positive, FP: false positive, TN: true negative, FN: false negative, SEN: sensitivity, SPE: specificity.

Reference

- [1] Ruslie R H, Tjipta D G, Samosir C T, et al. Bacterial pattern, and role of laboratory parameters as marker for neonatal sepsis[C]//IOP Conference Series: Earth and Environmental Science. *IOP Publishing*, 2018, 125(1): 012057.
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- [4] Wilar R. Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset neonatal sepsis[J]. *Korean Journal of Pediatrics*, 2018, 62(6): p. 217-223.
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- [10] Mahmoud N M S A, Baheeg G, Abdelhakeem M, et al. Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio as New Diagnostic Markers for Detection of Early-onset Neonatal Sepsis in Full-term Newborns. 2019.
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Table 2 The result of meta-regression**Sensitivity and Specificity**

Parameter	Category	Studies	Sen	P1	Spe	P2
Asia	Yes	11	0.75	0.92	0.84	0.28
	No	3	0.67		0.98	
Year (2019)	Yes (≥ 2019)	10	0.69	0.08	0.87	0.87
	No (< 2019)	4	0.83		0.91	
Preterm	Yes	2	0.71	0.73	0.81	0.91
	No	12	0.74		0.89	
Prospective	Yes	3	0.84	0.62	0.98	0.01
	No	11	0.70		0.83	

Joint Model

Parameter	Category	LRTChi ²	<i>P</i> value	<i>I</i> ²	<i>I</i> ² lo	<i>I</i> ² hi
Asia	Yes	2.74	0.25	27	0	100
	No					
Year (2019)	Yes (≥ 2019)	1.82	0.40	0	0	100
	No (< 2019)					
Preterm	Yes	0.31	0.86	0	0	100
	No					
Prospective	Yes	5.28	0.07	62	15	100
	No					

Table 3 The results of sensitivity analysis

Studies	Studies	Sen(95%CI)	Spe(95%CI)	LR ⁻ (95%CI)	LR ⁺ (95%CI)	DOR (95%CI)	AUC (95%CI)	Q
Overall	14[1-14]	0.74[0.61-0.83]	0.88[0.73-0.95]	0.30[0.19-0.46]	6.3[2.6-15.5]	21[7-65]	0.87[0.84-0.89]	140.85
Remove non-Asian	11[2-9,12-14]	0.75[0.59-0.87]	0.83[0.68-0.92]	0.30[0.17-0.52]	4.4[2.2-8.9]	15[5-42]	0.86[0.83-0.89]	120.59
Remove preterm	12[1,3-11,13-14]	0.74[0.59-0.85]	0.90[0.72-0.97]	0.29[0.17-0.48]	7.6[2.4-24.0]	27[7-107]	0.88[0.85-0.90]	147.40
Remove LOS	11[1,4-11,13,14]	0.73[0.56-0.85]	0.92[0.72-0.98]	0.29[0.17-0.51]	8.6[2.3-32.8]	29[6-145]	0.88[0.85-0.90]	147.96
Remove Prospective study	11[1,3-8,11-14]	0.70[0.56-0.81]	0.83[0.66-0.92]	0.36[0.25-0.53]	4.1[2.1-8.1]	11[5-25]	0.82[0.79-0.85]	133.33

Note: Sen: sensitivity; Spe: specificity; LR⁻: negative likelihood ratio; LR⁺: positive likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve;

Reference

[1] Ruslie R H, Tjipta D G, Samosir C T, et al. Bacterial pattern, and role of laboratory parameters as marker for neonatal sepsis[C]//IOP Conference Series: Earth and Environmental Science. *IOP Publishing*, 2018, 125(1): 012057.

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Table 4 Subgroup analysis of neutrophil-to-lymphocyte ratio in the diagnosis of neonatal sepsis.

Subgroup	Study number	Sen	Spe	LR ⁺	LR ⁻	DOR	AUC
All	14 [1-14]	0.74	0.88	6.35	0.30	21.27	0.87
Neonates							
EOS	6 [4,7,9-11,14]	0.75	0.99	63.30	0.26	247	0.97
LOS	4 [2,3,12,14]	0.60	0.85	3.71	0.41	11.14	0.85
Areas							
Asian	11 [2-9,12-14]	0.75	0.83	4.40	0.30	15	0.86
Non-Asian	3 [1,10,11]	0.67	0.90	18.64	0.38	45.94	0.95
Cut off							
0-2	8 [2-4,6,8,10-12]	0.74	0.90	7.1	0.29	25	0.77
2-4	3 [5,7,13]	0.79	0.62	2.21	0.33	6.73	0.85
>4	3 [1,9,14]	0.60	0.91	9.00	0.27	31.51	0.95

Note: SEN: sensitivity; SPE: specificity; LR⁻: negative likelihood ratio; LR⁺: positive likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve;

Reference

- [1] Ruslie R H, Tjipta D G, Samosir C T, et al. Bacterial pattern, and role of laboratory parameters as marker for neonatal sepsis[C]//IOP Conference Series: Earth and Environmental Science. *IOP Publishing*, 2018, 125(1): 012057.
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