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The 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 neutrophil to lymphocyte ratio diagnoses of neonatal sepsis from inception to August 2021. Two investigators independently conducted the literature search, screening, data extraction, and quality evaluation with the QUADAS-2. Statistical analysis was performed using Review Manager 5.3, Stata 16.0, and Meta-DISC1.4.

Results: A total of 13 studies comprising 1365 newborns were involved in this meta-analysis. The pooled sensitivity of the ratio in the diagnosis of neonatal sepsis was 0.77 (95 % confidence interval [CI]：0.71-0.83), the pooled specificity was 0.86 (95 % CI 0.70-0.94), the positive likelihood ratio was 5.6(95 % CI 2.3-13.8), the negative likelihood ratio was 0.26(95 % CI 0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(95 % CI 0.81-0.87). In the subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.83 (95 % CI 0.68-0.91), the pooled specificity was 0.99 (95 % CI 0.78-1.00), the positive likelihood ratio was 91.3 (95 % CI 3.0-2823.6), the negative likelihood ratio was 0.18 (95 % CI 0.09-

0.34), the diagnostic odds ratio was 519 (95 % CI 14-19952), and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97). The Deeks funnel showed that there was no statistically significant difference in the publication bias of the study (P>0.05).

Conclusions: The neutrophil to lymphocyte ratio has a moderate diagnostic capacity with high sensitivity and specificity for diagnosing neonatal sepsis. It can provide a reference value for the early diagnosis of neonatal sepsis.

Keywords: Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis

Strengths and limitations

(1). As a cheap and readily available new comprehensive inflammatory indicator, Neutrophil to lymphocyte ratio (NLR) is relatively stable and unaffected by in vitro blood sample processing and conventional physiological conditions.

(2). Neutrophil to lymphocyte ratio (NLR) is more accurate than blood culture (gold standard) in the diagnosis of neonatal sepsis. This new laboratory index improves the diagnostic efficiency of neonatal sepsis, providing clinical evidence for the diagnosis of neonatal sepsis.

(3). Due to the limited number of articles, we cannot accurately distinguish the accuracy of the ratio of neutrophils to lymphocytes in early-onset neonatal sepsis and late-onset sepsis

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 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] Due to the sensitivity of disease diagnosis methods and the timeliness and effectiveness of the whole treatment process, the mortality rate of neonatal sepsis is increasing year by year.

According to a survey, the global mortality rate of neonatal sepsis reached 1.0 % to 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-consuming, low diagnostic performance, 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 disease, tumors, and cancers. [6] Many studies have shown that the ratio of neutrophils to lymphocytes 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 Additional file 1 and 2.

Patient and Public Involvement

No patient 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 August 2021. 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 Additional file 3.

Study eligibility

Inclusion criteria: (1). The purpose of the study was to evaluate or explore the diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case group included newborns with confirmed neonatal sepsis, and the control group included newborns with nonneonatal sepsis. 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis. The language is English or Chinese.

Exclusion criteria: (1). Unable to 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 independently 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, cutoff value, true positive value, false-positive value, false-negative value, true negative value, sensitivity, and specificity. Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.

Statistical analyses

The I^2 test evaluated study heterogeneity. I^2>50 % indicated that the heterogeneity generated in the study would have a specific impact. Meta Disc1.4 software was used to analyze the threshold effect heterogeneity. If the effect sizes of the studies were

homogeneous, a fixed-effects model was used; if they were heterogeneous, a random-effects model was used. If there was heterogeneity between the studies, the source of the heterogeneity was further explored, and threshold effect and nonthreshold effect analyses were carried out. The combined sensitivity, combined specificity, combined diagnostic odds ratio (DOR), combined positive likelihood ratio (PLR), combined negative likelihood ratio, and its 95 % confidence interval (95 % CI) were determined using Stata 16.0. Simultaneously, a combined receiver operating characteristic curve (SROC) fitting analysis was performed. At the same time, the Deeks test was used to evaluate the publication bias of the included literature. If $P<0.05$, it was considered that the included literature had publication bias.

Results

Identification of studies

After checking duplicates and reading abstracts and excluding relevant literature according to the exclusion criteria, 13 studies were finally included. The specific process is shown in (Fig 1). The references were included from 2017 to 2021, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 had late-onset sepsis, 5 had early-onset sepsis, and 2 were preterm infants. Ten studies were from Asia, and three studies were from non-Asia. Basic information of the included literature is shown in Table 1.

Quality of studies

We imported the literature into Review Manager 5.2 and used the QUADAS-2 tool to evaluate the quality of the 13 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 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. (Fig 2, 3).

Heterogeneity exploration

Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly composed of threshold effect heterogeneity and nonthreshold effect heterogeneity. Through the combination of data, we found that the sensitivity and specificity of I^2 were 68.61 % and 90.87 %, respectively. This indicates that there is considerable heterogeneity. We first conducted a threshold effect test. By using metadisc14.0, we found that the Spearman correlation coefficient was -0.093 (p= 0.762) (p>0.05). Furthermore, the proportion of heterogeneity is likely due to threshold effect = 0.23 in stata16.0. It shows no threshold effect heterogeneity, so to further find the source of heterogeneity, we carried out meta-regression and sensitivity analysis. The meta-regression results show that articles in non-Asian regions are the main source of heterogeneity (Table 2). Sensitivity analysis removes non-Asian, preterm, and late-

onset sepsis research literature results and shows that the region is the main source of heterogeneity. (Table 3)

Data synthesis and Subgroup analysis

(1). The pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonates were 0.77 (95 % CI 0.71-0.83) and 0.86 (95 % CI 0.70-0.94), respectively; PLR was 5.6 (95 % CI 2.3-13.8), NLR was 0.26 (95 % CI 0.19-0.37), DOR was 21 (95 % CI 7-69), and area under the curve (AUC) was 0.84 (95 % CI 0.81-0.87) (Figs 4, 5, 6, 7).

(2). The results of the EOS subgroup analysis showed that the pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis were 0.83 (95 % CI 0.68-0.91) and 0.99 (95 % CI 0.78-1.00); PLR was 91.3 (95 % CI 3.0-2823.6), NLR was 0.18 (95 % CI 0.09-0.34), DOR was 519 (95 % CI 14-19952), and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97).

(3). Cutoff value>2, pooled sensitivity and specificity are, respectively 0.83(95 % CI 0.66-0.93) and 0.80(95 % CI 0.44-0.95), respectively; PLR is 4.1(95 % CI 1.0-17.2), NLR is 0.21(95 % CI 0.07-0.60), DOR is 20 (95 % CI 2-218), the area under the curve (AUC) is 0.88 (95 % CI 0.85-0.91).

(4). Cutoff value <2, pooled sensitivity and specificity are, respectively 0.74(95 % CI 0.69-0.78) and 0.90(95 % CI 0.71-0.97); PLR is 7.1(95 % CI 2.3-21.8), NLR is 0.29(95 % CI 0.23-0.36), DOR is 25(95 % CI 7-88) The area under the curve (AUC) is 0.77(95 % CI 0.73-0.81).

Publication bias exploration

The results of Deeks's funnel plot asymmetry test showed that p=0.40 and p>0.05. This result indicated that the 13 articles included had no publication bias. (Fig 8)

Discussion

The early identification of neonatal sepsis remains challenging in the clinic, and the neutrophil to lymphocyte ratio (NLR) is broadly used in diagnosing immune system diseases, tumors, and cancers. However, the accurate diagnosis of neonatal sepsis is still questionable. [22,23,24] We used a systematic review and meta-analysis to investigate the accuracy of the neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis. The meta-analysis included all 13 studies from 7 nations, including 1365 patients with neonatal sepsis. Moreover, the results revealed that the combined AUC of the neutrophil to lymphocyte ratio (NLR) in the diagnosis of neonatal sepsis was 0.84 (95 % CI=0.81, 0.87), showing that the neutrophil to lymphocyte ratio (NLR) has a moderate diagnostic value for neonatal sepsis, so the neutrophil to lymphocyte ratio (NLR) can be used as an independent predictor of neonatal sepsis.

Subgroup analysis indicated that pooled sensitivity and specificity were higher for detecting the ratio of neutrophils to lymphocytes (NLR) in a group of early-onset neonatal sepsis. The results are expressed stability of the results. Neonatal early-onset sepsis mainly emphasizes that the bacteria originate from intrauterine tissue and during delivery, and the spectrum of pathogenic bacteria is relatively concentrated. [25,26] 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 neutrophil to lymphocyte ratio (NLR) diagnosis of early-onset sepsis.

Our study included homogeneous research as much as possible, but the included studies still had heterogeneity, in which nonthreshold effects can be explained to partial heterogeneity; non-Asian areas were the primary source of heterogeneity (Table 2). Sensitive analysis results also indicate that the non-Asian region is the primary source of heterogeneity (Table 3). However, after removing all non-Asian articles, heterogeneity still existed, indicating this study's heterogeneity for other reasons.

In addition, several limitations of this study should be put forward. (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 is 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 in newborns of different races and genders. Therefore, it is necessary to carry out the same race, large sample, multicenter prospective clinical study, and the value of the neutrophil to lymphocyte ratio (NLR) in diagnosing neonatal sepsis in the future.

Conclusion

In summary, the neutrophil to lymphocyte ratio (NLR) has a moderate value in the diagnosis of neonatal sepsis and can be used to diagnose routine examination of neonatal sepsis. However, it is limited to the research site and research type. Further research is needed to carry out multicenter prospective studies with multiple samples to verify the accuracy of neutrophil to lymphocyte ratio (NLR) diagnosis and improve neonatal sepsis prognosis.

Abbreviations

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; CI: confidence interval; SEN: sensitivity; SPE: specificity; NLR: negative likelihood ratio; PLR: positive likelihood ratio; DOR: diagnostic odds ratio; SEN: sensitivity; SPE: specificity; TP: true positive; FP: false positive; TN: true negative; FN: false negative; EOS: early-onset sepsis; LOS: late-onset sepsis; AUC: area under the curve; SROC: summary receiver operating characteristic.

Contributors

XY wrote the manuscript. LHX, ZYX, and MWJ performed the literature review. XY and SYS performed the statistical analysis. MWJ and WCS revised the text. All authors read and approved the final manuscript.

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Competing interests: The authors declare that they have no competing interests.

Availability of data and materials: All data supporting the conclusions presented in this article are included in this published article.

Consent for publication: Not applicable.

Ethics approval and consent to participate: Not applicable.

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Reference

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Figure legends:

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

Figure 2: Risk of bias and applicability concerns summary

Figure 3: Risk of bias and applicability concerns graph

Figure 4: Forest plot of the pooled sensitivity and specificity

Figure 5: Forest plot of the pooled diagnostic odds ratio

Figure 6: Forest plot of the pooled positive LR and negative LR

Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

Figure 8: Funnel plot of studies included in the meta-analysis

Additional file legends:

Additional file 1:Screenshot of search strategy

Additional file 2:Table 1，Characteristics of the included 13 studies

Additional file 3:Table 2，The result of meta-regression

Additional file 4:Table 3，The results of sensitivity analysis

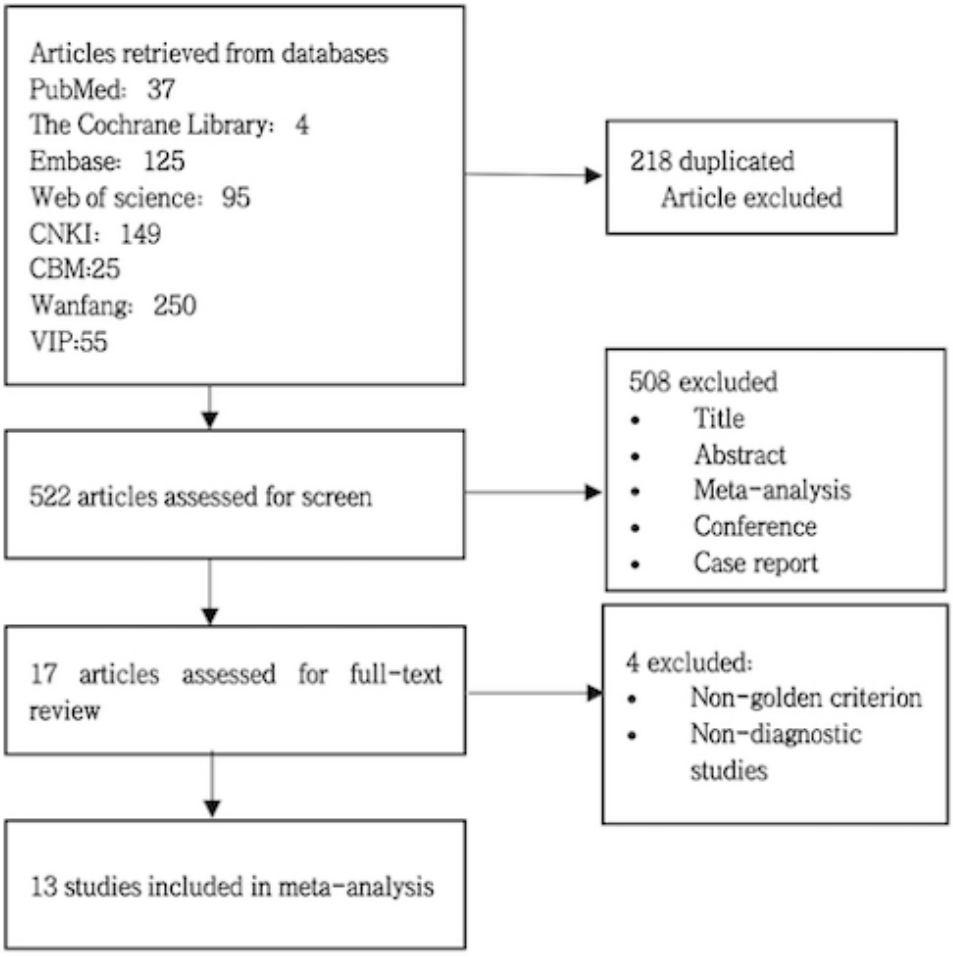

Figure 1: Flowchart of study selection, inclusion, and exclusion for the meta-analysis

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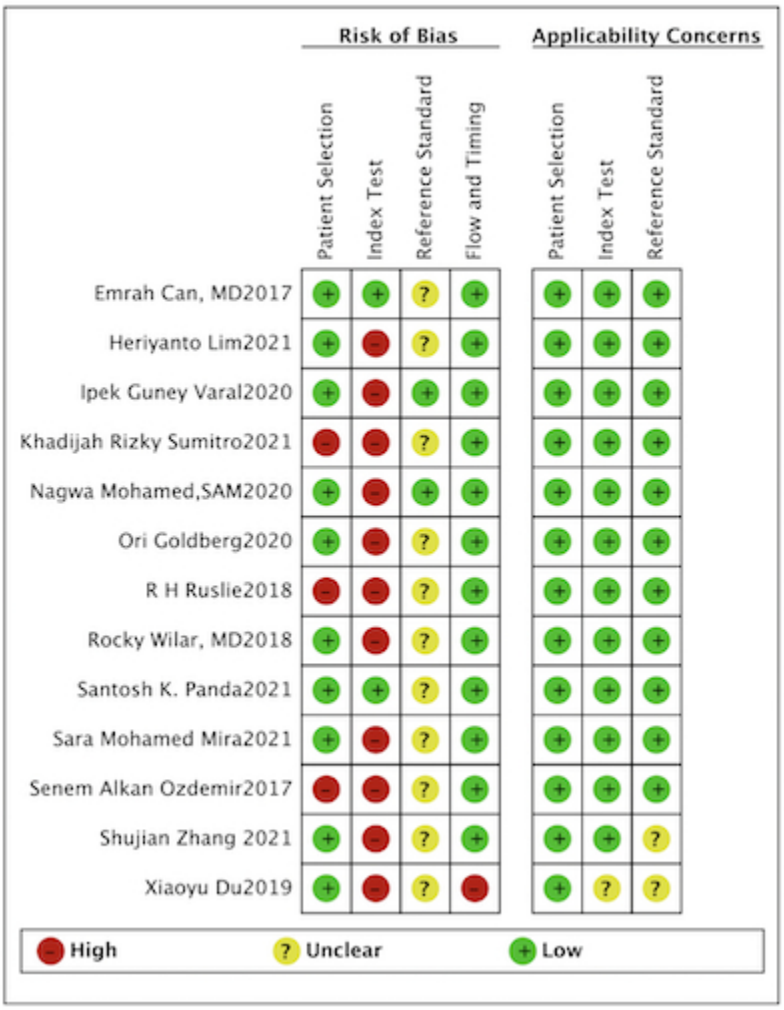

Figure 2: Risk of bias and applicability concerns summary

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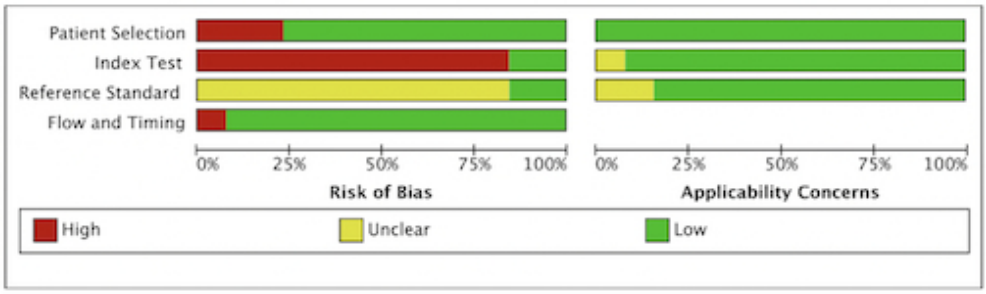

Figure 3: Risk of bias and applicability concerns graph

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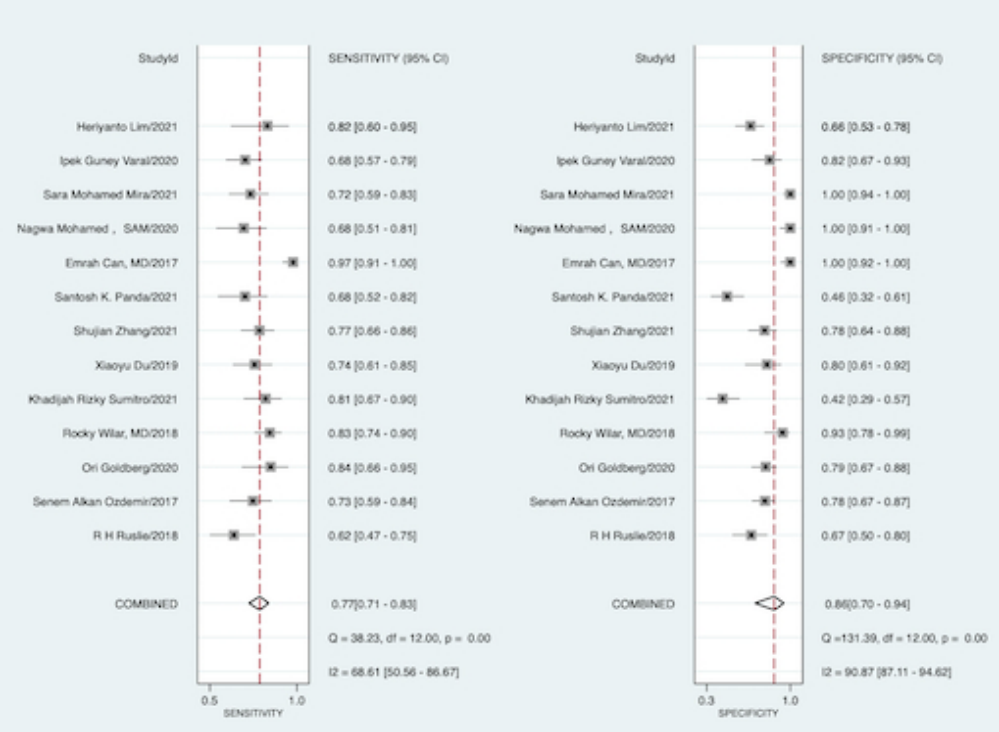

Figure 4: Forest plot of the pooled sensitivity and specificity

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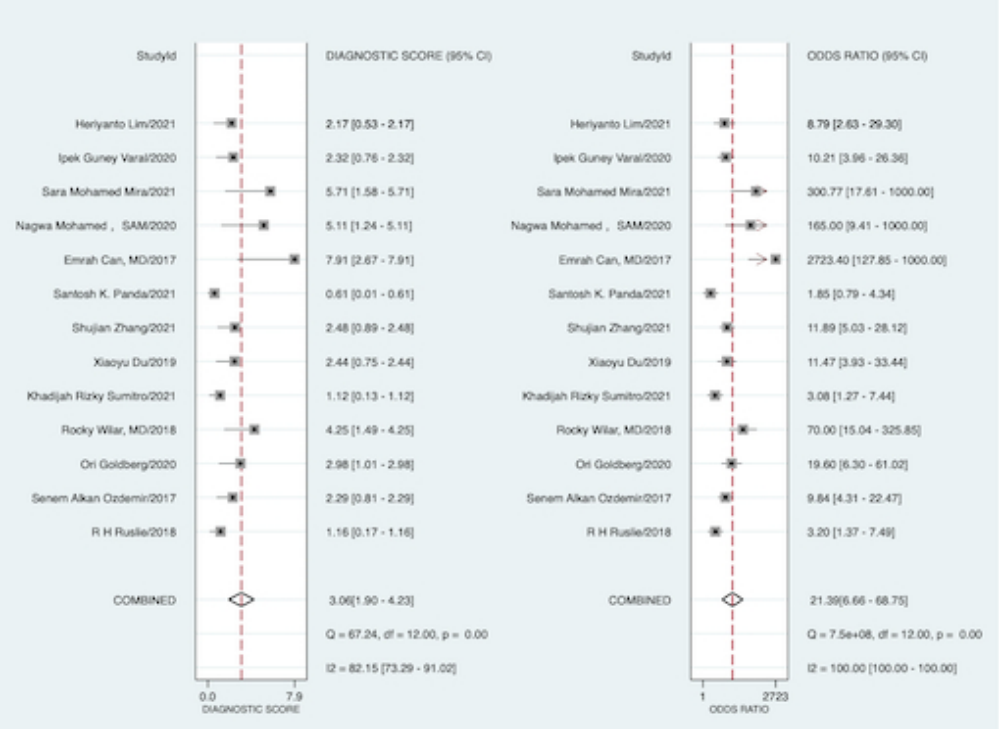

Figure 5: Forest plot of the pooled diagnostic odds ratio

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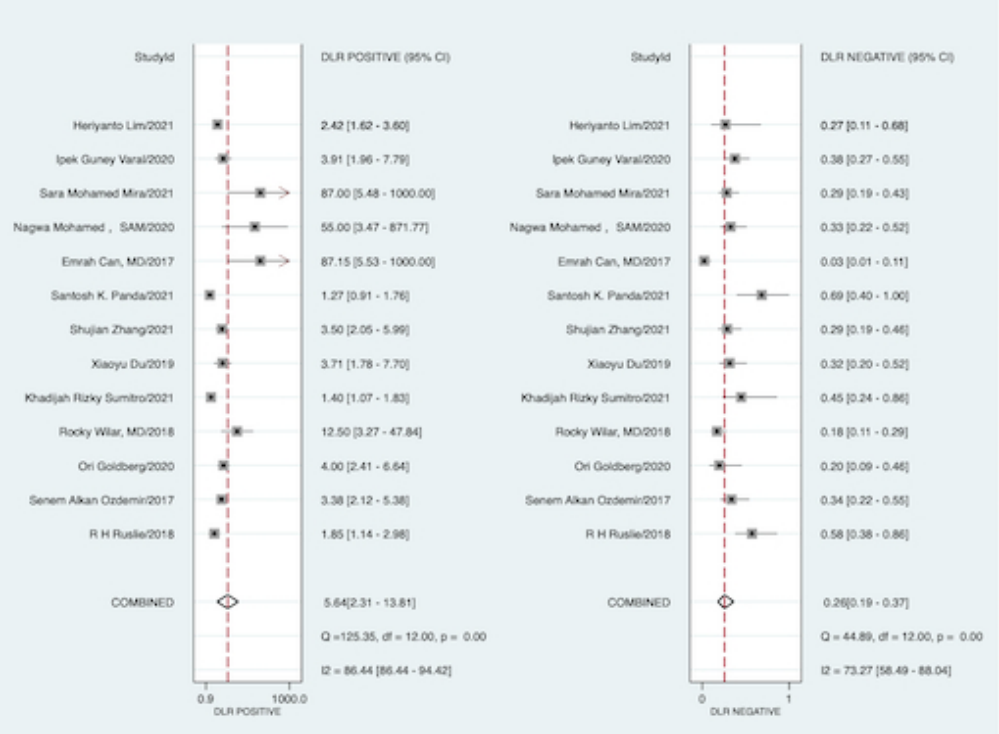

Figure 6: Forest plot of the pooled positive LR and negative LR

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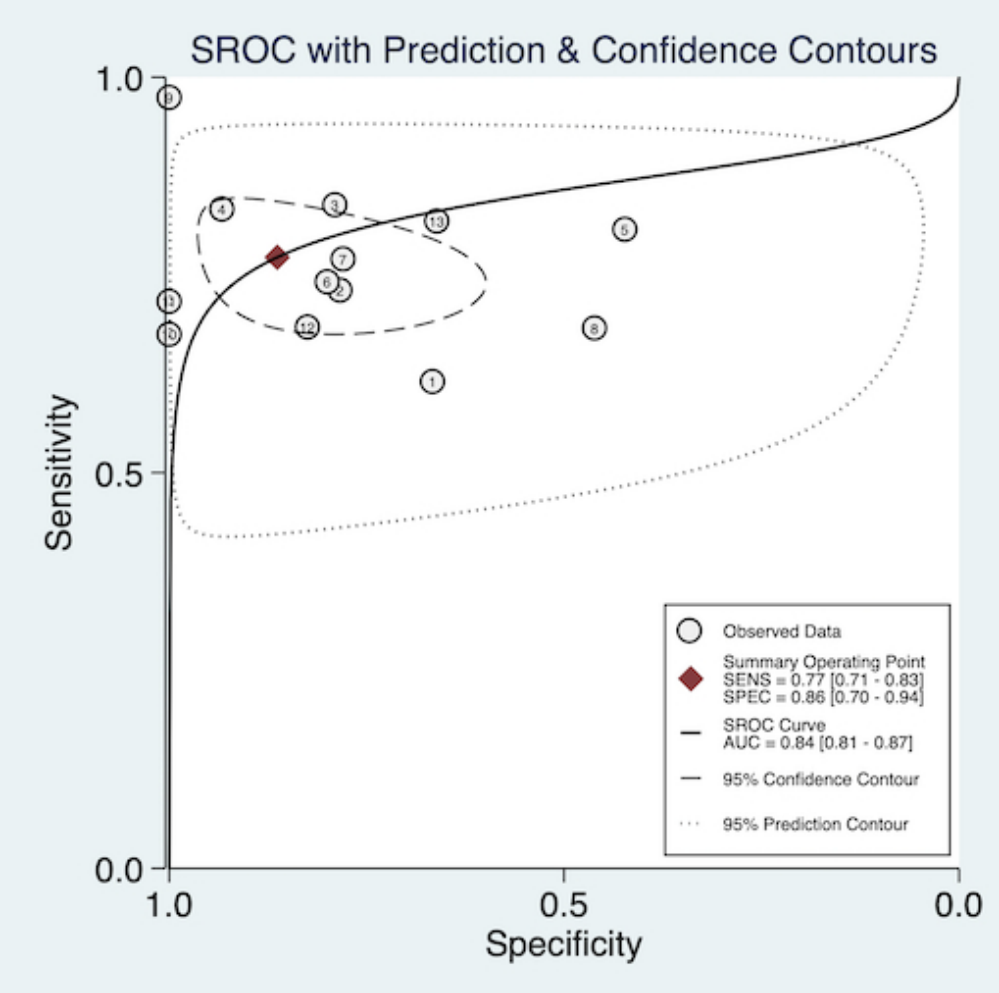

Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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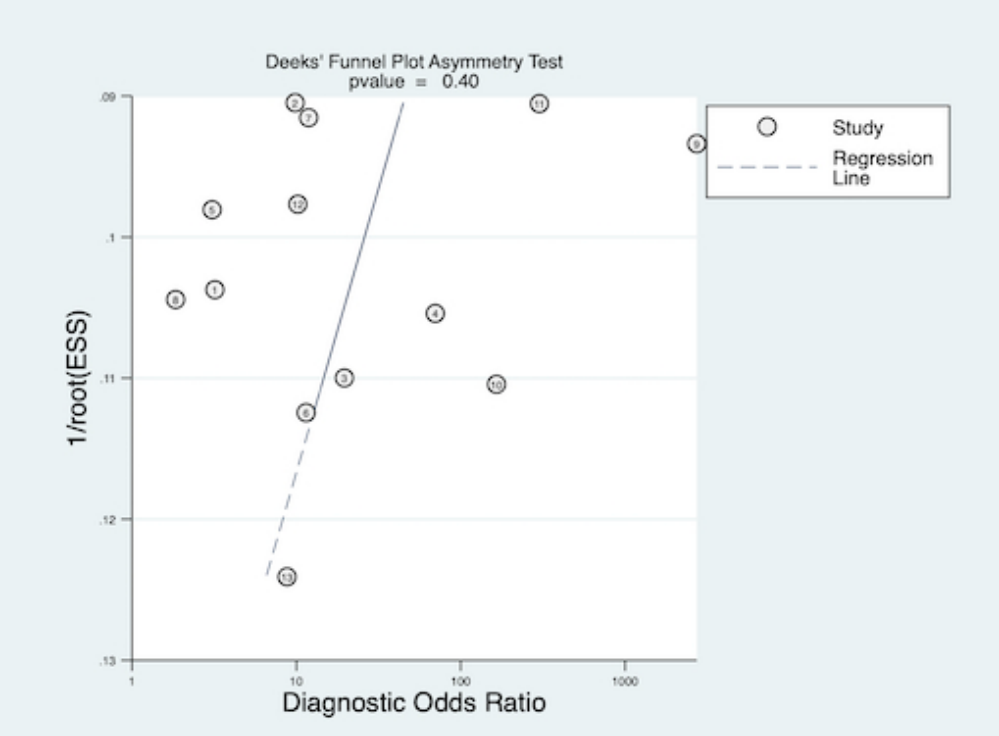

Figure 8: Funnel plot of studies included in the meta-analysis

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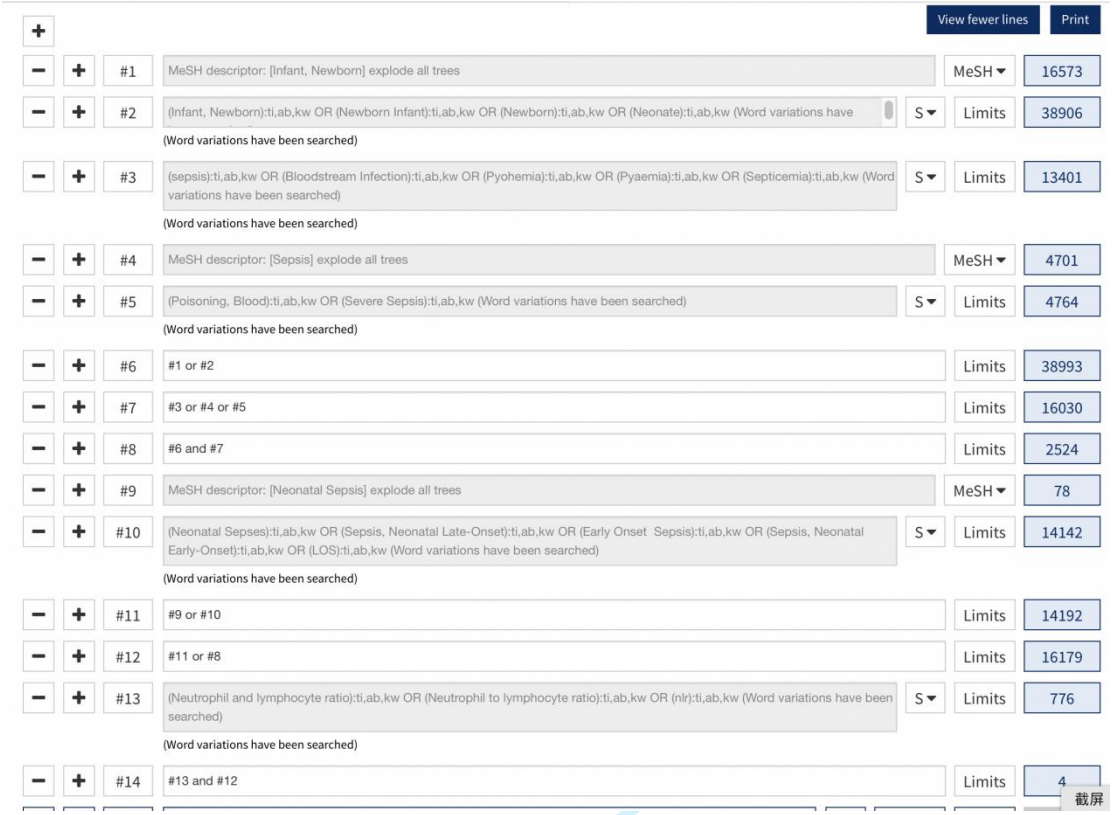
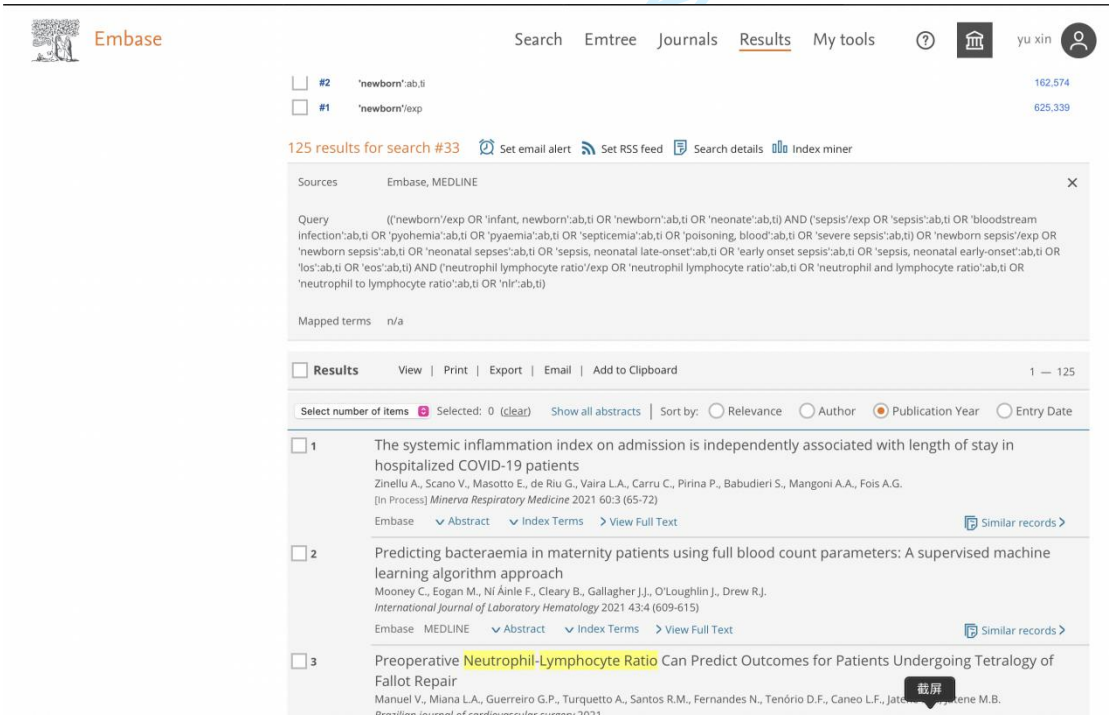
Screenshot of search strategy

1.Cochrane



2.Embase



3.Pubmed

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Search	Actions	Details	Query	Results	Time
#17	•••	⌄	Search: **((Neutrophil to lymphocyte ratio[Title/Abstract]) OR (nor[Title/Abstract])) AND ((((((((((Neonatal Sepsis[Title/Abstract]) OR (Neonatal Sepses[Title/Abstract])) OR (Late-Onset Sepsis[Title/Abstract])) OR (Sepsis, Neonatal Late-Onset[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"[Mesh]) OR (((((((sepsis[Title/Abstract]) OR (Bloodstream Infection[Title/Abstract])) OR (Pyemias[Title/Abstract])) OR (Pyohemia[Title/Abstract])) OR (Pyaemia[Title/Abstract])) OR (Septicemia[Title/Abstract])) OR (Poisoning, Blood[Title/Abstract])) OR (Severe Sepsis[Title/Abstract]))) AND (("Infant, Newborn"[Mesh]) OR ((((Infant, Newborn[Title/Abstract]) OR (Newborn Infant[Title/Abstract])) OR (Newborn[Title/Abstract])) OR (Neonate[Title/Abstract])))))** ("neutrophil to lymphocyte ratio"[Title/Abstract] OR "nor"[Title/Abstract]) AND ("Neonatal Sepsis"[Title/Abstract] OR "neonatal sepses"[Title/Abstract] OR "late onset sepsis"[Title/Abstract] OR (("Sepsis"[MeSH Terms] OR "Sepsis"[All Fields]) AND "neonatal late onset"[Title/Abstract]) OR "early onset sepsis"[Title/Abstract] OR (("Sepsis"[MeSH Terms] OR "Sepsis"[All Fields]) AND "neonatal early onset"[Title/Abstract]) OR "LOS"[Title/Abstract] OR "EOS"[Title/Abstract] OR "Neonatal Sepsis"[MeSH Terms] OR (("Sepsis"[MeSH Terms] OR ("Sepsis"[Title/Abstract] OR "bloodstream infection"[Title/Abstract] OR "Pyemias"[Title/Abstract] OR "Pyohemia"[Title/Abstract] OR "Pyaemia"[Title/Abstract] OR "Septicemia"[Title/Abstract] OR "poisoning blood"[Title/Abstract] OR "severe sepsis"[Title/Abstract])) AND ("infant, newborn"[MeSH Terms] OR ("infant newborn"[Title/Abstract] OR "newborn infant"[Title/Abstract] OR "Newborn"[Title/Abstract] OR "Neonate"[Title/Abstract])))) **Translations** **Sepsis:** "sepsis"[MeSH Terms] OR "sepsis"[All Fields] **Sepsis:** "sepsis"[MeSH Terms] OR "sepsis"[All Fields]	37	23:33:07

截屏

4.Web of science

检索历史:

检索式	检索结果	保存历史/创建跟踪 / 打开保存的检索历史	编辑检索式	组配检索式 (AND OR) 组配	删除检索式 全选 删除
# 7	95	#6 AND #5 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	取消	---	---
# 6	17,131	主题: (Neutrophil and lymphocyte ratio) OR 主题: (Neutrophil to lymphocyte ratio) OR 主题: (nlr) 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
# 5	109,354	#4 OR #3 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
# 4	105,899	主题: (Neonatal Sepsis) OR 主题: (Neonatal Sepses) OR 主题: (Late-Onset Sepsis) OR 主题: (Sepsis, Neonatal Late-Onset) OR 主题: (Early Onset Sepsis) OR 主题: (Sepsis, Neonatal Early-Onset) OR 主题: (LOS) OR 主题: (EOS) 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
# 3	10,142	#2 AND #1 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
# 2	161,176	主题: (sepsis) OR 主题: (Bloodstream Infection) OR 主题: (Pyohemia) OR 主题: (Pyaemia) OR 主题: (Septicemia) OR 主题: (Poisoning, Blood) OR 主题: (Severe Sepsis) 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
# 1	237,926	主题: (Infant, Newborn) OR 主题: (Newborn Infant) OR 主题: (Newborn) OR 主题: (Neonate) 索引=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑		
				AND OR 组配	全选 删除

5.CNKI

6.Wanfang

7.VIP

8.China Biomedical Literature Database

Table 1 characteristics of the included 13 studies

Author	Year	Selected time	Study design	Sepsis diagnosis	Region	Early/Late	Case/Control	TP	FP	FN	TN	SE	SP	Cutoff	Neonates
R H Ruslie[9]	2018	2016–2017	retrospective	Blood culture	USA	EOS、LOS	52/42	32	14	20	28	61.5	64.7	9.4	A、B、C
Sen em Alkan Ozdemir [10]	2017	2014–2015	Prospective	Blood culture	Turkey	LOS	52/75	38	16	14	58	73.8	78.4	1.77	A
Ori Goldberg [11]	2020	2016–2019	Retrospective	Blood culture	Israel	LOS	31/62	26	13	5	49	83.9	79.5	1.59	A、B、C

Rocky Wilar, MD [12]	2018	2017–2017	Cross-sectional study	Blood culture	Indonesia	EOS	90/30	75	21	58	28	93	1.4	A、B、C
Khadijah Rizky Sumitro[13]	2021	2019–2019	Cross-sectional study	Blood culture	Indonesia	EOS、LOS	52/52	42	31	00	28	42	2.2	A、B、C
Xiaoyu Du [14]	2019	2015–2017	Retrospective	Blood culture	China	EOS、LOS	58/30	43	61	54	27	83	0.3	unclear
Shujian Zhang	2021	2018–2020	Descriptive study	Blood culture	China	EOS	74/50	57	11	17	37	78	3.16 9	A、B、C

[15]														
Santosh K. Panda [16]	2021	2018–2018	Retrospective	Blood culture	Philippines	EOS、LOS	41/52	22	88	12	34	64	1.3	A、B、C
Emrah Can, MD [17]	2017	2015–2017	Prospective	Blood culture	Turkey	EOS	78/446	70	02	24	49	10	6.4	B
Nagwa Mohamed, SAM[18]	2020	2018–2019	Prospective	Blood culture	Egypt	EOS	40/407	20	01	14	30	69	0.1	B
Sara	202	2018	Retrosp	Blood	Eg	EOS	60/	4	0	1	6	7	1	A、

Mohamed Mira [19]	1	–2019	ective	culture	ypt	S	60	3		7	0	2	0 0	B
Ipek Gungey	2020	2016–2018	Retrospective	Blood culture	Turkey	LOS	76/40	5 2	7	2 4	3	6 8	8 2	1. 5 7	A
Varal [20]														
Heriyanto Limantara [21]	2021	2018–2018	Retrospective	Blood culture	Indonesia	EOS、LOS	22/62	1 8	2 1	4	4 1	8 1	6 . 8	2. 3 1	A、B

EOS: Early-onset sepsis, LOS: Late-onset sepsis, A: Preterm, B: Term, C: Late term

Table 2 The result of meta-regression

Parameter	category	LRTChi^2	*P* value	I^2	I^2lo	I^2hi
Asia	Yes	11.64	0	83	64	100
	No					
Year	Yes	1.61	0.45	0	0	100
	No					
Preterm	Yes	0.79	0.67	0	0	100
	No					
Prospective	Yes	4.86	0.09	59	7	100
	No					

Table 3 The results of sensitivity analysis

Studies	Number of studies	Sen(95% CI)	Spa(95% CI)	NLR (95%CI)	PLR (95%CI)	DOR (95% CI)	AUC (95%CI)	Q
Overall	13[9-21]	0.77[0.71-0.83]	0.86[0.70-0.94]	0.26[0.19-0.37]	5.6[2.3-13.8]	21[7-69]	0.84[0.81-0.87]	43.168
Remove non-Asian	10[10-17,20-21]	0.80[0.72-0.86]	0.80[0.63-0.91]	0.26[0.16-0.41]	4.0[1.9-8.5]	16[5-51]	0.85[0.82-0.88]	13.329
Remove preterm	11[9,11-19,21]	0.79[0.71-0.85]	0.88[0.67-0.96]	0.24[0.16-0.36]	6.7[2.1-21.5]	27[6-120]	0.86[0.82-0.89]	45.511
Remove LOS	10[9,12-19,21]	0.78[0.70-0.85]	0.90[0.65-0.98]	0.24[0.16-0.37]	7.6[1.9-31.1]	31[5-177]	0.86[0.82-0.88]	47.829

PRISMA-DTA for Abstracts Checklist

Section/topic	#	PRISMA-DTA for Abstracts Checklist item	Reported on page #
TITLE and PURPOSE			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis.	1
Objectives	2	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Eligibility criteria	3	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;（2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	4	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 August 2021.	4
Risk of bias & applicability	5	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6-7
Synthesis of results	A1	Random effects model.	
RESULTS			
Included studies	6	13 studies were finally included, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia.	6
Synthesis of results	7	The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (0.71-0.83), the pooled specificity was 0.86 (0.70-0.94), the positive likelihood ratio was 5.6(2.3-13.8), the negative likelihood ratio was 0.26(0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(0.81-0.87).	7
DISCUSSION			
Strengths and limitations	9	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Interpretation	10	The early diagnosis of neonatal sepsis is particularly important. The ratio of neutrophils to lymphocytes has high sensitivity and specificity for its early diagnosis. It can provide a warning for the clinic and take corresponding measures in time.	10
OTHER			
Funding	11	None	

PRISMA-DTA for Abstracts Checklist

Registration	12	Prospero：CRD42021278881	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

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PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	/
INTRODUCTION			
Rationale	3	The neutrophil to lymphocyte ratio (NLR) is an independent predictor in clinical that has been widely used in various diseases, such as Immune system disease, tumors, cancers, etc. Many studies have shown that the ratio of neutrophils to lymphocytes is more reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there still has a dispute about diagnosing the effectiveness of neonatal sepsis.	2
Clinical role of index test	D1	/	
Objectives	4	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Protocol and registration	5	Prospero：CRD42021278881	
Eligibility criteria	6	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;(2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	7	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 August 2021.	4
Search	8	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.	4
Study selection	9	Two reviewers independently screened the literature, extracted data and evaluated the included studies according to the inclusion criteria,exclusion criteria and methodological quality. In case of disagreement, discuss and resolve or hand over to a third party assist in ruling.	5
Data collection process	10	Two researchers extract the data according to the designed data extraction table, and finally cross-check the extraction situation. If there is any difference, it will be resolved through discussion and negotiation.	5
Definitions for data extraction	11	There are two authors independently 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.	5
Risk of bias and applicability	12	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6

PRISMA-DTA Checklist

Diagnostic accuracy measures	13	ROC curve analysis was used for the included studies to calculate the combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve (AUC). All results were expressed with 95% CI.	5-6
Synthesis of results	14	The I^2 test evaluated study heterogeneity. I^2>50% indicated that the heterogeneity generated in the study would have a specific impact. Meta Disc1.4 software was used to analyze the threshold effect heterogeneity. If the effect sizes of the studies are homogeneous, the fixed-effects model will be used; if they are heterogeneous, the random-effects model will be used. If there is heterogeneity between the studies, the source of the heterogeneity shall be further explored, and the threshold effect and non-threshold effect analysis shall be carried out. The combined sensitivity, combined specificity, combined diagnostic odds ratio (DOR), combined positive likelihood ratio (PLR), combined negative likelihood ratio, and its 95% confidence interval (95%CI) were performed through stata16.0; Simultaneously perform a combined receiver operating characteristic curve (SROC) fitting analysis. At the same time, the Deeks test was used to evaluate the publication bias of the included literature. If P<0.05, it is considered that the included literature has a publication bias.	5-6

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Reference no. 14	
Additional analyses	16	We conducted subgroup analysis on the early-onset sepsis group, cutoff>2, and cutoff<2, respectively. The sensitivity analysis was performed by excluding premature infants, non-Asian, and late-onset sepsis to explore the heterogeneity, meta-regression analysis of year, region , Study type and birth status of newborn.	7-8
RESULTS			
Study selection	17	Preliminary retrieval of 740 pieces of literature, after checking duplicates and reading abstracts, and excluding relevant literature according to the exclusion criteria, 13 studies were finally included. The specific process is shown in (Fig1).	6
Study characteristics	18	The references were included from 2017 to 2021, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia. Basic information of the included literature is shown in (Table 1).	6
Risk of bias and applicability	19	The evaluation results of the risk of bias of the included studies are shown in (Fig2、3).	7
Results of individual studies	20	The research results are displayed in the form of tables and forest diagrams	
Synthesis of results	21	we found that the sensitivity and specificity of I^2 are respectively 68.61% and 90.87%. This indicates that there is considerable heterogeneity. We first conducted a threshold effect test. By using metadisc14.0, we found that the Spearman correlation coefficient was -0.093 p= 0.762 (p>0.05). Furthermore, the Proportion of heterogeneity is likely due to threshold effect = 0.23 in stata16.0. It shows no threshold effect heterogeneity,The pooled sensitivity and specificity of neutrophil to lymphocyte ratio in the diagnosis of neonates were 0.77 (95 % CI 0.71-0.83) and 0.86 (95 % CI 0.70-0.94), respectively; PLR was 5.6 (95 % CI 2.3-13.8), and NLR was 0.26 (95 % CI 0.19-0.37) , DOR is 21(95 % CI 7-69), area under the curve (AUC) is 0.84(95 % CI 0.81-0.87) (Fig 4,5,6,7).	7-8

PRISMA-DTA Checklist

Additional analysis	23	The meta-regression results show that articles in non-Asian regions are the main source of heterogeneity (Table 2). Sensitivity analysis removes non-Asian, preterm, and late-onset sepsis research literature results also show that the region is the main source of heterogeneity. (Table 3) (1).The results of the EOS subgroup analysis showed that the pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis were 0.83 (95 % CI 0.68-0.91) and 0.99 (95 % CI 0.78-1.00); PLR was 91.3 (95 % CI 3.0-2823.6), NLR was 0.18 (95 % CI 0.09-0.34), DOR was 519 (95 % CI 14-19952), and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97). (2).Cutoff value>2, pooled sensitivity and specificity are respectively 0.83(95 % CI 0.66-0.93) and 0.80(95 % CI 0.44-0.95) respectively; PLR is 4.1(95 % CI 1.0-17.2), NLR is 0.21(95 % CI 0.07-0.60), DOR is 20 (95 % CI 2-218), the area under the curve (AUC) is 0.88 (95 % CI 0.85-0.91). (3).Cutoff value <2, pooled sensitivity and specificity are respectively 0.74(95 % CI 0.69-0.78) and 0.90(95 % CI 0.71-0.97); PLR is 7.1(95 % CI 2.3-21.8), NLR is 0.29(95 % CI 0.23-0.36), DOR is 25(95 % CI 7-88) The area under the curve (AUC) is 0.77(95 % CI 0.73-0.81).	7-8
DISCUSSION			
Summary of evidence	24	A total of 13 studies comprising 1365 newborns were involved in this meta-analysis. The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (95 % confidence interval [CI]：0.71-0.83), the pooled specificity was 0.86 (95 % CI 0.70-0.94), the positive likelihood ratio was 5.6(95 % CI 2.3-13.8), the negative likelihood ratio was 0.26(95 % CI 0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(95 % CI 0.81-0.87). The results show that the ratio of neutrophils to lymphocytes has moderate diagnostic value for neonatal sepsis.	8-9
Limitations	25	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Conclusions	26	The neutrophils to lymphocytes ratio is moderate diagnostic capacity with high sensitivity and specificity for diagnosing neonatal sepsis. It can provide a reference value for the early diagnosis of neonatal sepsis.	10
FUNDING			
Funding	27	None	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

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BMJ Open

The accuracy of the neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis: a systematic review and meta-analysis

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Manuscript ID	bmjopen-2021-060391.R1
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Date Submitted by the Author:	01-Aug-2022
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Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Infectious diseases, Intensive care, Paediatrics
Keywords:	INFECTIOUS DISEASES, NEONATOLOGY, Diagnostic microbiology < INFECTIOUS DISEASES

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The 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 neutrophil to lymphocyte ratio diagnoses of neonatal sepsis from inception to June 2022. Two investigators independently conducted the literature search, screening, data extraction. And quality evaluation with the QUADAS-2 checklist. Statistical analysis was performed using Review Manager 5.3, Stata 16.0, and Meta-DISC1.4.

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 neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis was 0.74 (95% confidence interval [CI]: 0.61-0.83), the pooled specificity was 0.88 (95% CI 0.73-0.95), the positive likelihood ratio was 6.35(95% CI 2.6-15.47), the negative likelihood ratio was 0.30(95% CI 0.19-0.46), the diagnostic odds ratio was 21.27(95% CI 6.98-64.84), area under the curve (AUC) was 0.87(95% CI 0.84-0.89). In the subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.75 (95% CI 0.47-0.91), the pooled specificity was 0.99 (95% CI 0.88-1.00), the positive

likelihood ratio was 63.3 (95% CI 5.7-696.8), the negative likelihood ratio was 0.26 (95% CI 0.10-0.63), the diagnostic odds ratio was 247(95% CI 16-3785), and the area under the curve (AUC) was 0.97 (95% CI 0.95-0.98).

Conclusions: Our findings suggest that the neutrophil to lymphocyte ratio 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.

Keywords: Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis

Strengths and limitations

- 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.

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 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% to 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 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-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 (Additional file 1).

Study eligibility

Inclusion criteria: (1). The purpose of the study was to evaluate or explore the diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case group included newborns with confirmed neonatal sepsis, and the control group included newborns with neonates without sepsis. 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 neutrophil-lymphocyte ratio 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(XY, SYS) independently conducted the literature screening, data extraction, and quality evaluation. In case of disagreement, the third author (MWJ) 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 of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist. We used Review Manager (version 5.3) for quality assessment.

Statistical analyses

The heterogeneity of the included studies was evaluated by the Cochrane Q test and I^2 statistic. I^2 could be calculated from the Formula of $I^2=100\%\times(Q - df)/Q$. If I^2 was<50%

or the *p* value was>0.1, a fixed effects model was used for pooling the data; whereas, if I^2 was>50%or the *p* value was<0.1, then there is more heterogeneity among studies, and a bivariate random effects model was used for pooling the data; if I^2 was<50% or the *p* value was<0.1, a fixed effects model could be used; if I^2 was>50% or the *p* value was>0.1, a bivariate random effects model could be used. If there was heterogeneity between the studies, the source of the heterogeneity was further explored, and threshold effect and nonthreshold effect analyses were carried out. Meta Disc1.4 software was used to analyze 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 odds ratio (DOR), combined positive likelihood ratio (LR^+), combined negative likelihood ratio(LR^-), and its 95% confidence interval (95% CI) were determined using Stata 16.0. Simultaneously, a combined receiver operating characteristic curve (SROC) fitting 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 (version 16.0) and MetaDiSc (version 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. [9-22] The specific process is shown in Fig 1. Of these, 783 neonates in the sepsis group and 716 neonates in the nonsepsis group were studied and evaluated. (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 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 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. (Figs. 2, 3)

Heterogeneity exploration

Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly composed of threshold effect heterogeneity and nonthreshold effect heterogeneity. Through the combination of data, we found that the sensitivity and specificity of I^2 were 91.62% and 92.54%, respectively. This indicates that there is considerable heterogeneity. We first conducted a threshold effect test. By using metadisc1.4, 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) (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. (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 0.61-0.83) and 0.88 (95% CI 0.73-0.95), respectively; LR^+ was 6.35 (95% CI 2.5-15.47), LR^- was 0.30 (95% CI 0.19-0.46), DOR was 21.27 (95% CI 6.98-64.84), and area under the curve (AUC) was 0.87 (95% CI 0.84-0.89) (Figs. 4, 5, 6, 7).

The results of the EOS subgroup analysis showed that the pooled sensitivity and specificity of the NLR in the diagnosis of neonatal sepsis were 0.75 (95% CI 0.47-0.91) and 0.99 (95% CI 0.88-1.00); LR^+ was 63.3 (95% CI 5.7-696.8), LR^- was 0.26 (95% CI 0.10-0.63), DOR was 247 (95% CI 16-3785), and the area under the curve (AUC) was 0.97 (95% CI 0.95-0.98). 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 0.53-0.67) and 0.85 (95% CI 0.80-0.90); LR^+ was 3.71 (95% CI 2.73-5.02), LR^- was 0.41 (95% CI 0.08-1.94), DOR was 11.14 (95% CI 6.54-18.98), and the area under the curve (AUC) was 0.85. Cut-off value: 0-2, pooled sensitivity and specificity were 0.74(95% CI 0.69-0.78) and 0.90(95% CI 0.71-0.97), respectively; LR^+ was 7.1(95% CI 2.3-21.8), LR^- was 0.29(95% CI 0.23-0.36), DOR was 25 (95% CI 7-88), the area under the curve (AUC) was 0.77. Cut-off value: 2-4, pooled sensitivity and specificity were 0.79(95% CI 0.72-0.85) and 0.62(95% CI 0.54-0.70); LR^+ was 2.21(95% CI 1.24-3.92), LR^- was0.33(95% CI 0.23-0.46), DOR was 6.73(95% CI 2.81-16.14) The area under the curve (AUC) was 0.85. Cut-off value: >4, pooled sensitivity and specificity were 0.60(95% CI 0.53-0.67) and 0.91(95% CI 0.85-0.95); LR^+ was 9.0(95% CI 0.3-270.24), LR^- was 0.29(95% CI 0.03-2.68), DOR was 31.51(95% CI 0.81-1229.29) The area under the curve (AUC) was 0.95.(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.. (Fig. 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. [23,24,25] 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 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, 0.89), showing that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis.

Omran A et al. found that NLR is closely related to neonatal sepsis. Within a few hours after neonatal sepsis, NLR can rapidly increase in a short time compared to CRP. The use of NLR makes it possible to identify neonatal sepsis early [26] can be used as an auxiliary diagnostic index for the diagnosis of neonatal sepsis, [27] timely diagnosis and early appropriate antibiotic treatment. Seymour CW 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 PCT, [28, 29] suggesting that NLR has better diagnostic performance. Mahmoud NMSA et al. found that when the cut-off value was 0.1, NLR showed the best specificity and negative predictive value for neonatal sepsis (SPE was 99%, NPV was 75%), compared with CRP and PCT, NLR showed higher specificity with better diagnostic power. [18] A study by Alkan Ozdemir S 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.[10] In the study of Goldberg O, 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, [12] 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 emphasizes that the bacteria originate from intrauterine tissue and during delivery, and the spectrum of pathogenic bacteria is relatively concentrated. [30, 31] 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 nonthreshold 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. (Additional file 3). The sensitive analysis results also indicate that the non-Asian region is the primary source of heterogeneity (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 value of the NLR in diagnosing neonatal sepsis in the future.

Conclusion

In summary, our findings suggest that the neutrophil to lymphocyte ratio 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 neutrophil to lymphocyte ratio (NLR) diagnosis and improve neonatal sepsis prognosis.

Abbreviations

NLR: neutrophil to lymphocyte ratio; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; CI: confidence interval; SEN: sensitivity; SPE: specificity; LR^-: negative likelihood ratio; LR^+: positive likelihood ratio; DOR: diagnostic odds ratio; TP: true positive; FP: false positive; TN: true negative; FN: false negative; EOS: early-onset sepsis; LOS: late-onset sepsis; AUC: area under the curve; SROC: summary receiver operating characteristic.

Contributors

XY wrote the manuscript. LHX, ZYX, and MWJ performed the literature review. XY and SYS performed the statistical analysis. MWJ and WCS revised the text. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: Not applicable.

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Reference

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Figure legends:

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

Figure 2: Risk of bias and applicability concerns summary

Figure 3: Risk of bias and applicability concerns graph

Figure 4: Forest plot of the pooled sensitivity and specificity

Figure 5: Forest plot of the pooled diagnostic odds ratio

Figure 6: Forest plot of the pooled positive LR and negative LR

Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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

Additional file legends:

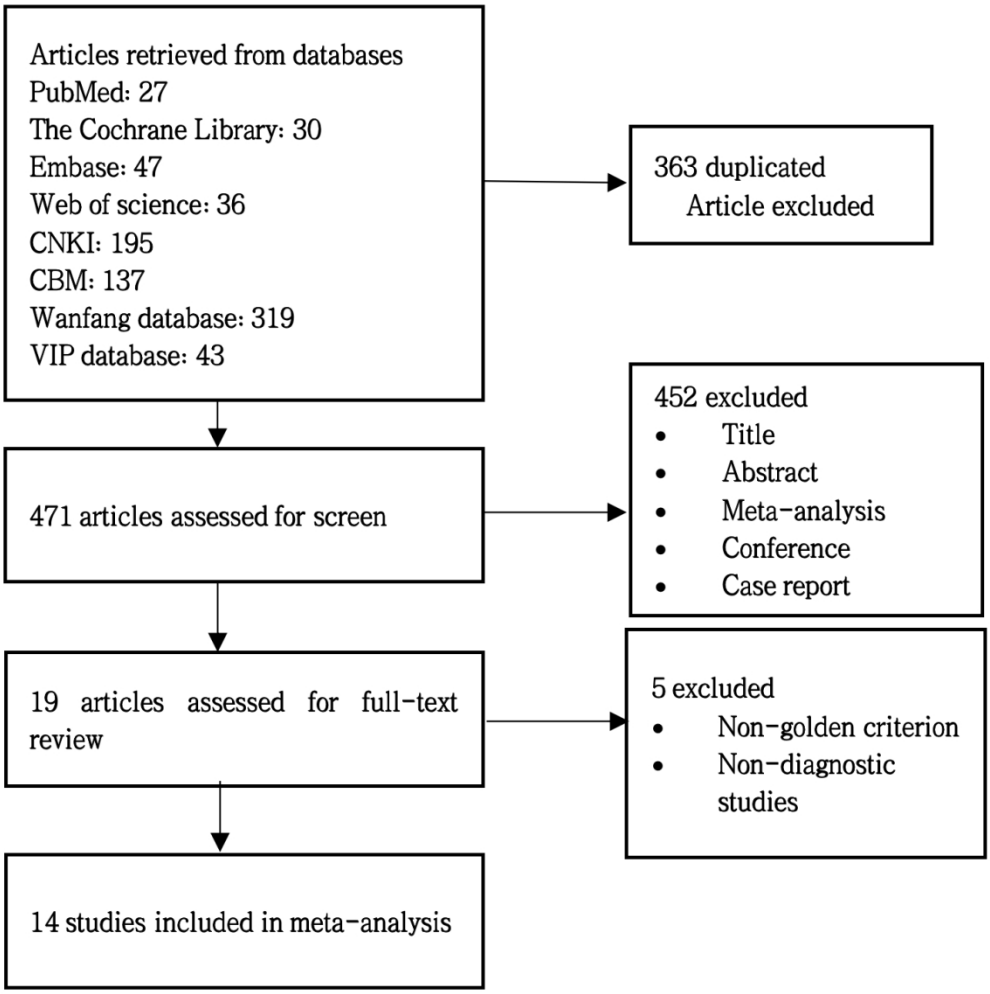
Additional file 1: Detailed literature search strategy

Additional file 2: Characteristics of the included 14 studies

Additional file 3: The result of meta-regression.

Additional file 4: The results of sensitivity analysis.

Additional file 5: Subgroup analysis of neutrophil-to-lymphocyte ratio in the diagnosis of neonatal sepsis



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

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Risk of bias and applicability concerns summary

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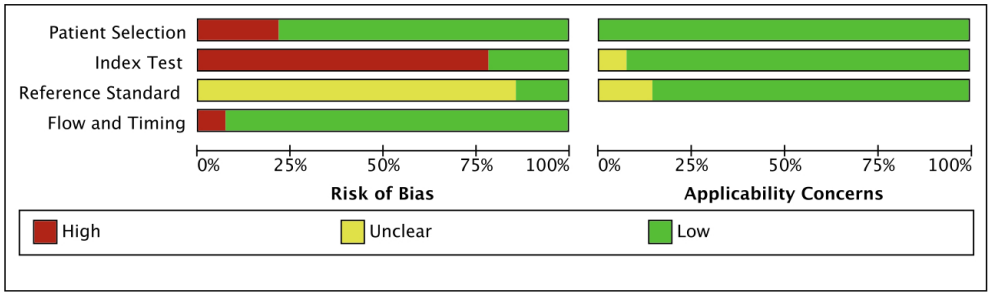

Risk of bias and applicability concerns graph

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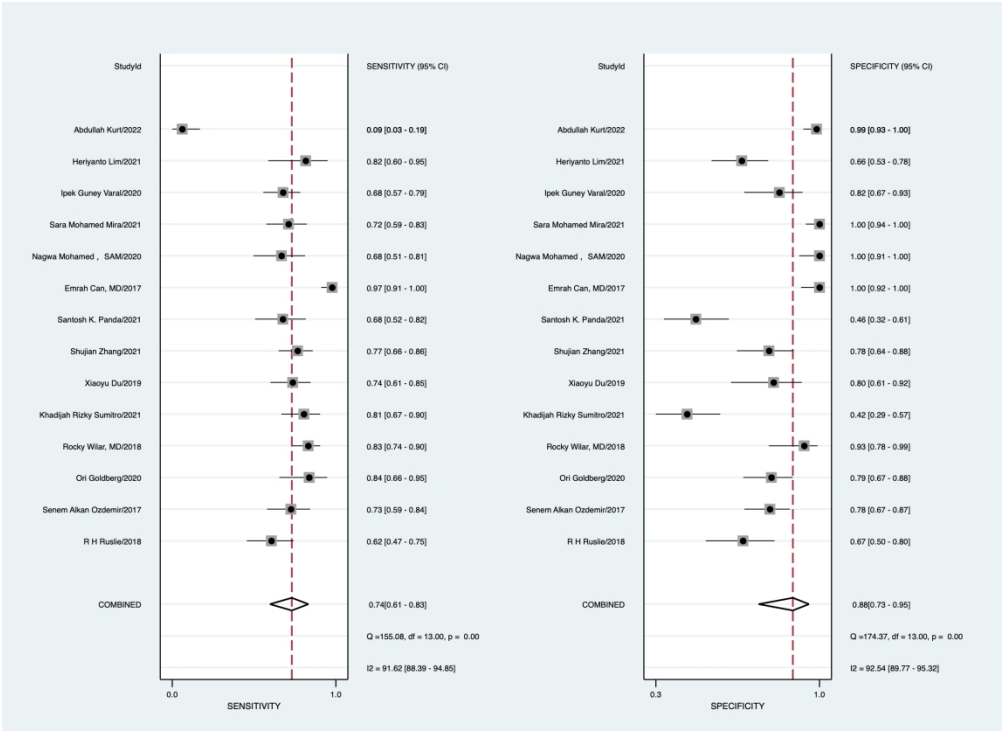

Forest plot of the pooled sensitivity and specificity

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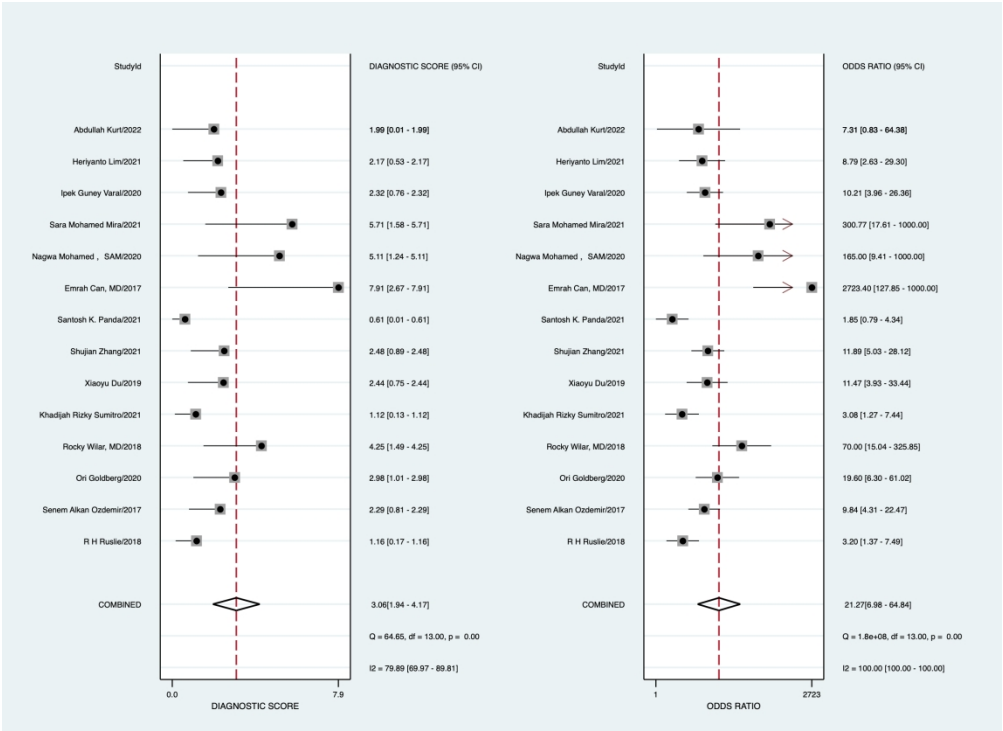

Forest plot of the pooled diagnostic odds ratio

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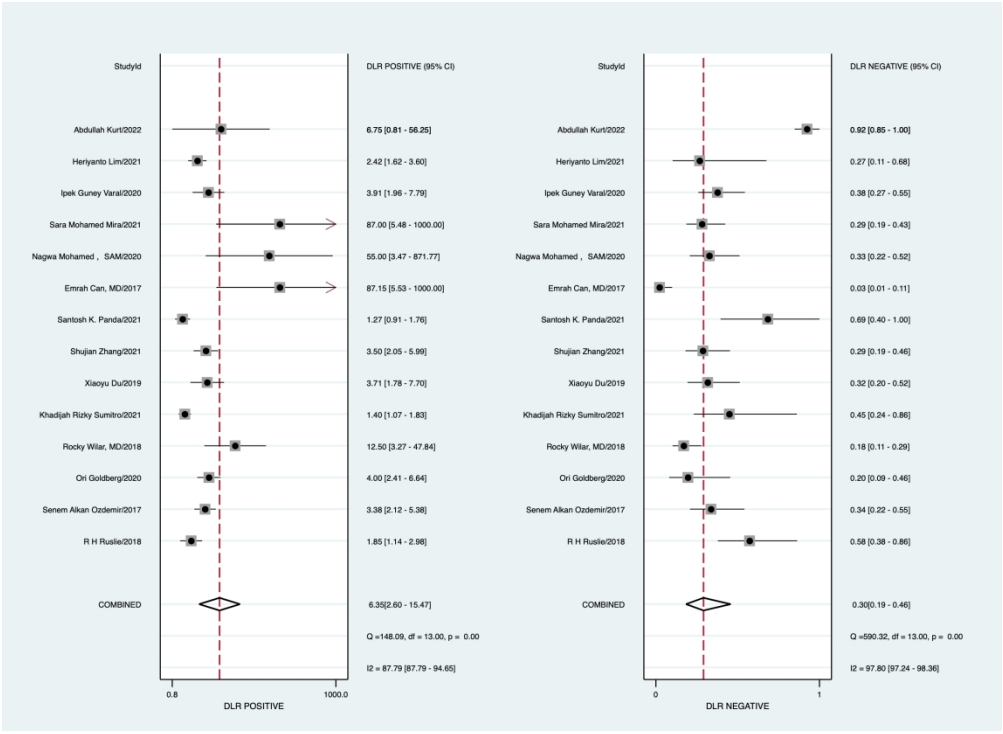

Forest plot of the pooled positive LR and negative LR

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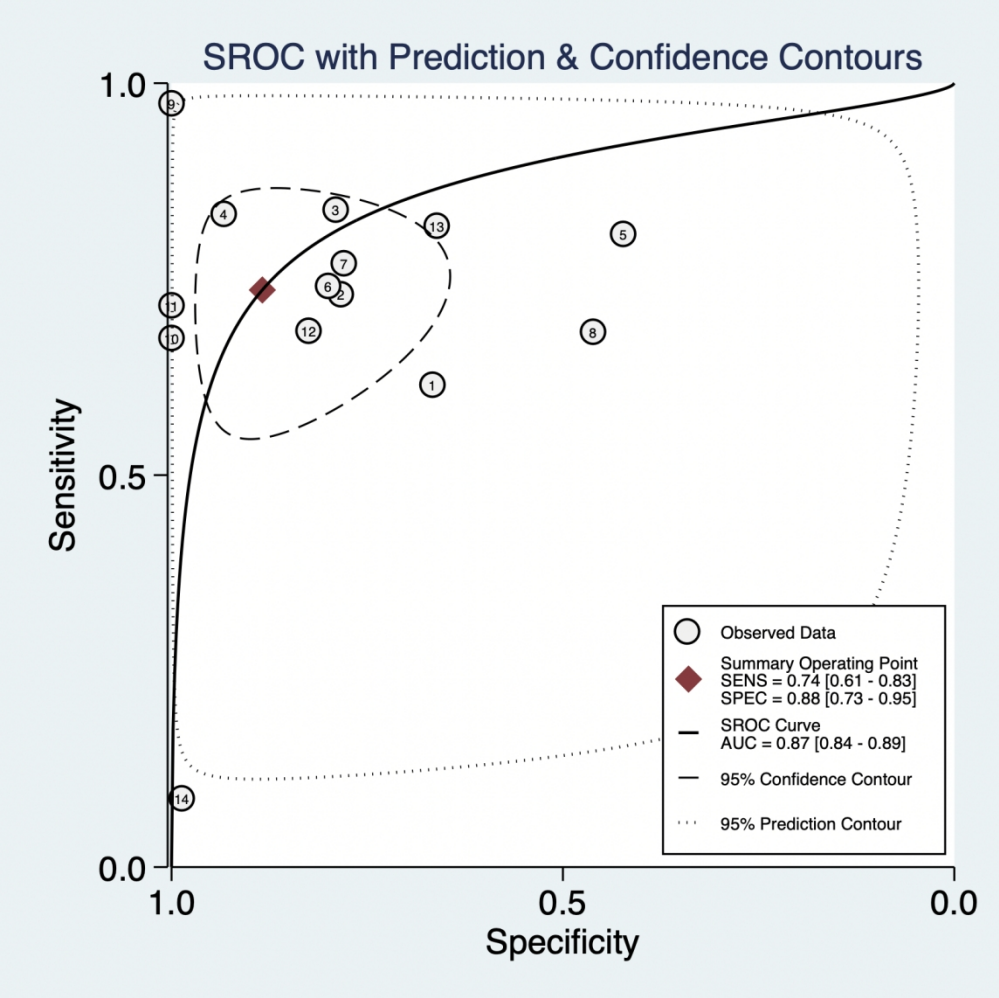

SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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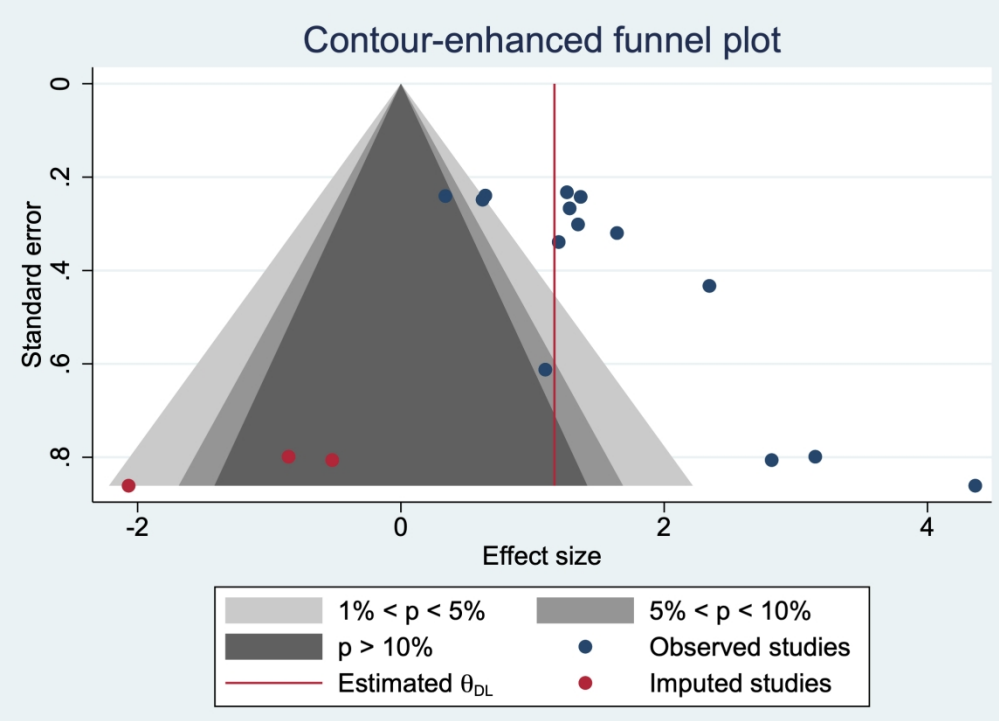

Contour-enhanced funnel plot of studies included in the meta-analysis

404x292mm (144 x 144 DPI)

Detailed retrieval strategy

Database	Pubmed
Website	https://pubmed.ncbi.nlm.nih.gov
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 Sepses[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 (Pyaemia[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 sepses':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

	#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
Database	Web of science
Website	http://www.webofscience.com
Time	database building - 2022.06.28
Results	36
Search details	#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
Database	Cochrane
Website	https://www.cochrane.org
Time	database building - 2022.06.28
Results	30
Search details	ID Search Hits #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

	#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 (*Chinese database*)
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 (*Chinese database*)
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 (*Chinese database*)
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 (*Chinese database*)
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/Control	TP	FP	FN	TN	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、LOS	57/77	5	1	52	76	8.8	98.7	4.79	NA
						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.

[2] Alkan Ozdemir S ,S, Arun Ozer E , Ilhan O , et al. Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?[infants? [J]. *Journal of Clinical Laboratory Analysis*, 2017:e22338.

[3] Goldberg O, Amitai N, Chodick G, et al. Can we improve early identification of neonatal late-onset sepsis? A validated prediction model[J]. *Journal of Perinatology*, 2020, 40(9): p. 1315-1322.

[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.

[5] Sumitro K R , Utomo M T , Widodo A . Neutrophil-to-Lymphocyte Ratio as an Alternative Marker of Neonatal Sepsis in Developing Countries[J]. *Oman Medical Journal*, 2021, 36(1):e214-e214.

[6] Du xiaoyu,Ai liang. Changes and clinical significance of NLR, CRP and PCT in neonates with sepsis. *Experimental and Laboratory Medicine*,2019.37(01): p.110-112.

[7] Zhang, S.J.Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratio as Predictive Biomarkers for Early-onset Neonatal Sepsis. *Jcpsp-Journal of the College of Physicians and Surgeons Pakistan*, 2021. 31(7): p. 821-824.

[8] Panda S K, Nayak M K, Rath S, et al. The Utility of the Neutrophil-Lymphocyte Ratio as an Early Diagnostic Marker in Neonatal Sepsis[J]. *Cureus*, 2021, 13(1): e12891.

[9] E.C, H.S,C.C,et al.The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Journal of pediatric hematology/oncology*, 2018. 40(4) E229-E232.

[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.

[11] Mira S M, Alkhalegy H A, Abd-Elraheem S I, et al. Neutrophil and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis[J]. *International Journal of Medical Arts*, 2021, 3(2): 1274-1281.

[12] Varal I,Dogan P. Can neutrophil-lymphocyte ratio be a predictor of late-onset sepsis in preterm infants? [J]. *Annals of Medical Research*, 2020, 27(1):23.

[13] Lim, H.Sukmawati.M, Artana.W. D,et al.Validity of neutrophil lymphocyte count ratio in neonatal sepsis. *International Journal of Health Sciences*, (2021).5(2), 53-61.

[14] Kurt A, Tosun MS, Altuntaş N: Diagnostic accuracy of complete blood cell count and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios for neonatal infection. *Asian Biomedicine* 2022, 16(1):43-52.

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	Pvalue	I^2	I^2lo	I^2hi
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.

[2] Alkan Ozdemir S ,S, Arun Ozer E , Ilhan O , et al. Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?[infants? [J]. *Journal of Clinical Laboratory Analysis*, 2017:e22338.

[3] Goldberg O, Amitai N, Chodick G, et al. Can we improve early identification of neonatal late-onset sepsis? A validated prediction model[J]. *Journal of Perinatology*, 2020, 40(9): p. 1315-1322.

[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.

[5] Sumitro K R , Utomo M T , Widodo A . Neutrophil-to-Lymphocyte Ratio as an Alternative Marker of Neonatal Sepsis in Developing Countries[J]. *Oman Medical Journal*, 2021, 36(1):e214-e214.

[6] Du xiaoyu,Ai liang. Changes and clinical significance of NLR, CRP and PCT in neonates with sepsis. *Experimental and Laboratory Medicine*,2019.37(01): p.110-112.

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[8] Panda S K, Nayak M K, Rath S, et al. The Utility of the Neutrophil-Lymphocyte Ratio as an Early Diagnostic Marker in Neonatal Sepsis[J]. *Cureus*, 2021, 13(1): e12891.

[9] E.C, H.S,C.C,et al.The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Journal of pediatric hematology/oncology*, 2018. 40(4) E229-E232.

[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.

[11] Mira S M, Alkhalegy H A, Abd-Elraheem S I, et al. Neutrophil and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis[J]. *International Journal of Medical Arts*, 2021, 3(2): 1274-1281.

[12] Varal I,Dogan P. Can neutrophil-lymphocyte ratio be a predictor of late-onset sepsis in preterm infants? [J]. *Annals of Medical Research*, 2020, 27(1):23.

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[14] Kurt A, Tosun MS, Altuntaş N: Diagnostic accuracy of complete blood cell count and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios for neonatal infection. *Asian Biomedicine* 2022, 16(1):43-52.

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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[6] Du xiaoyu,Ai liang. Changes and clinical significance of NLR, CRP and PCT in neonates with sepsis. *Experimental and Laboratory Medicine*,2019.37(01): p.110-112.

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[8] Panda S K, Nayak M K, Rath S, et al. The Utility of the Neutrophil-Lymphocyte Ratio as an Early Diagnostic Marker in Neonatal Sepsis[J]. *Cureus*, 2021, 13(1): e12891.

[9] E.C, H.S,C.C,et al.The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Journal of pediatric hematology/oncology*, 2018. 40(4) E229-E232.

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PRISMA-DTA for Abstracts Checklist

Section/topic	#	PRISMA-DTA for Abstracts Checklist item	Reported on page #
TITLE and PURPOSE			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis.	1
Objectives	2	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Eligibility criteria	3	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;（2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	4	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 August 2021.	4
Risk of bias & applicability	5	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6-7
Synthesis of results	A1	Random effects model.	
RESULTS			
Included studies	6	13 studies were finally included, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia.	6
Synthesis of results	7	The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (0.71-0.83), the pooled specificity was 0.86 (0.70-0.94), the positive likelihood ratio was 5.6(2.3-13.8), the negative likelihood ratio was 0.26(0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(0.81-0.87).	7
DISCUSSION			
Strengths and limitations	9	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Interpretation	10	The early diagnosis of neonatal sepsis is particularly important. The ratio of neutrophils to lymphocytes has high sensitivity and specificity for its early diagnosis. It can provide a warning for the clinic and take corresponding measures in time.	10
OTHER			
Funding	11	None	

PRISMA-DTA for Abstracts Checklist

Registration	12	Prospero：CRD42021278881	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

For more information, visit: **www.prisma-statement.org**.

PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	/
INTRODUCTION			
Rationale	3	The neutrophil to lymphocyte ratio (NLR) is an independent predictor in clinical that has been widely used in various diseases, such as Immune system disease, tumors, cancers, etc. Many studies have shown that the ratio of neutrophils to lymphocytes is more reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there still has a dispute about diagnosing the effectiveness of neonatal sepsis.	2
Clinical role of index test	D1	/	
Objectives	4	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Protocol and registration	5	Prospero：CRD42021278881	
Eligibility criteria	6	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;(2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	7	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 August 2021.	4
Search	8	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.	4
Study selection	9	Two reviewers independently screened the literature, extracted data and evaluated the included studies according to the inclusion criteria,exclusion criteria and methodological quality. In case of disagreement, discuss and resolve or hand over to a third party assist in ruling.	5
Data collection process	10	Two researchers extract the data according to the designed data extraction table, and finally cross-check the extraction situation. If there is any difference, it will be resolved through discussion and negotiation.	5
Definitions for data extraction	11	There are two authors independently 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.	5
Risk of bias and applicability	12	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6

PRISMA-DTA Checklist

Diagnostic accuracy measures	13	ROC curve analysis was used for the included studies to calculate the combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve (AUC). All results were expressed with 95% CI.	5-6
Synthesis of results	14	The I^2 test evaluated study heterogeneity. I^2>50% indicated that the heterogeneity generated in the study would have a specific impact. Meta Disc1.4 software was used to analyze the threshold effect heterogeneity. If the effect sizes of the studies are homogeneous, the fixed-effects model will be used; if they are heterogeneous, the random-effects model will be used. If there is heterogeneity between the studies, the source of the heterogeneity shall be further explored, and the threshold effect and non-threshold effect analysis shall be carried out. The combined sensitivity, combined specificity, combined diagnostic odds ratio (DOR), combined positive likelihood ratio (PLR), combined negative likelihood ratio, and its 95% confidence interval (95%CI) were performed through stata16.0; Simultaneously perform a combined receiver operating characteristic curve (SROC) fitting analysis. At the same time, the Deeks test was used to evaluate the publication bias of the included literature. If P<0.05, it is considered that the included literature has a publication bias.	5-6

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Reference no. 14	
Additional analyses	16	We conducted subgroup analysis on the early-onset sepsis group, cutoff>2, and cutoff<2, respectively. The sensitivity analysis was performed by excluding premature infants, non-Asian, and late-onset sepsis to explore the heterogeneity, meta-regression analysis of year, region , Study type and birth status of newborn.	7-8
RESULTS			
Study selection	17	Preliminary retrieval of 740 pieces of literature, after checking duplicates and reading abstracts, and excluding relevant literature according to the exclusion criteria, 13 studies were finally included. The specific process is shown in (Fig1).	6
Study characteristics	18	The references were included from 2017 to 2021, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia. Basic information of the included literature is shown in (Table 1).	6
Risk of bias and applicability	19	The evaluation results of the risk of bias of the included studies are shown in (Fig2、3).	7
Results of individual studies	20	The research results are displayed in the form of tables and forest diagrams	
Synthesis of results	21	we found that the sensitivity and specificity of I^2 are respectively 68.61% and 90.87%. This indicates that there is considerable heterogeneity. We first conducted a threshold effect test. By using metadisc14.0, we found that the Spearman correlation coefficient was -0.093 p= 0.762 (p>0.05). Furthermore, the Proportion of heterogeneity is likely due to threshold effect = 0.23 in stata16.0. It shows no threshold effect heterogeneity,The pooled sensitivity and specificity of neutrophil to lymphocyte ratio in the diagnosis of neonates were 0.77 (95 % CI 0.71-0.83) and 0.86 (95 % CI 0.70-0.94), respectively; PLR was 5.6 (95 % CI 2.3-13.8), and NLR was 0.26 (95 % CI 0.19-0.37) , DOR is 21(95 % CI 7-69), area under the curve (AUC) is 0.84(95 % CI 0.81-0.87) (Fig 4,5,6,7).	7-8

PRISMA-DTA Checklist

Additional analysis	23	The meta-regression results show that articles in non-Asian regions are the main source of heterogeneity (Table 2). Sensitivity analysis removes non-Asian, preterm, and late-onset sepsis research literature results also show that the region is the main source of heterogeneity. (Table 3) (1).The results of the EOS subgroup analysis showed that the pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis were 0.83 (95 % CI 0.68-0.91) and 0.99 (95 % CI 0.78-1.00); PLR was 91.3 (95 % CI 3.0-2823.6), NLR was 0.18 (95 % CI 0.09-0.34), DOR was 519 (95 % CI 14-19952), and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97). (2).Cutoff value>2, pooled sensitivity and specificity are respectively 0.83(95 % CI 0.66-0.93) and 0.80(95 % CI 0.44-0.95) respectively; PLR is 4.1(95 % CI 1.0-17.2), NLR is 0.21(95 % CI 0.07-0.60), DOR is 20 (95 % CI 2-218), the area under the curve (AUC) is 0.88 (95 % CI 0.85-0.91). (3).Cutoff value <2, pooled sensitivity and specificity are respectively 0.74(95 % CI 0.69-0.78) and 0.90(95 % CI 0.71-0.97); PLR is 7.1(95 % CI 2.3-21.8), NLR is 0.29(95 % CI 0.23-0.36), DOR is 25(95 % CI 7-88) The area under the curve (AUC) is 0.77(95 % CI 0.73-0.81).	7-8
DISCUSSION			
Summary of evidence	24	A total of 13 studies comprising 1365 newborns were involved in this meta-analysis. The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (95 % confidence interval [CI]：0.71-0.83), the pooled specificity was 0.86 (95 % CI 0.70-0.94), the positive likelihood ratio was 5.6(95 % CI 2.3-13.8), the negative likelihood ratio was 0.26(95 % CI 0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(95 % CI 0.81-0.87). The results show that the ratio of neutrophils to lymphocytes has moderate diagnostic value for neonatal sepsis.	8-9
Limitations	25	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Conclusions	26	The neutrophils to lymphocytes ratio is moderate diagnostic capacity with high sensitivity and specificity for diagnosing neonatal sepsis. It can provide a reference value for the early diagnosis of neonatal sepsis.	10
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The 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 neutrophil to lymphocyte ratio diagnoses of neonatal sepsis from inception to June 2022. Two investigators independently conducted the literature search, screening, data extraction. And quality evaluation with the QUADAS-2 checklist. Statistical analysis was performed using Review Manager 5.3, Stata 16.0, R(version 3.6.0) and Meta-DISC1.4.

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 neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis was 0.74 (95% confidence interval [CI]: 0.61-0.83), the pooled specificity was 0.88 (95% CI 0.73-0.95), the positive likelihood ratio was 6.35(95% CI 2.6-15.47), the negative

likelihood ratio was 0.30(95% CI 0.19-0.46), the diagnostic odds ratio was 12.88 (95% CI 4.47-37.08), area under the curve (AUC) was 0.87(95% CI 0.84-0.89). In the subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.75 (95% CI 0.47-0.91), the pooled specificity was 0.99 (95% CI 0.88-1.00), the positive likelihood ratio was 63.3 (95% CI 5.7-696.8), the negative likelihood ratio was 0.26 (95% CI 0.10-0.63), the diagnostic odds ratio was 247(95% CI 16-3785), and the area under the curve (AUC) was 0.97 (95% CI 0.95-0.98).

Conclusions: Our findings suggest that the neutrophil to lymphocyte ratio 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.

Keywords: Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis

Strengths and limitations

- 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.

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 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% to 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 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-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 (Additional file 1).

Study eligibility

Inclusion criteria: (1). The purpose of the study was to evaluate or explore the diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case group included newborns with confirmed neonatal sepsis, and the control group included newborns with neonates without sepsis. 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 neutrophil-lymphocyte ratio 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(XY, SYS) independently conducted the literature screening, data extraction, and quality evaluation. In case of disagreement, the third author (MWJ) 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 of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist. We used Review Manager (version 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 nonthreshold effect analyses were carried out. Meta Disc1.4 software was used to analyze 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 odds ratio (DOR), combined positive likelihood ratio (LR+), combined negative likelihood ratio(LR-), and its 95% confidence interval (95% CI) were determined using Stata 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 (version 16.0), R(version 3.6.0) and MetaDiSc (version 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 Fig 1. Of these, 783 neonates in the sepsis group and 716 neonates in the nonsepsis group were studied and evaluated. (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 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 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. (Figs. 2, 3)

Heterogeneity exploration

Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly composed of threshold effect heterogeneity and nonthreshold 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 metadisc1.4, 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) (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. (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 0.61-0.83) and 0.88 (95% CI 0.73-0.95), respectively; LR^+ was 6.35 (95% CI 2.5-15.47), LR^- was 0.30 (95% CI 0.19-0.46), DOR was 12.88 (95% CI 4.47-37.08), and area under the curve (AUC) was 0.87 (95% CI 0.84-0.89) (Figs. 4, 5, 6, 7).

The results of the 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-

0.91) and 0.99 (95% CI 0.88-1.00); LR^+ was 63.3 (95% CI 5.7-696.8), LR^- was 0.26 (95% CI 0.10-0.63), DOR was 247 (95% CI 16-3785), and the area under the curve (AUC) was 0.97 (95% CI 0.95-0.98). 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 0.53-0.67) and 0.85 (95% CI 0.80-0.90); LR^+ was 3.71 (95% CI 2.73-5.02), LR^- was 0.41 (95% CI 0.08-1.94), DOR was 11.14 (95% CI 6.54-18.98), and the area under the curve (AUC) was 0.85. Cut-off value: 0-2, pooled sensitivity and specificity were 0.74(95% CI 0.69-0.78) and 0.90(95% CI 0.71-0.97), respectively; LR^+ was 7.1(95% CI 2.3-21.8), LR^- was 0.29(95% CI 0.23-0.36), DOR was 25 (95% CI 7-88), the area under the curve (AUC) was 0.77. Cut-off value: 2-4, pooled sensitivity and specificity were 0.79(95% CI 0.72-0.85) and 0.62(95% CI 0.54-0.70); LR^+ was 2.21(95% CI 1.24-3.92), LR^- was0.33(95% CI 0.23-0.46), DOR was 6.73(95% CI 2.81-16.14) The area under the curve (AUC) was 0.85. Cut-off value: >4, pooled sensitivity and specificity were 0.60(95% CI 0.53-0.67) and 0.91(95% CI 0.85-0.95); LR^+ was 9.0(95% CI 0.3-270.24), LR^- was 0.29(95% CI 0.03-2.68), DOR was 31.51(95% CI 0.81-1229.29) The area under the curve (AUC) was 0.95.(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.. (Fig. 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. [24,25,26] 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 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, 0.89), showing that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis.

Omran A et al. found that NLR is closely related to neonatal sepsis. Within a few hours after neonatal sepsis, NLR can rapidly increase in a short time compared to CRP. The use of NLR makes it possible to identify neonatal sepsis early [27] can be used as an auxiliary diagnostic index for the diagnosis of neonatal sepsis, [28] timely diagnosis and early appropriate antibiotic treatment. Seymour CW 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 PCT, [29, 30] suggesting that NLR has better diagnostic performance. Mahmoud NMSA et al. found that when the cut-off value was 0.1, NLR showed the best

specificity and negative predictive value for neonatal sepsis (SPE was 99%, NPV was 75%), compared with CRP and PCT, NLR showed higher specificity with better diagnostic power. [19] A study by Alkan Ozdemir S 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 Goldberg O, 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 emphasizes 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 nonthreshold 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. (Additional file 3). The sensitive analysis results also indicate that the non-Asian region is the primary source of heterogeneity

(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 value of the NLR in diagnosing neonatal sepsis in the future.

Conclusion

In summary, our findings suggest that the neutrophil to lymphocyte ratio 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 neutrophil to lymphocyte ratio (NLR) diagnosis and improve neonatal sepsis prognosis.

Abbreviations

NLR: neutrophil to lymphocyte ratio; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; CI: confidence interval; SEN: sensitivity; SPE: specificity; LR^-: negative likelihood ratio; LR^+: positive likelihood ratio; DOR: diagnostic odds ratio; TP: true positive; FP: false positive; TN: true negative; FN: false negative; EOS: early-onset sepsis; LOS: late-onset sepsis; AUC: area under the curve; SROC: summary receiver operating characteristic.

Contributors

XY wrote the manuscript. LHX, ZYX, and MWJ performed the literature review. XY and SYS performed the statistical analysis. MWJ and WCS revised the text. All authors read and approved the final manuscript.

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Figure legends:

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

Figure 2: Risk of bias and applicability concerns summary

Figure 3: Risk of bias and applicability concerns graph

Figure 4: Forest plot of the pooled sensitivity and specificity

Figure 5: Forest plot of the pooled diagnostic odds ratio

Figure 6: Forest plot of the pooled positive LR and negative LR

Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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

Additional file legends:

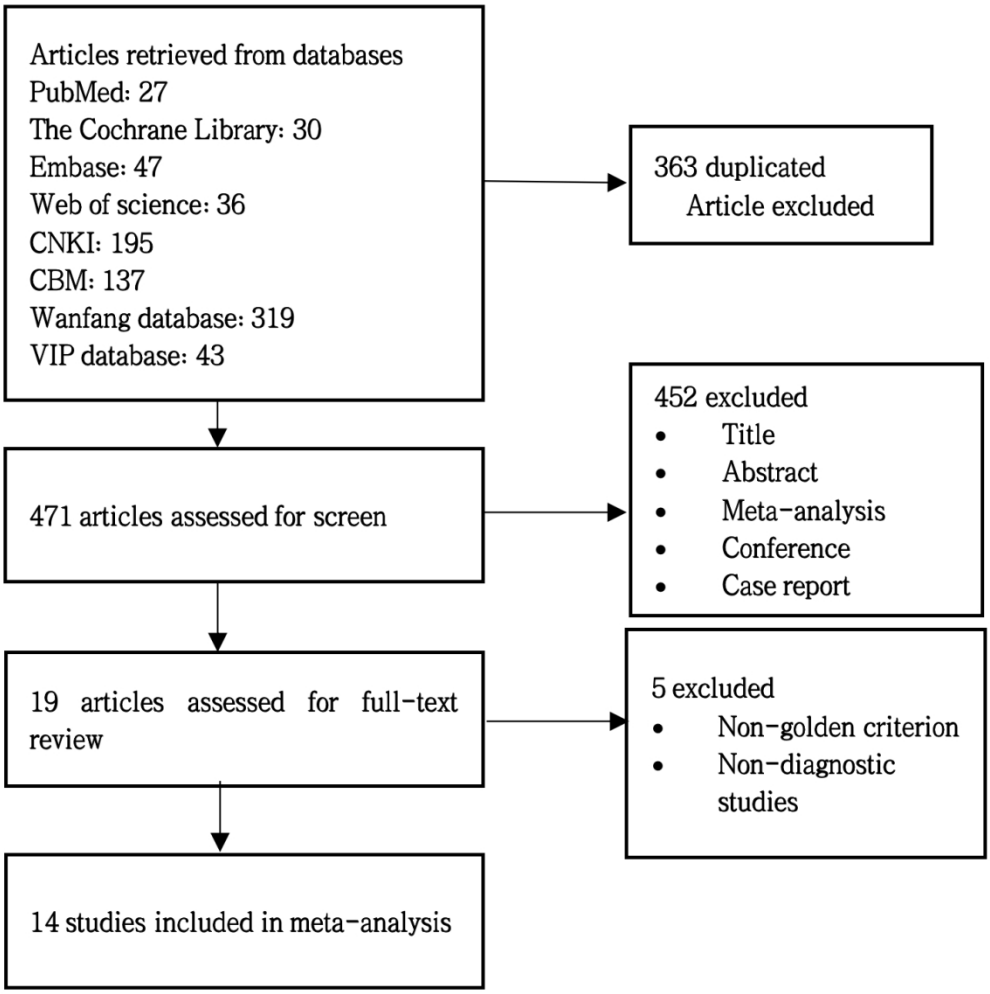
Additional file 1: Detailed literature search strategy

Additional file 2: Characteristics of the included 14 studies

Additional file 3: The result of meta-regression.

Additional file 4: The results of sensitivity analysis.

Additional file 5: Subgroup analysis of neutrophil-to-lymphocyte ratio in the diagnosis of neonatal sepsis

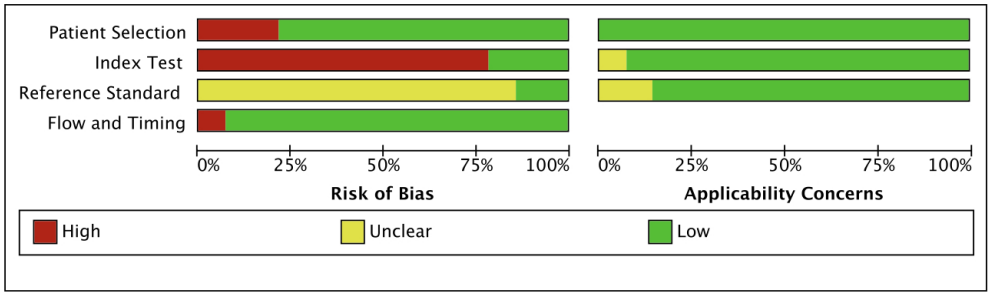


Flowchart of study selection, inclusion, and exclusion for the meta-analysis

254x253mm (144 x 144 DPI)

Risk of bias and applicability concerns summary

228x309mm (144 x 144 DPI)



Risk of bias and applicability concerns graph

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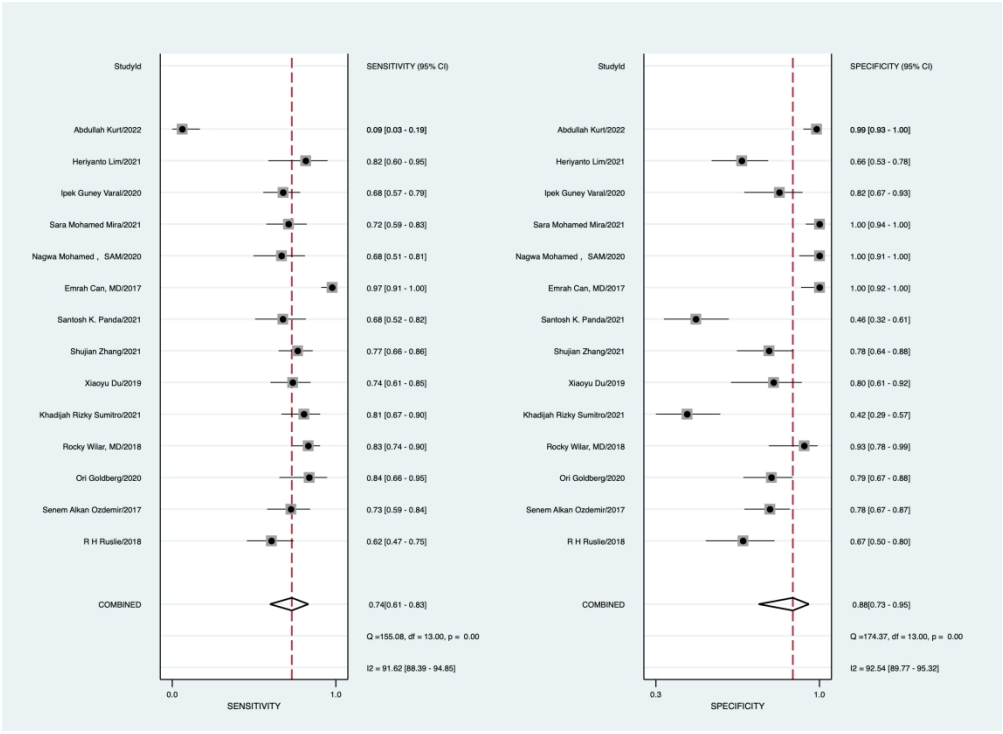
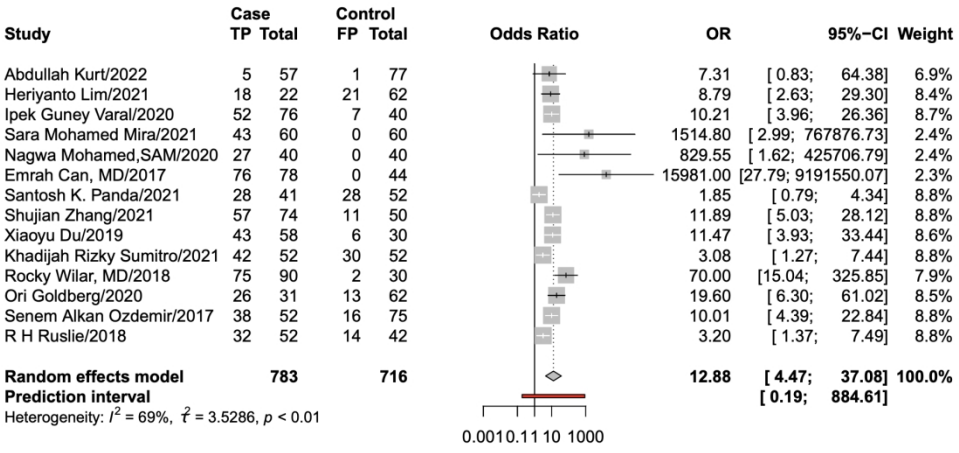


Forest plot of the pooled sensitivity and specificity

445x323mm (144 x 144 DPI)



Forest plot of the pooled diagnostic odds ratio

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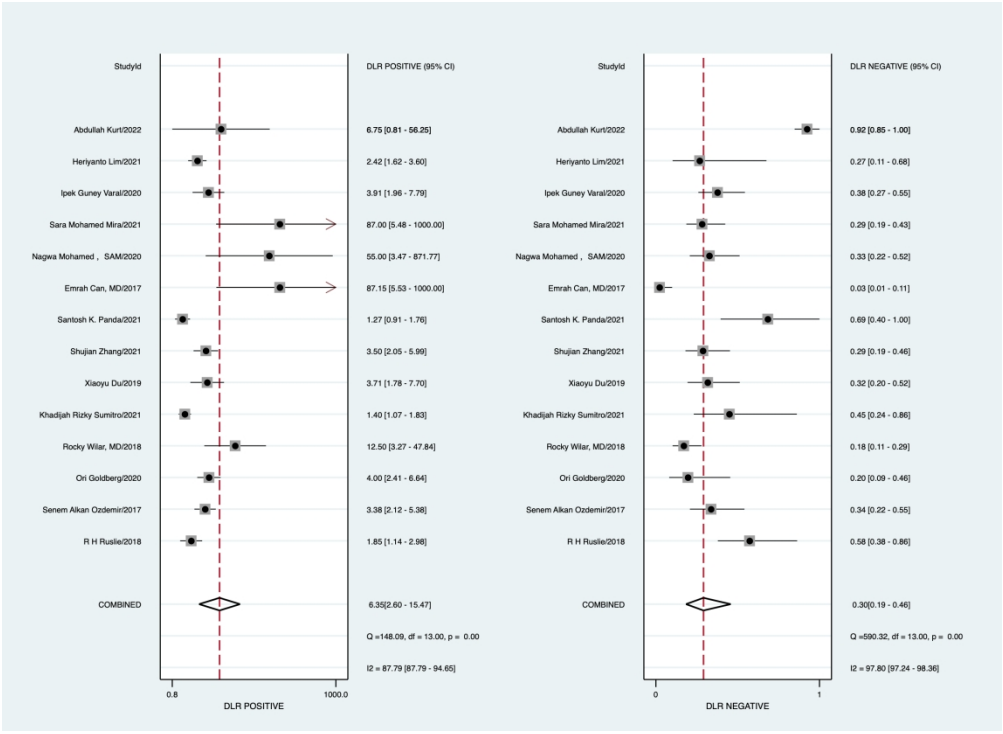
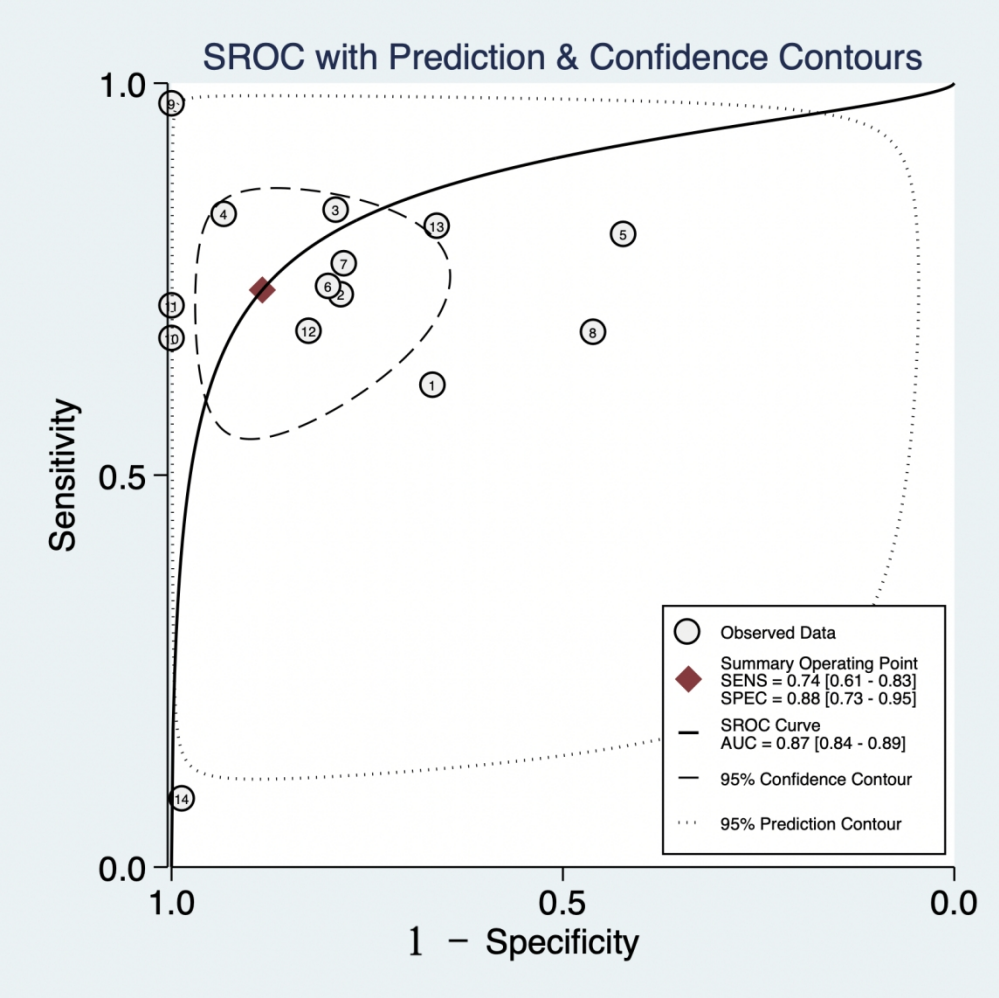


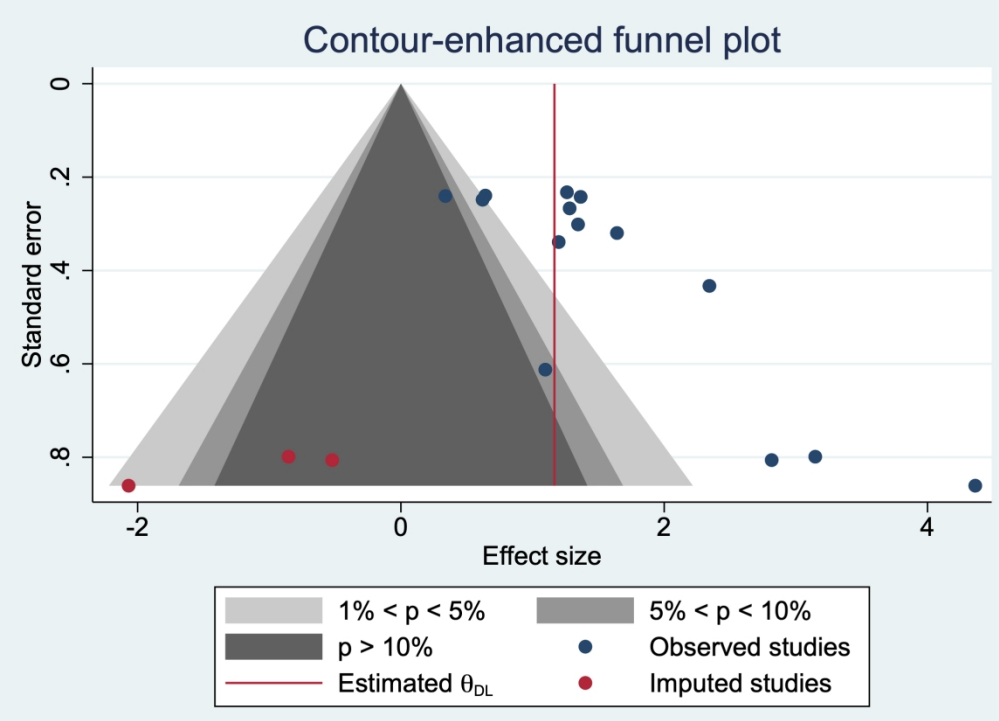
Forest plot of the pooled positive LR and negative LR

445x323mm (144 x 144 DPI)



SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

288x287mm (144 x 144 DPI)



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

404x292mm (144 x 144 DPI)

Detailed retrieval strategy

Database	Pubmed
Website	https://pubmed.ncbi.nlm.nih.gov
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 Sepses[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 (Pyaemia[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 sepses':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

	#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
Database	Web of science
Website	http://www.webofscience.com
Time	database building - 2022.06.28
Results	36
Search details	#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
Database	Cochrane
Website	https://www.cochrane.org
Time	database building - 2022.06.28
Results	30
Search details	ID Search Hits #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

	#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 (*Chinese database*)
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 (*Chinese database*)
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 (*Chinese database*)
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 (*Chinese database*)
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/Control	TP	FP	FN	TN	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、LOS	57/77	5	1	52	76	8.8	98.7	4.79	NA
						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.

[2] Alkan Ozdemir S ,S, Arun Ozer E , Ilhan O , et al. Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?[infants? [J]. *Journal of Clinical Laboratory Analysis*, 2017:e22338.

[3] Goldberg O, Amitai N, Chodick G, et al. Can we improve early identification of neonatal late-onset sepsis? A validated prediction model[J]. *Journal of Perinatology*, 2020, 40(9): p. 1315-1322.

[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.

[5] Sumitro K R , Utomo M T , Widodo A . Neutrophil-to-Lymphocyte Ratio as an Alternative Marker of Neonatal Sepsis in Developing Countries[J]. *Oman Medical Journal*, 2021, 36(1):e214-e214.

[6] Du xiaoyu,Ai liang. Changes and clinical significance of NLR, CRP and PCT in neonates with sepsis. *Experimental and Laboratory Medicine*,2019.37(01): p.110-112.

[7] Zhang, S.J.Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratio as Predictive Biomarkers for Early-onset Neonatal Sepsis. *Jcpsp-Journal of the College of Physicians and Surgeons Pakistan*, 2021. 31(7): p. 821-824.

[8] Panda S K, Nayak M K, Rath S, et al. The Utility of the Neutrophil-Lymphocyte Ratio as an Early Diagnostic Marker in Neonatal Sepsis[J]. *Cureus*, 2021, 13(1): e12891.

[9] E.C, H.S,C.C,et al.The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Journal of pediatric hematology/oncology*, 2018. 40(4) E229-E232.

[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.

[11] Mira S M, Alkhalegy H A, Abd-Elraheem S I, et al. Neutrophil and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis[J]. *International Journal of Medical Arts*, 2021, 3(2): 1274-1281.

[12] Varal I,Dogan P. Can neutrophil-lymphocyte ratio be a predictor of late-onset sepsis in preterm infants? [J]. *Annals of Medical Research*, 2020, 27(1):23.

[13] Lim, H.Sukmawati.M, Artana.W. D,et al.Validity of neutrophil lymphocyte count ratio in neonatal sepsis. *International Journal of Health Sciences*, (2021).5(2), 53-61.

[14] Kurt A, Tosun MS, Altuntaş N: Diagnostic accuracy of complete blood cell count and neutrophil-to-lymphocyte, lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios for neonatal infection. *Asian Biomedicine* 2022, 16(1):43-52.

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	Pvalue	I^2	I^2lo	I^2hi
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.

[2] Alkan Ozdemir S ,S, Arun Ozer E , Ilhan O , et al. Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?[infants? [J]. *Journal of Clinical Laboratory Analysis*, 2017:e22338.

[3] Goldberg O, Amitai N, Chodick G, et al. Can we improve early identification of neonatal late-onset sepsis? A validated prediction model[J]. *Journal of Perinatology*, 2020, 40(9): p. 1315-1322.

[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.

[5] Sumitro K R , Utomo M T , Widodo A . Neutrophil-to-Lymphocyte Ratio as an Alternative Marker of Neonatal Sepsis in Developing Countries[J]. *Oman Medical Journal*, 2021, 36(1):e214-e214.

[6] Du xiaoyu,Ai liang. Changes and clinical significance of NLR, CRP and PCT in neonates with sepsis. *Experimental and Laboratory Medicine*,2019.37(01): p.110-112.

[7] Zhang, S.J.Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratio as Predictive Biomarkers for Early-onset Neonatal Sepsis. *Jcpsp-Journal of the College of Physicians and Surgeons Pakistan*, 2021. 31(7): p. 821-824.

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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

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PRISMA-DTA for Abstracts Checklist

Section/topic	#	PRISMA-DTA for Abstracts Checklist item	Reported on page #
TITLE and PURPOSE			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis.	1
Objectives	2	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Eligibility criteria	3	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;（2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	4	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 August 2021.	4
Risk of bias & applicability	5	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6-7
Synthesis of results	A1	Random effects model.	
RESULTS			
Included studies	6	13 studies were finally included, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia.	6
Synthesis of results	7	The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (0.71-0.83), the pooled specificity was 0.86 (0.70-0.94), the positive likelihood ratio was 5.6(2.3-13.8), the negative likelihood ratio was 0.26(0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(0.81-0.87).	7
DISCUSSION			
Strengths and limitations	9	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Interpretation	10	The early diagnosis of neonatal sepsis is particularly important. The ratio of neutrophils to lymphocytes has high sensitivity and specificity for its early diagnosis. It can provide a warning for the clinic and take corresponding measures in time.	10
OTHER			
Funding	11	None	

PRISMA-DTA for Abstracts Checklist

Registration	12	Prospero：CRD42021278881	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

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PRISMA-DTA Checklist

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	The accuracy of neutrophil to lymphocyte ratio for the diagnosis of neonatal sepsis：a systematic review and meta-analysis	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	/
INTRODUCTION			
Rationale	3	The neutrophil to lymphocyte ratio (NLR) is an independent predictor in clinical that has been widely used in various diseases, such as Immune system disease, tumors, cancers, etc. Many studies have shown that the ratio of neutrophils to lymphocytes is more reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there still has a dispute about diagnosing the effectiveness of neonatal sepsis.	2
Clinical role of index test	D1	/	
Objectives	4	The purpose of this study was systematically and quantitatively to assess the value of neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal sepsis by systematic review and meta-analysis.	2
METHODS			
Protocol and registration	5	Prospero：CRD42021278881	
Eligibility criteria	6	(1).The purpose of the study is to evaluate or explore the diagnostic value of the neutrophils to lymphocytes ratio in neonatal sepsis;(2).The case group is newborns with confirmed neonatal sepsis, and the control group is newborns with non-neonatal 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 neutrophil-lymphocyte ratio in the diagnosis of neonatal sepsis; (5).The language is English or Chinese.	5
Information sources	7	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 August 2021.	4
Search	8	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.	4
Study selection	9	Two reviewers independently screened the literature, extracted data and evaluated the included studies according to the inclusion criteria,exclusion criteria and methodological quality. In case of disagreement, discuss and resolve or hand over to a third party assist in ruling.	5
Data collection process	10	Two researchers extract the data according to the designed data extraction table, and finally cross-check the extraction situation. If there is any difference, it will be resolved through discussion and negotiation.	5
Definitions for data extraction	11	There are two authors independently 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.	5
Risk of bias and applicability	12	Assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.	6

PRISMA-DTA Checklist

Diagnostic accuracy measures	13	ROC curve analysis was used for the included studies to calculate the combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve (AUC). All results were expressed with 95% CI.	5-6
Synthesis of results	14	The I^2 test evaluated study heterogeneity. I^2>50% indicated that the heterogeneity generated in the study would have a specific impact. Meta Disc1.4 software was used to analyze the threshold effect heterogeneity. If the effect sizes of the studies are homogeneous, the fixed-effects model will be used; if they are heterogeneous, the random-effects model will be used. If there is heterogeneity between the studies, the source of the heterogeneity shall be further explored, and the threshold effect and non-threshold effect analysis shall be carried out. The combined sensitivity, combined specificity, combined diagnostic odds ratio (DOR), combined positive likelihood ratio (PLR), combined negative likelihood ratio, and its 95% confidence interval (95%CI) were performed through stata16.0; Simultaneously perform a combined receiver operating characteristic curve (SROC) fitting analysis. At the same time, the Deeks test was used to evaluate the publication bias of the included literature. If P<0.05, it is considered that the included literature has a publication bias.	5-6

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Meta-analysis	D2	Reference no. 14	
Additional analyses	16	We conducted subgroup analysis on the early-onset sepsis group, cutoff>2, and cutoff<2, respectively. The sensitivity analysis was performed by excluding premature infants, non-Asian, and late-onset sepsis to explore the heterogeneity, meta-regression analysis of year, region , Study type and birth status of newborn.	7-8
RESULTS			
Study selection	17	Preliminary retrieval of 740 pieces of literature, after checking duplicates and reading abstracts, and excluding relevant literature according to the exclusion criteria, 13 studies were finally included. The specific process is shown in (Fig1).	6
Study characteristics	18	The references were included from 2017 to 2021, with 1365 newborns, including 726 in the study group and 639 in the control group. Among them, 3 were late-onset sepsis, 5 were early-onset sepsis, and 2 were preterm infants. Ten studies are from Asia, and three studies are from non-Asia. Basic information of the included literature is shown in (Table 1).	6
Risk of bias and applicability	19	The evaluation results of the risk of bias of the included studies are shown in (Fig2、3).	7
Results of individual studies	20	The research results are displayed in the form of tables and forest diagrams	
Synthesis of results	21	we found that the sensitivity and specificity of I^2 are respectively 68.61% and 90.87%. This indicates that there is considerable heterogeneity. We first conducted a threshold effect test. By using metadisc14.0, we found that the Spearman correlation coefficient was -0.093 p= 0.762 (p>0.05). Furthermore, the Proportion of heterogeneity is likely due to threshold effect = 0.23 in stata16.0. It shows no threshold effect heterogeneity,The pooled sensitivity and specificity of neutrophil to lymphocyte ratio in the diagnosis of neonates were 0.77 (95 % CI 0.71-0.83) and 0.86 (95 % CI 0.70-0.94), respectively; PLR was 5.6 (95 % CI 2.3-13.8), and NLR was 0.26 (95 % CI 0.19-0.37) , DOR is 21(95 % CI 7-69), area under the curve (AUC) is 0.84(95 % CI 0.81-0.87) (Fig 4,5,6,7).	7-8

PRISMA-DTA Checklist

Additional analysis	23	The meta-regression results show that articles in non-Asian regions are the main source of heterogeneity (Table 2). Sensitivity analysis removes non-Asian, preterm, and late-onset sepsis research literature results also show that the region is the main source of heterogeneity. (Table 3) (1).The results of the EOS subgroup analysis showed that the pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis were 0.83 (95 % CI 0.68-0.91) and 0.99 (95 % CI 0.78-1.00); PLR was 91.3 (95 % CI 3.0-2823.6), NLR was 0.18 (95 % CI 0.09-0.34), DOR was 519 (95 % CI 14-19952), and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97). (2).Cutoff value>2, pooled sensitivity and specificity are respectively 0.83(95 % CI 0.66-0.93) and 0.80(95 % CI 0.44-0.95) respectively; PLR is 4.1(95 % CI 1.0-17.2), NLR is 0.21(95 % CI 0.07-0.60), DOR is 20 (95 % CI 2-218), the area under the curve (AUC) is 0.88 (95 % CI 0.85-0.91). (3).Cutoff value <2, pooled sensitivity and specificity are respectively 0.74(95 % CI 0.69-0.78) and 0.90(95 % CI 0.71-0.97); PLR is 7.1(95 % CI 2.3-21.8), NLR is 0.29(95 % CI 0.23-0.36), DOR is 25(95 % CI 7-88) The area under the curve (AUC) is 0.77(95 % CI 0.73-0.81).	7-8
DISCUSSION			
Summary of evidence	24	A total of 13 studies comprising 1365 newborns were involved in this meta-analysis. The pooled sensitivity of the ratio of in the diagnosis of neonatal sepsis was 0.77 (95 % confidence interval [CI]：0.71-0.83), the pooled specificity was 0.86 (95 % CI 0.70-0.94), the positive likelihood ratio was 5.6(95 % CI 2.3-13.8), the negative likelihood ratio was 0.26(95 % CI 0.19-0.37), the diagnostic odds ratio was 21(95 % CI 7-69), area under the curve (AUC) was 0.84(95 % CI 0.81-0.87). The results show that the ratio of neutrophils to lymphocytes has moderate diagnostic value for neonatal sepsis.	8-9
Limitations	25	(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, which will result in false positive and false negative results for the diagnosis of neonatal sepsis, which in turn leads to bias. (3). A part of the included research is 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 in newborns of different races and gender.	9
Conclusions	26	The neutrophils to lymphocytes ratio is moderate diagnostic capacity with high sensitivity and specificity for diagnosing neonatal sepsis. It can provide a reference value for the early diagnosis of neonatal sepsis.	10
FUNDING			
Funding	27	None	

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

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