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.

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

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

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

BACKGROUND

Neonatal sepsis is a systemic inflammatory response syndrome caused by a bacterial infection in the neonatal stage. The clinical manifestations gradually surface in the whole body of the inflammatory response and finally progress into organ failure, leading to death. 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). At present, neonatal sepsis is faced with insufficient diagnostic methods, resulting in the inability to guide clinical treatment in a timely manner, thereby affecting its therapeutic effect.

According to a survey, the global mortality rate of neonatal sepsis reached 1.0%–5.0%. Early and precise identification of neonatal sepsis is crucial for slowing the progression of the disease and decreasing mortality. 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.

The accurate identification of neonatal sepsis is critical to provide sufficient treatment time and improve clinical outcomes. In contrast, the neutrophil-to-lymphocyte ratio (NLR) is an independent predictor in the clinic that has been widely used in various diseases, such as immune system diseases, tumours and cancers. Many studies have
shown that the NLR is more reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there is still a dispute about diagnosing the effectiveness of neonatal sepsis.7 8

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

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

Patient and public involvement
No patients were involved.

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

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

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

Data extraction and quality assessment
Two authors (YX and YS) independently conducted the literature screening, data extraction and quality evaluation. In case of disagreement, the third author (WM) decided extracted data from the included literature, including the year of publication, country of origin, study design, author, publication year, newborn birth situation, study location, sample size, case and control numbers, cut-off value, true positive value, false positive value, false negative value, true negative value, sensitivity and specificity. We assess the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist. We used Review Manager (V.5.3) for quality assessment.

Statistical analyses
Statistical heterogeneity was assessed using forest plots with 95% prediction interval, the tau-squared ($\tau^2$) value and I² statistic. The 95% prediction interval was applied to estimate the effect size range in further studies.9 If there was heterogeneity between the studies, the source of the heterogeneity was further explored, and threshold effect and non-threshold effect analyses were carried out. Meta Disc V.1.4 software was used to analyse the threshold effect heterogeneity. For heterogeneity caused by non-threshold effects, we performed meta-regression analysis and sensitivity analysis to find the source of heterogeneity. At the same time, we performed subgroup analyses by cut-off value, neonatal birth status and type of sepsis to assess the stability of the results. The combined sensitivity, combined specificity, combined diagnostic OR (DOR), combined positive likelihood ratio (LR’), combined negative likelihood ratio (LR’) and its 95% CI were determined using Stata V.16.0. Simultaneously, summary receiver operating characteristic (SROC) curve analysis was performed. All studies are presented as a circle and plotted with the SROC curve. The summary point is represented by a dot which was surrounded by a 95% confidence region. The area under the SROC curve was calculated. At the same time, we assessed the bias of included studies by contour-enhanced funnel plots. If there was bias, we judged the stability of the results by the cut-and-fill method. We used Stata (V.16.0), R (V.3.6.0) and MetaDiSc (V.1.4) to perform the analyses.

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

Quality of studies
We imported the literature into Review Manager V.5.3 and used the QUADAS-2 tool to evaluate the quality of the 14 included references. According to the methodological evaluation results, the gold standard for the diagnosis of all patients is blood culture. For patient selection, three references were considered high risk. Since most studies do not specify a threshold in advance, there may
be a risk of bias. Most articles did not mention whether the interpretation of the experimental results to be evaluated was performed without knowing the results of the gold standard, indicating that it is not clear whether the interpretation of the results will produce a risk of bias (figures 2 and 3).

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

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

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

The early identification of neonatal sepsis remains challenging in the clinic, and the NLR is broadly used in diagnosing immune system diseases, tumors and cancers. However, the accurate diagnosis of neonatal sepsis is still questionable.24–26 For the first time, we conducted a meta-analysis and systematic review of the diagnostic performance of NLR in neonatal sepsis, which may provide a better reference value for the early diagnosis of neonatal...
sepsis and for NLR to diagnose neonatal sepsis, providing evidence-based evidence. The meta-analysis included all 14 studies from 7 nations, including 1499 patients with neonatal sepsis. Moreover, the results revealed that the combined AUC of the NLR in the diagnosis of neonatal sepsis was 0.874 (95% CI: 0.84 to 0.89), showing that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis.

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

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

**Figure 6** Forest plot of the pooled positive likelihood ratio (LR) and negative LR.
The neutrophil-to-lymphocyte ratio (NLR) is a useful tool in the early detection of neonatal sepsis. In a recent study, NLR showed better diagnostic performance compared to C-reactive protein (CRP) and procalcitonin (PCT) in neonates with sepsis. The results suggest that NLR could be a valuable indicator to exclude neonatal sepsis. Subgroup analysis indicated that pooled sensitivity and specificity were higher for detecting the NLR in a group of early-onset neonatal sepsis. The results express the stability of the results. Neonatal early-onset sepsis mainly emphasises that the bacteria originate from intrauterine tissue and during delivery, and the spectrum of pathogenic bacteria is relatively concentrated. 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.

CONCLUSION
In summary, our findings suggest that the NLR is a helpful indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined with other laboratory tests and specific clinical manifestations. However, it is limited to the research site and research type. Further research is needed to carry out multicentre prospective studies with larger sample size to determine the value of the NLR in diagnosing neonatal sepsis.
multiple samples to verify the accuracy of NLR diagnosis and improve neonatal sepsis prognosis.

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

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