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

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4 19 **Abstract**

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7 20 **Objectives:** The purpose of this study was systematically and quantitatively to assess
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9 21 the value of the neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal
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12 22 sepsis by systematic review and meta-analysis.

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15 23 **Design:** Systematic review and meta-analysis.

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18 24 **Methods:** Eight major databases, including The Cochrane, PubMed, Embase, Web of
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21 25 Science, CNKI, Wanfang, China Biomedical Literature Database, and VIP Database,
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23
24 26 were systematically searched for neutrophil to lymphocyte ratio diagnoses of neonatal
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27 27 sepsis from inception to August 2021. Two investigators independently conducted the
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30 28 literature search, screening, data extraction, and quality evaluation with the
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33 29 QUADAS-2. Statistical analysis was performed using Review Manager 5.3, Stata 16.0,
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36 30 and Meta-DISC1.4.

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38
39 31 **Results:** A total of 13 studies comprising 1365 newborns were involved in this meta-
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41
42 32 analysis. The pooled sensitivity of the ratio in the diagnosis of neonatal sepsis was
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44
45 33 0.77 (95 % confidence interval [CI] : 0.71-0.83), the pooled specificity was 0.86 (95
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48 34 % CI 0.70-0.94), the positive likelihood ratio was 5.6(95 % CI 2.3-13.8), the negative
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50
51 35 likelihood ratio was 0.26(95 % CI 0.19-0.37), the diagnostic odds ratio was 21(95 %
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54 36 CI 7-69), area under the curve (AUC) was 0.84(95 % CI 0.81-0.87). In the subgroup
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56
57 37 analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.83 (95 % CI 0.68-
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59
60 38 0.91), the pooled specificity was 0.99 (95 % CI 0.78-1.00), the positive likelihood ratio
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41 39 was 91.3 (95 % CI 3.0-2823.6), the negative likelihood ratio was 0.18 (95 % CI 0.09-

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4 40 0.34), the diagnostic odds ratio was 519 (95 % CI 14-19952), and the area under the
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6
7 41 curve (AUC) was 0.95 (95 % CI 0.93-0.97). The Deeks funnel showed that there was
8
9 42 no statistically significant difference in the publication bias of the study ($P>0.05$).

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11
12 43 **Conclusions:** The neutrophil to lymphocyte ratio has a moderate diagnostic capacity
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14
15 44 with high sensitivity and specificity for diagnosing neonatal sepsis. It can provide a
16
17
18 45 reference value for the early diagnosis of neonatal sepsis.

19
20 46 **Keywords:** Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis
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23 24 25 26 48 **Strengths and limitations**

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29 49 (1). As a cheap and readily available new comprehensive inflammatory indicator,
30
31
32 50 Neutrophil to lymphocyte ratio (NLR) is relatively stable and unaffected by in vitro
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35 51 blood sample processing and conventional physiological conditions.

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39 53 (2). Neutrophil to lymphocyte ratio (NLR) is more accurate than blood culture (gold
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42 54 standard) in the diagnosis of neonatal sepsis. This new laboratory index improves the
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45 55 diagnostic efficiency of neonatal sepsis, providing clinical evidence for the diagnosis
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48 56 of neonatal sepsis.

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51 57 (3). Due to the limited number of articles, we cannot accurately distinguish the
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54 58 accuracy of the ratio of neutrophils to lymphocytes in early-onset neonatal sepsis and
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57 59 late-onset sepsis

58 59 60 60 **Background**

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4 61 Neonatal sepsis is a systemic inflammatory response syndrome caused by a bacterial
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7 62 infection in the neonatal stage. The clinical manifestations gradually surface in the
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10 63 whole body of the inflammatory response and finally progress into organ failure,
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12 64 leading to death. [1] Studies have shown that the morbidity of neonatal sepsis is 1 %
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15 65 - 20 % in newborns and is also the third highest after premature delivery and neonatal
16
17 66 encephalopathy (perinatal asphyxia and trauma). [2] Due to the sensitivity of disease
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20 67 diagnosis methods and the timeliness and effectiveness of the whole treatment process,
21
22
23 68 the mortality rate of neonatal sepsis is increasing year by year.
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25
26 69 According to a survey, the global mortality rate of neonatal sepsis reached 1.0 % to
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28 70 5.0 %. [3] Early and precise identification of neonatal sepsis is crucial for slowing the
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31 71 progression of the disease and decreasing mortality. [4] Notwithstanding, there are
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34 72 many clinical biomarkers in the clinic for the diagnosis of neonatal sepsis, and due to
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37 73 the long time-consuming, low diagnostic performance, the rapid progress of the
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40 74 disease, missed identification of neonatal sepsis delays diagnosis and treatment,
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42 75 increasing the risk of death. [5]
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45 76 The accurate identification of neonatal sepsis is critical to provide sufficient treatment
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48 77 time and improve clinical outcomes. In contrast, the neutrophil to lymphocyte ratio
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51 78 (NLR) is an independent predictor in the clinic that has been widely used in various
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54 79 diseases, such as immune system disease, tumors, and cancers. [6] Many studies have
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57 80 shown that the ratio of neutrophils to lymphocytes is more reliable for diagnosing
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4 81 neonatal sepsis than neutrophil counts or lymphocyte counts alone. Nevertheless, there
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7 82 is still a dispute about diagnosing the effectiveness of neonatal sepsis. [7, 8]
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10 83 We assessed the accuracy as a biomarker for diagnosing neonatal sepsis in newborns
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12 84 by performing a systematic literature review and a meta-analysis, comparing the
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15 85 predictive value, and providing a reference for the clinical diagnosis of neonatal sepsis.
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19 20 87 **Methods**

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23 88 The present meta-analysis was conducted and reported according to the Preferred
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25 89 Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA).

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27 90 For details, see Additional file 1 and 2.

28 29 30 91 **Patient and Public Involvement**

31
32 92 No patient involved

33 34 35 93 **Data source**

36
37
38 94 We searched the Cochrane, PubMed, Embase, Web of Science, CNKI, Wanfang,
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41 95 China Biomedical Literature Database, and VIP Database for studies on the diagnostic
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43
44 96 accuracy of neonatal sepsis published before August 2021. We used a combination of
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46
47 97 subject words and free words to search the study and the following keywords:
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49 98 "Neutrophil and lymphocyte ratio," "Infant," "Newborn," "Neonate," "sepsis,"
50
51 99 "septicemia," "Neonatal Sepsis. "In addition, we checked the reference lists of each
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53
54 100 of the primary studies to identify additional publications. The retrieval format is shown
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56
57 101 in Additional file 3.
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102 **Study eligibility**

103 Inclusion criteria: (1). The purpose of the study was to evaluate or explore the
104 diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case
105 group included newborns with confirmed neonatal sepsis, and the control group
106 included newborns with nonneonatal sepsis. The diagnostic gold standard is blood
107 culture (4). It can directly or indirectly obtain the true positive, false positive, true
108 negative, and false negative values of the neutrophil-lymphocyte ratio in the diagnosis
109 of neonatal sepsis. The language is English or Chinese.

110 Exclusion criteria: (1). Unable to extracted from the full text (2). Reviews, conference
111 reports, individual cases, and animal experiments; (3). A duplicated study.

112 **Data extraction and Quality Assessment**

113 Two authors independently extracted data from the included literature, including the
114 year of publication, country of origin, study design, author, publication year, newborn
115 birth situation, study location, sample size, case and control numbers, cutoff value,
116 true positive value, false-positive value, false-negative value, true negative value,
117 sensitivity, and specificity. Assess the quality of the Diagnostic Accuracy Studies-2
118 (QUADAS-2) checklist.

119 **Statistical analyses**

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

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4 123 homogeneous, a fixed-effects model was used; if they were heterogeneous, a random-
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7 124 effects model was used. If there was heterogeneity between the studies, the source of
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10 125 the heterogeneity was further explored, and threshold effect and nonthreshold effect
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12 126 analyses were carried out. The combined sensitivity, combined specificity, combined
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15 127 diagnostic odds ratio (DOR), combined positive likelihood ratio (PLR), combined
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18 128 negative likelihood ratio, and its 95 % confidence interval (95 % CI) were determined
19
20 129 using Stata 16.0. Simultaneously, a combined receiver operating characteristic curve
21
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23 130 (SROC) fitting analysis was performed. At the same time, the Deeks test was used to
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26 131 evaluate the publication bias of the included literature. If $P < 0.05$, it was considered
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29 132 that the included literature had publication bias.

31 133 **Results**

34 134 **Identification of studies**

35
36 135 After checking duplicates and reading abstracts and excluding relevant literature
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39 136 according to the exclusion criteria, 13 studies were finally included. The specific
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42 137 process is shown in (Fig 1). The references were included from 2017 to 2021, with
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45 138 1365 newborns, including 726 in the study group and 639 in the control group. Among
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48 139 them, 3 had late-onset sepsis, 5 had early-onset sepsis, and 2 were preterm infants.
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50 140 Ten studies were from Asia, and three studies were from non-Asia. Basic information
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53 141 of the included literature is shown in Table 1.

56 142 **Quality of studies**

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4 143 We imported the literature into Review Manager 5.2 and used the QUADAS-2 tool to
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7 144 evaluate the quality of the 13 included references. According to the methodological
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10 145 evaluation results, the gold standard for the diagnosis of all patients is blood culture.
11
12 146 For patient selection, three references were considered high-risk. Since most studies
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15 147 do not specify a threshold in advance, there may be a risk of bias. Most articles did
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18 148 not mention whether the interpretation of the experimental results to be evaluated was
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21 149 performed without knowing the results of the gold standard, indicating that it is not
22
23 150 clear whether the interpretation of the results will produce a risk of bias. (Fig 2, 3).

151 **Heterogeneity exploration**

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

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4 163 onset sepsis research literature results and shows that the region is the main source of
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7 164 heterogeneity. (Table 3)

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10 165 **Data synthesis and Subgroup analysis**

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12 166 (1). The pooled sensitivity and specificity of the neutrophil to lymphocyte ratio in the
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15 167 diagnosis of neonates were 0.77 (95 % CI 0.71-0.83) and 0.86 (95 % CI 0.70-0.94),
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17
18 168 respectively; PLR was 5.6 (95 % CI 2.3-13.8), NLR was 0.26 (95 % CI 0.19-0.37),
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21 169 DOR was 21 (95 % CI 7-69), and area under the curve (AUC) was 0.84 (95 % CI 0.81-
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23 170 0.87) (Figs 4, 5, 6, 7).

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25
26 171 (2). The results of the EOS subgroup analysis showed that the pooled sensitivity and
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29 172 specificity of the neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis
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31
32 173 were 0.83 (95 % CI 0.68-0.91) and 0.99 (95 % CI 0.78-1.00); PLR was 91.3 (95 % CI
33
34 174 3.0-2823.6), NLR was 0.18 (95 % CI 0.09-0.34), DOR was 519 (95 % CI 14-19952),
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36
37 175 and the area under the curve (AUC) was 0.95 (95 % CI 0.93-0.97).

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39
40 176 (3). Cutoff value >2, pooled sensitivity and specificity are, respectively 0.83(95 % CI
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43 177 0.66-0.93) and 0.80(95 % CI 0.44-0.95), respectively; PLR is 4.1(95 % CI 1.0-17.2),
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46 178 NLR is 0.21(95 % CI 0.07-0.60), DOR is 20 (95 % CI 2-218), the area under the curve
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48
49 179 (AUC) is 0.88 (95 % CI 0.85-0.91).

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52 180 (4). Cutoff value <2, pooled sensitivity and specificity are, respectively 0.74(95 % CI
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55 181 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
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57
58 182 0.29(95 % CI 0.23-0.36), DOR is 25(95 % CI 7-88) The area under the curve (AUC)
59
60 183 is 0.77(95 % CI 0.73-0.81).

184 **Publication bias exploration**

185 The results of Deeks's funnel plot asymmetry test showed that $p=0.40$ and $p>0.05$.

186 This result indicated that the 13 articles included had no publication bias. (Fig 8)

187 **Discussion**

188 The early identification of neonatal sepsis remains challenging in the clinic, and the
189 neutrophil to lymphocyte ratio (NLR) is broadly used in diagnosing immune system
190 diseases, tumors, and cancers. However, the accurate diagnosis of neonatal sepsis is
191 still questionable. [22,23,24] We used a systematic review and meta-analysis to
192 investigate the accuracy of the neutrophil to lymphocyte ratio (NLR) for the diagnosis
193 of neonatal sepsis. The meta-analysis included all 13 studies from 7 nations, including
194 1365 patients with neonatal sepsis. Moreover, the results revealed that the combined
195 AUC of the neutrophil to lymphocyte ratio (NLR) in the diagnosis of neonatal sepsis
196 was 0.84 (95 % CI=0.81, 0.87), showing that the neutrophil to lymphocyte ratio (NLR)
197 has a moderate diagnostic value for neonatal sepsis, so the neutrophil to lymphocyte
198 ratio (NLR) can be used as an independent predictor of neonatal sepsis.

199 Subgroup analysis indicated that pooled sensitivity and specificity were higher for
200 detecting the ratio of neutrophils to lymphocytes (NLR) in a group of early-onset
201 neonatal sepsis. The results are expressed stability of the results. Neonatal early-onset
202 sepsis mainly emphasizes that the bacteria originate from intrauterine tissue and
203 during delivery, and the spectrum of pathogenic bacteria is relatively concentrated.
204 [25,26] Streptococcus B and Escherichia coli are the most common pathogens of

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4 205 early-onset neonatal sepsis. In the future, more research can be incorporated to further
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7 206 verify the accuracy of the neutrophil to lymphocyte ratio (NLR) diagnosis of early-
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10 207 onset sepsis.

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12 208 Our study included homogeneous research as much as possible, but the included
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15 209 studies still had heterogeneity, in which nonthreshold effects can be explained to
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18 210 partial heterogeneity; non-Asian areas were the primary source of heterogeneity
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21 211 (Table 2). Sensitive analysis results also indicate that the non-Asian region is the
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24 212 primary source of heterogeneity (Table 3). However, after removing all non-Asian
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27 213 articles, heterogeneity still existed, indicating this study's heterogeneity for other
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30 214 reasons.

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32 215 In addition, several limitations of this study should be put forward. (1). Although it is
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35 216 homogeneous to reduce the choice of bias applications, heterogeneity is still in the
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38 217 inclusive research. (2). The diagnosis of newborns will also have differences due to
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41 218 different researchers, resulting in false positive and false negative results for the
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44 219 diagnosis of neonatal sepsis, which leads to bias. (3). A part of the included research
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47 220 is a retrospective study, so there may be a selection of research objects. (4). The
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50 221 included research comes from different countries, and newborns have different
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53 222 immunity in newborns of different races and genders. Therefore, it is necessary to
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56 223 carry out the same race, large sample, multicenter prospective clinical study, and the
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59 224 value of the neutrophil to lymphocyte ratio (NLR) in diagnosing neonatal sepsis in the
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225 future.

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227 Conclusion

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

234

235 Abbreviations

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

242 Contributors

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

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16
17 252 **Competing interests:** The authors declare that they have no competing interests.

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19
20 253 **Availability of data and materials:** All data supporting the conclusions presented in
21
22
23 254 this article are included in this published article.

24
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27 256 **Ethics approval and consent to participate:** Not applicable.

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30 257 **Funding:** None.

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31 336 **Figure legends:**

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34 337 Figure 1: Flowchart of study selection, inclusion, and exclusion for the meta-analysis

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36 338 Figure 2: Risk of bias and applicability concerns summary

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38 339 Figure 3: Risk of bias and applicability concerns graph

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46 343 Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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48 344 Figure 8: Funnel plot of studies included in the meta-analysis

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- 347 Additional file 1:Screenshot of search strategy
- 348 Additional file 2:Table 1 , Characteristics of the included 13 studies
- 349 Additional file 3:Table 2 , The result of meta-regression
- 350 Additional file 4:Table 3 , The results of sensitivity analysis

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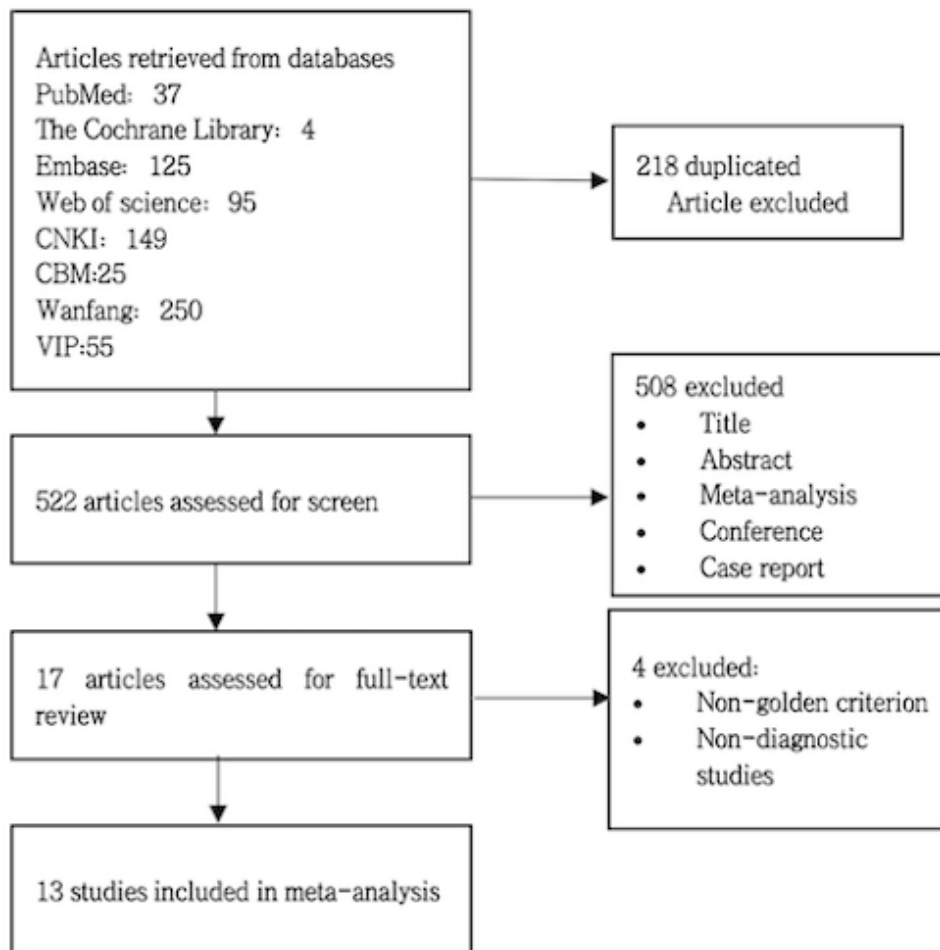


Figure 1: Flowchart of study selection, inclusion, and exclusion for the meta-analysis

89x91mm (144 x 144 DPI)

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

● High ? Unclear + Low

Figure 2: Risk of bias and applicability concerns summary

69x89mm (144 x 144 DPI)

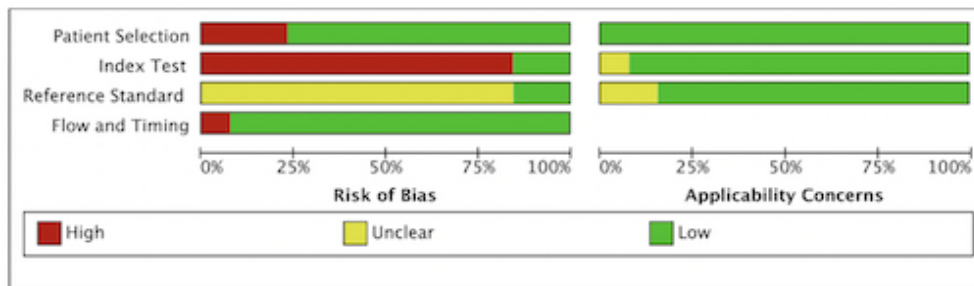


Figure 3: Risk of bias and applicability concerns graph

89x27mm (144 x 144 DPI)

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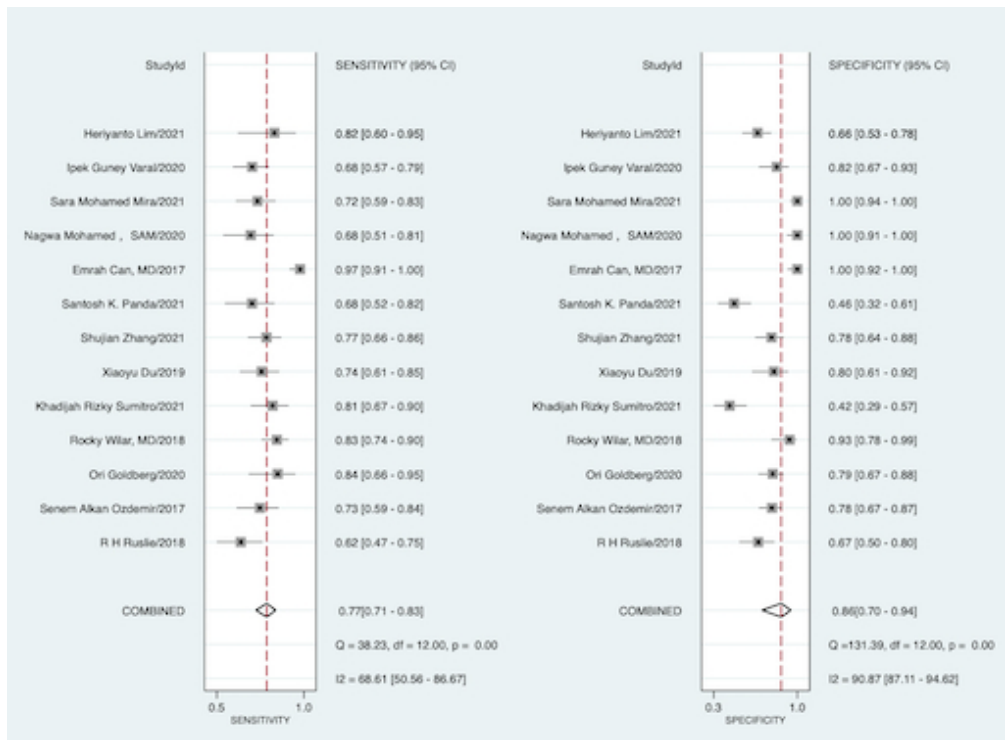


Figure 4: Forest plot of the pooled sensitivity and specificity

89x65mm (144 x 144 DPI)

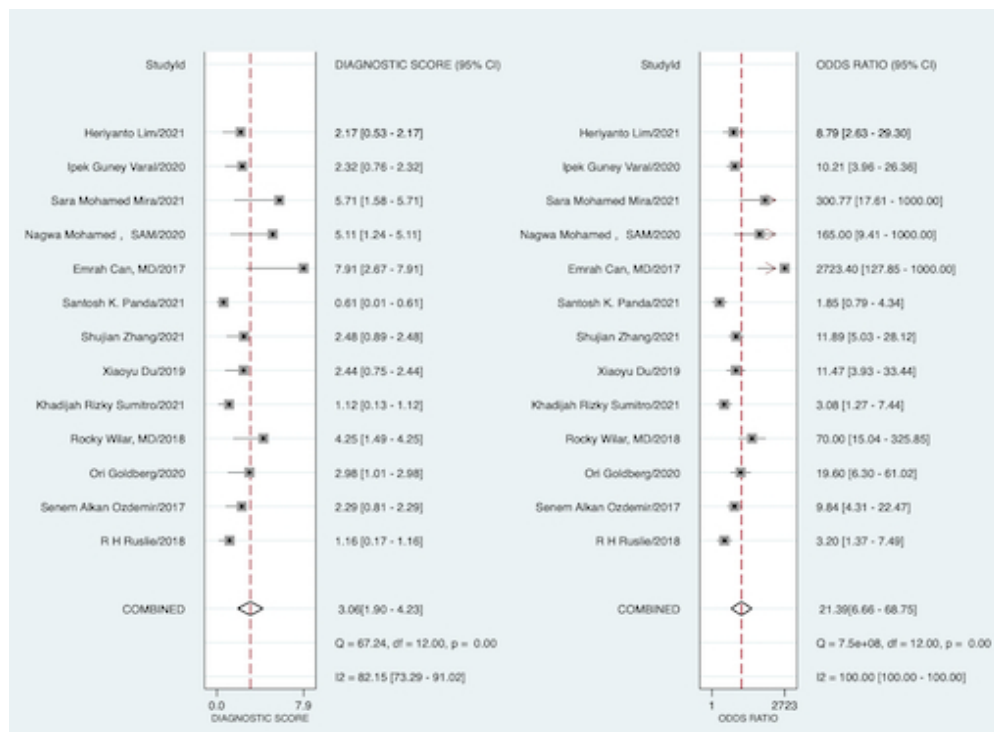


Figure 5: Forest plot of the pooled diagnostic odds ratio

89x65mm (144 x 144 DPI)

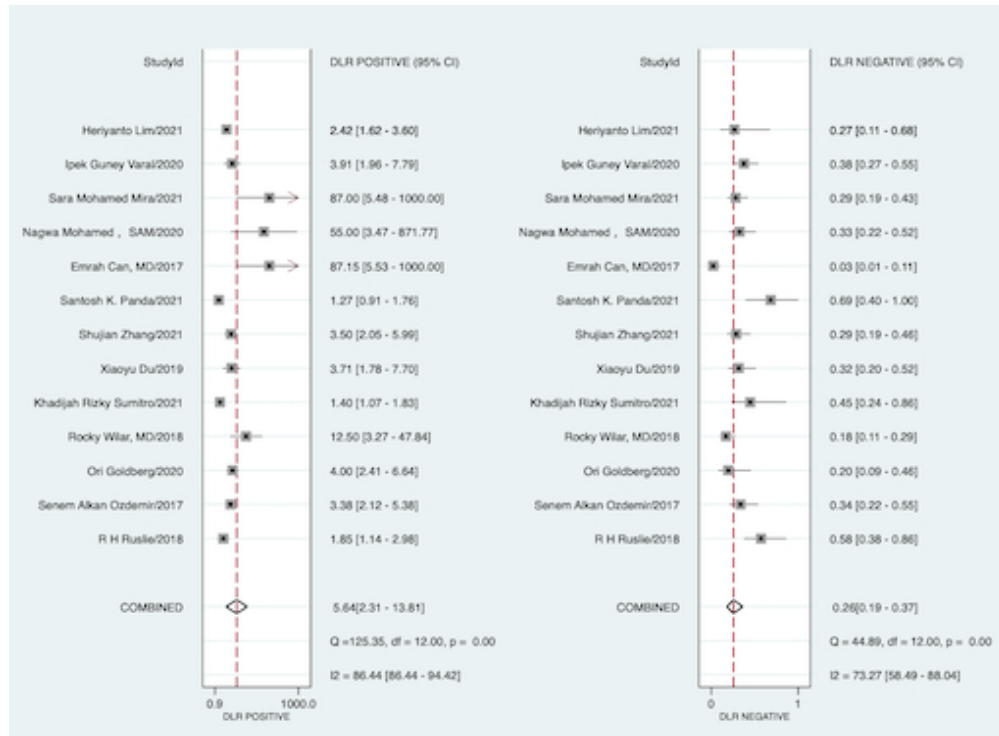


Figure 6: Forest plot of the pooled positive LR and negative LR

89x66mm (144 x 144 DPI)

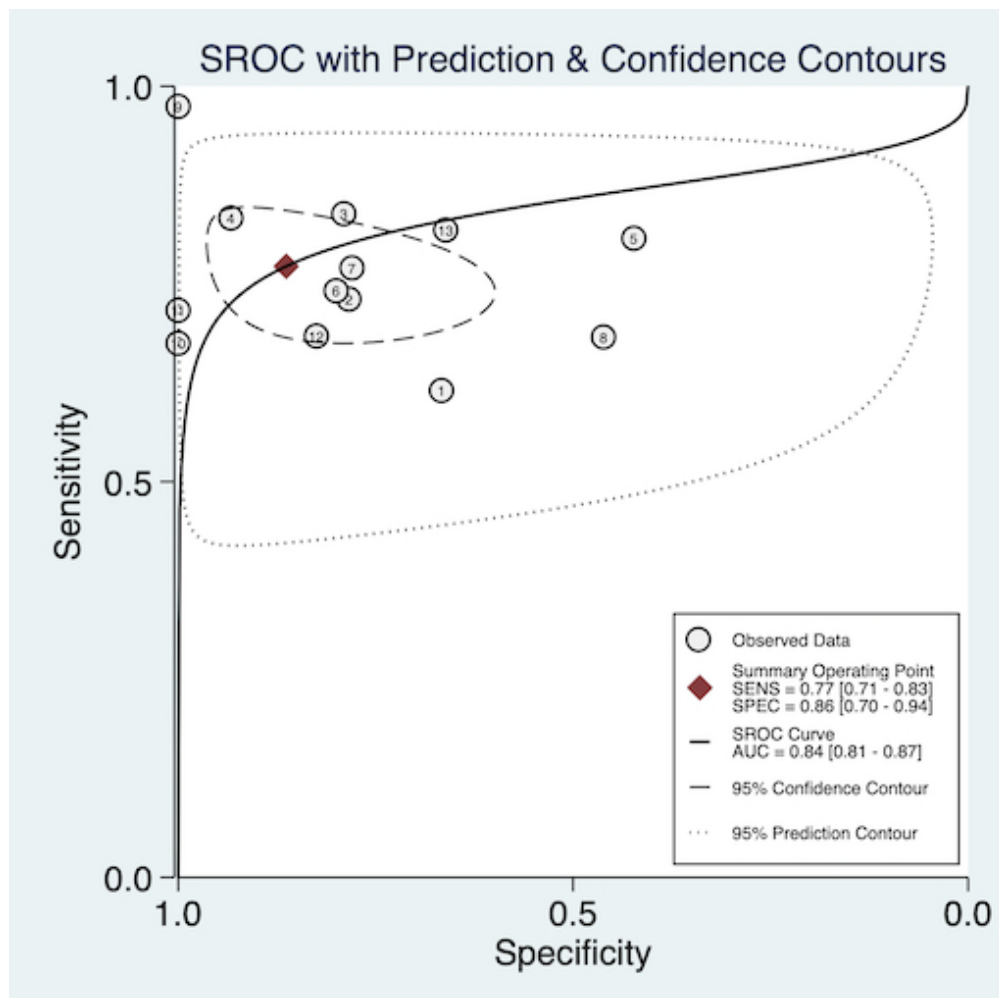


Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis

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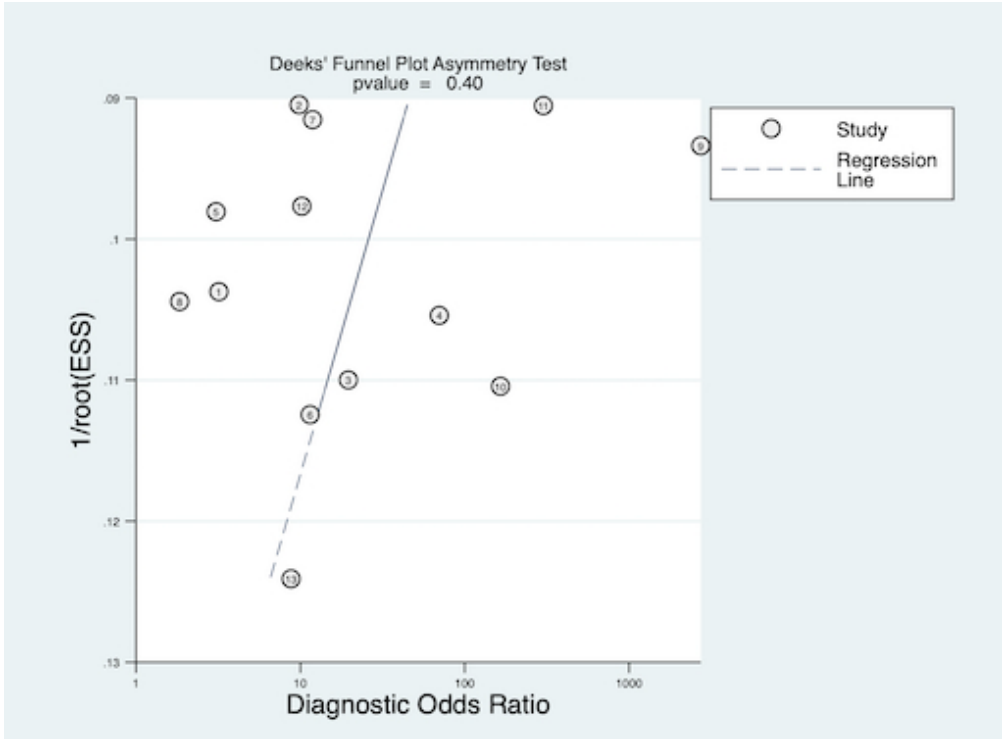


Figure 8: Funnel plot of studies included in the meta-analysis
89x66mm (144 x 144 DPI)

Screenshot of search strategy

1.Cochrane

View fewer lines Print

+ #1	MeSH descriptor: [Infant, Newborn] explode all trees	MeSH	16573
- + #2	(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)	S	Limits 38906
- + #3	(sepsis):ti,ab,kw OR (Bloodstream Infection):ti,ab,kw OR (Pyohemia):ti,ab,kw OR (Pyemia):ti,ab,kw OR (Septicemia):ti,ab,kw (Word variations have been searched)	S	Limits 13401
- + #4	MeSH descriptor: [Sepsis] explode all trees	MeSH	4701
- + #5	(Poisoning, Blood):ti,ab,kw OR (Severe Sepsis):ti,ab,kw (Word variations have been searched)	S	Limits 4764
- + #6	#1 or #2	Limits	38993
- + #7	#3 or #4 or #5	Limits	16030
- + #8	#6 and #7	Limits	2524
- + #9	MeSH descriptor: [Neonatal Sepsis] explode all trees	MeSH	78
- + #10	(Neonatal Sepsis):ti,ab,kw OR (Sepsis, Neonatal Late-Onset):ti,ab,kw OR (Early Onset Sepsis):ti,ab,kw OR (Sepsis, Neonatal Early-Onset):ti,ab,kw OR (LOS):ti,ab,kw (Word variations have been searched)	S	Limits 14142
- + #11	#9 or #10	Limits	14192
- + #12	#11 or #8	Limits	16179
- + #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)	S	Limits 776
- + #14	#13 and #12	Limits	4

2.Embase

Embase Search Emtree Journals Results My tools ? yu xin

#2 'newborn':ab,ti 162,574
#1 'newborn':exp 625,339

125 results for search #33 Set email alert Set RSS feed Search details Index miner

Sources Embase, MEDLINE

Query ((('newborn':exp OR 'infant, newborn':ab,ti OR 'newborn':ab,ti OR 'neonate':ab,ti) AND ('sepsis':exp OR 'sepsis':ab,ti OR 'bloodstream infection':ab,ti OR 'pyohemia':ab,ti OR 'pyemia':ab,ti OR 'septicemia':ab,ti OR 'poisoning, blood':ab,ti OR 'severe sepsis':ab,ti) OR 'newborn sepsis':exp OR 'newborn sepsis':ab,ti OR 'neonatal sepsis':ab,ti OR 'sepsis, neonatal late-onset':ab,ti OR 'early onset sepsis':ab,ti OR 'sepsis, neonatal early-onset':ab,ti OR 'los':ab,ti OR 'eos':ab,ti) AND ('neutrophil lymphocyte ratio':exp OR 'neutrophil lymphocyte ratio':ab,ti OR 'neutrophil and lymphocyte ratio':ab,ti OR 'neutrophil to lymphocyte ratio':ab,ti OR 'nlr':ab,ti))

Mapped terms n/a

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Zinellu A, Scano V, Masotto E, de Riu G, Vaira LA, Carru C, Pirina P, Babudieri S, Mangoni AA, Fois AG. [In Process] *Minerva Respiratory Medicine* 2021 43:4 (609-615)
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- Predicting bacteraemia in maternity patients using full blood count parameters: A supervised machine learning algorithm approach
Mooney C, Eogan M, Ni Ainle F, Cleary B, Gallagher JJ, O'Loughlin J, Drew RJ. *International Journal of Laboratory Hematology* 2021 43:4 (609-615)
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- Preoperative Neutrophil-Lymphocyte Ratio Can Predict Outcomes for Patients Undergoing Tetralogy of Fallot Repair
Manuel V, Miana LA, Guerreiro G.P., Turquetto A., Santos R.M., Fernandes N., Tenório D.F., Canejo L.F., Jatene M.B. *Brazilian Journal of Cardiac Surgery* 2021
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3. Pubmed

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Search	Actions	Details	Query	Results	Time
#17	...	▼	<p>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])))))))</p> <p>("neutrophil to lymphocyte ratio"[Title/Abstract] OR "nor"[Title/Abstract]) AND ("Neonatal Sepsis"[Title/Abstract] OR "neonatal sepsis"[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]))))</p> <p>Translations</p> <p>Sepsis: "sepsis"[MeSH Terms] OR "sepsis"[All Fields]</p> <p>Sepsis: "sepsis"[MeSH Terms] OR "sepsis"[All Fields]</p>	37	23:33:07

截屏

4. Web of science

检索历史:

检索式	检索结果	操作	编辑检索式	删除检索式	
#7	95	#6 AND #5 索引=SCI-EXPANDED, SSCI, A&HCI, CPCJ-S, CPCL-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, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>
#5	109,354	#4 OR #3 索引=SCI-EXPANDED, SSCI, A&HCI, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>
#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, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>
#3	10,142	#2 AND #1 索引=SCI-EXPANDED, SSCI, A&HCI, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>
#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, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>
#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, CPCJ-S, CPCL-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC 时间跨度=所有年份	编辑	<input type="checkbox"/>	<input type="checkbox"/>

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条件: 主题 = (早产儿+新生儿+脓毒症+败血症+新生儿脓毒症+血液中毒+早发性败血症+晚发性败血症+中英文扩展(Los)+中英文扩展(EOS)) AND 主题 = (中性粒细胞比值+中英文扩展(nlr)) 或者 (题名 = (早产儿+新生儿+脓毒症+败血症+新生儿脓毒症+血液中毒+早发性败血症+晚发性败血症+中英文扩展(Los)+中英文扩展(EOS)) 或者 题名 = (中性粒细胞比值+中英文扩展(nlr)) 或者 (title=中英文扩展((早产儿+中英文扩展(新生儿+中英文扩展(脓毒症+中英文扩展(败血症)+中英文扩展(新生儿脓毒症)+中英文扩展(血液中毒)+中英文扩展(早发性败血症)+中英文扩展(晚发性败血症)+Los)+EOS)) 或者 title=中英文扩展((中性粒细胞比值+nlr)) 或者 (v_subject=中英文扩展((早产儿+中英文扩展(新生儿+中英文扩展(脓毒症+中英文扩展(败血症)+中英文扩展(新生儿脓毒症)+中英文扩展(血液中毒)+中英文扩展(早发性败血症)+中英文扩展(晚发性败血症)+Los)+EOS)) 或者 v_subject=中英文扩展((中性粒细胞比值+nlr))) (模糊匹配)						
<input checked="" type="checkbox"/>	中性粒细胞/淋巴细胞比值辅助诊断老年社区获得性细菌感染的研究	李佩琳;王春梅;	中国临床医生杂志	2021-08-04	期刊	<input type="button" value="X"/>
<input checked="" type="checkbox"/>	外周血EOS、NLR联合检测诊断慢性鼻-鼻窦炎价值分析	连刚;徐静;雷小平;	中国实验诊断学	2021-07-25	期刊	<input type="button" value="X"/>
<input checked="" type="checkbox"/>	中性粒细胞与淋巴细胞比值及其变化率与血小板容积指数对脓毒症患儿预后的预测价值	崔娜娜;肖璐芳;李斌;杜玲;潘星宇;	检验医学与临床	2021-07-14	期刊	<input type="button" value="X"/>
<input checked="" type="checkbox"/>	经腹腔镜取石术后脓毒症血症发生情况及髓样细胞可溶性触发受体-1、超敏C反应蛋白、中性粒细胞与淋巴细胞比值联合检测的预测价值	杨海涛;谭毅群;贺德华;王以兵;	临床外科杂志	2021-06-20	期刊	<input type="button" value="X"/>
<input checked="" type="checkbox"/>	通腑泻肺方治疗脓毒症相关急性呼吸窘迫综合征疗效观察	秦杰;黄道超;张陶;冯百晓;	浙江中医杂志	2021-06-16	期刊	<input type="button" value="X"/>

6.Wanfang

高级检索 专业检索 作者发文检索

文献类型:

检索信息: 主题: 新生儿 or 早产儿 or 脓毒症 or 败血症 or 新生儿败血症 or 新生儿脓毒症 or 早发性败 模糊

与 主题: 中性粒细胞淋巴细胞比值 or nlr 模糊

与 题名: 模糊

发表时间: -

智能检索:

or 主题:(败血症) x 主题:(新生儿 or ... x 主题:(新生儿 or ... x 主题:(新生儿 ... x 主题:(新生儿 or ... x

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资源类型: (116) (44) (63)

排序: 获取范围 批量选择 (已选择 0 条) 只看核心期刊论文

1.早发型新生儿败血症NLR、ELR和PLR指标变化及临床意义

找到 250 条结果

7.VIP

任意字段=新生儿败血症+... x 任意字段=新生儿败血症+... x 任意字段=新生儿败血症+... x 题名或关键词=新生儿败血症... x 任意字段=新生儿败血症+... x

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+nos+eos+早发性败血症+晚发性败血症+neonatal sepsis+neonatal septicemia+neonate septicemia+septicemia of newborn 新生儿败血症+新生儿败血症 AND 任意字段=中性粒细胞与淋巴细胞比值+Neutrophil and lymphocyte ratio+neutrophil-to-lymphocyte ratio+中性粒细胞与淋巴细胞比值+中性粒细胞淋巴细胞比值

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在结果中检索 在结果中去除

年份

- 2021 4
- 2020 6
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学科

- 医药卫生 53

期刊收录

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超敏C反应蛋白、白细胞计数及中性粒细胞分类在新生儿败血症早期诊断中的临床分析

被引量: 3

作者: 李梅, 夏宏林. 《牡丹江医学院学报》. 2014年第4期20-22,共3页

目的: 探讨超敏C反应蛋白、外周血白细胞计数、中性粒细胞分类检测在新生儿败血症的早期诊断和治疗的应用。方法: 选2011-12-2013-06间在我院治疗的已确诊的细菌感染40例新生儿, 另外选取同期住院治疗确诊的病毒感染40例新生儿, ... 展开更多

关键词: 新生儿败血症 超敏C反应蛋白 白细胞计数 中性粒细胞分类

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血中性粒细胞/淋巴细胞比值嗜酸性粒细胞对急性呼吸窘迫综合征患者28天死亡风险的预测价值

被引量: 2

作者: 严晓燕, 隋立伟, 46位作者 李小东. 《中国急救医学》(CAS) (CSCD) (北大核心). 2020年第5期427-431,共5页

目的: 评估血中性粒细胞/淋巴细胞比值(NLR)、嗜酸性粒细胞(EOS)对急性呼吸窘迫综合征(ARDS)患者28 d死亡风险的预测价值, 探讨预测ARDS患者预后的方法。方法: 回顾性分析2017年1月至2019年1月承德医学院附属医院收治的85例ARDS患者的临床... 展开更多

关键词: 急性呼吸窘迫综合征(ARDS) 中性粒细胞与淋巴细胞比值(NLR) 嗜酸性粒细胞(EOS) 预测

文章速读 外周血EOS、NLR联合检测诊断慢性鼻-鼻窦炎价值分析

作者: 连刚, 涂静, 董小平. 《中国实验诊断学》(北大核心). 2021年第7期962-965,共4页

目的: 探讨外周血嗜酸性粒细胞(EOS)、中性粒细胞与淋巴细胞计数比值(NLR)联合检测诊断慢性鼻-鼻窦炎(CRS)价值。方法: 选取2017年6月-2020

8.China Biomedical Literature Database

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快速检索 高级检索 主题检索 分类检索 跨库检索

结果筛选

来源

- 中文文献(5)
- 西文文献(20)
- 博硕论文(0)
- 科普文献(0)

主题 学科 时间 期刊 作者 文献类型

详细检索表达式

(((“败血症”[常用字段:智能] OR “败血症”[常用字段:智能]) AND (“新生儿”[常用字段:智能] OR “早产儿”[常用字段:智能]) OR (“新生儿败血症”[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]) AND (“中性粒细胞/淋巴细胞比”[常用字段:智能] OR “nlr”[常用字段:智能]))

检索

二次检索

检索条件: (((“败血症”[常用字段:智能] OR “败血症”[常用字段:智能]) AND (“新生儿”[常用字段:智能] OR “早产儿”[常用字段:智能]) OR (“新生儿败血症”[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]) AND (“中性粒细胞/淋巴细胞比”[常用字段:智能] OR “nlr”[常用字段:智能]))

年代

全部: 20 | 免费全文: 6 | 协和馆藏: 8 | SCI收录: 0 | FI000: 0 | 循证文献: 1

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1. Nitric oxide inhibits interleukin-1-mediated protection against Escherichia coli K1-induced sepsis and meningitis in a neonatal murine model

作者: Chambers CA(1); Lacey CA(1,2); Brown DC(1); Skyberg JA(1)

作者单位: (1)Department of Veterinary Pathobiology, University of Missouri, Columbia, MO, USA; (2)Department of Immunology, Duke University Medical Center, Durham, NC, USA.

语种: eng

出处: Immunology and cell biology 2021 Jul; 99(6) : 596-610

Table 1 characteristics of the included 13 studies

Auth or	Year	Selected time	Study design	Sepsis diagnosis	Region	Ear/ly/Late	Case/control	T	F	F	T	S	S	C	Neonates
R H	201	2016	retrosp	Blood	US	EO	52/	3	1	2	2	6	6	9.	A、
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Ori	202	2016	Retrosp	Blood	Isr	LO	31/	2	1	5	4	8	7	1.	A、
Gold	0	-201	ective	cultur	ael	S	62	6	3		9	3	9	5	B、
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[11]															9

Roc	201	2017	Cross-	Blood	Ind	EO	90/	7	2	1	2	8	9	1.	A、
ky	8	-201	section	cultur	on	S	30	5		5	8	3	3	2	B、
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[12]															
Kha	202	2019	Cross-	Blood	Ind	EO	52/	4	3	1	2	8	4	2.	A、
dija	1	-201	section	cultur	on	S、	52	2	0	0	2	0	2	1	B、
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ian	1	-202	tive	cultur	ina	S	50	7	1	7	9	7	8	1	B、
Zha		0	study	e										6	C
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Emr 2017 2015 Prospe Blood Tu EO 78/ 7 0 2 4 9 1 6. B
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Lim					a	S						8	1	
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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	<i>P</i> value	<i>I</i> ²	<i>I</i> ² lo	<i>I</i> ² hi
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]	43.1
Removal of non-Astorian	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]	13.3
Removal of 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]	45.5
Removal of 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]	47.8



PRISMA-DTA for Abstracts Checklist

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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

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Registration	12	Prospero: CRD42021278881	
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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.

For peer review only



PRISMA-DTA Checklist

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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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6



PRISMA-DTA Checklist

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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

Page 1 of 2

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	

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

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4 19 **Abstract**

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7 20 **Objectives:** The purpose of this study was systematically and quantitatively to assess
8
9 21 the value of the neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal
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12 22 sepsis by systematic review and meta-analysis.

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15 23 **Design:** Systematic review and meta-analysis.

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18 24 **Methods:** Eight major databases, including The Cochrane, PubMed, Embase, Web of
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20 25 Science, CNKI, Wanfang, China Biomedical Literature Database, and VIP Database,
21
22
23 26 were systematically searched for neutrophil to lymphocyte ratio diagnoses of neonatal
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26 27 sepsis from inception to June 2022. Two investigators independently conducted the
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28
29 28 literature search, screening, data extraction. And quality evaluation with the
30
31
32 29 QUADAS-2 checklist. Statistical analysis was performed using Review Manager 5.3,
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34 30 Stata 16.0, and Meta-DISC1.4.

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36
37 31 **Results:** A total of 14 studies comprising 1499 newborns were included in this meta-
38
39
40 32 analysis. With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity of the
41
42
43 33 neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis was 0.74 (95%
44
45 34 confidence interval [CI]: 0.61-0.83), the pooled specificity was 0.88 (95% CI 0.73-
46
47
48 35 0.95), the positive likelihood ratio was 6.35(95% CI 2.6-15.47), the negative
49
50
51 36 likelihood ratio was 0.30(95% CI 0.19-0.46), the diagnostic odds ratio was 21.27(95%
52
53
54 37 CI 6.98-64.84), area under the curve (AUC) was 0.87(95% CI 0.84-0.89). In the
55
56
57 38 subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.75 (95%
58
59 39 CI 0.47-0.91), the pooled specificity was 0.99 (95% CI 0.88-1.00), the positive
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4 40 likelihood ratio was 63.3 (95% CI 5.7-696.8), the negative likelihood ratio was 0.26
5
6
7 41 (95% CI 0.10-0.63), the diagnostic odds ratio was 247(95% CI 16-3785), and the area
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9
10 42 under the curve (AUC) was 0.97 (95% CI 0.95-0.98).

11
12 43 **Conclusions:** Our findings suggest that the neutrophil to lymphocyte ratio is a helpful
13
14
15 44 indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined
16
17
18 45 with other laboratory tests and specific clinical manifestations.

19
20 46 **Keywords:** Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis
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24 25 26 48 **Strengths and limitations**

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28 49 ● We conducted a comprehensive search of each literature database and formulated
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31 50 detailed inclusion and ranking criteria to ensure the quantity and quality of the
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33
34 51 included literature.
- 35
36 52 ● Subgroup analyses were performed according to sepsis type, study area, and cut-
37
38
39 53 off value as described in the methodology section of this study.
- 40
41 54 ● Our included articles lack more multicentre and large sample studies.
- 42
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44 55 ● There may be other clinical and statistical heterogeneity in the included studies.
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48 49 50 51 52 53 58 **Background**

54
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56 59 Neonatal sepsis is a systemic inflammatory response syndrome caused by a bacterial
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59 60 infection in the neonatal stage. The clinical manifestations gradually surface in the
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4 61 whole body of the inflammatory response and finally progress into organ failure,
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6
7 62 leading to death. [1] Studies have shown that the morbidity of neonatal sepsis is 1 - 20
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10 63 % in newborns and is also the third highest after premature delivery and neonatal
11
12 64 encephalopathy (perinatal asphyxia and trauma). [2] At present, neonatal sepsis is
13
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15 65 faced with insufficient diagnostic methods, resulting in the inability to guide clinical
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18 66 treatment in a timely manner, thereby affecting its therapeutic effect.
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20
21 67 According to a survey, the global mortality rate of neonatal sepsis reached 1.0% to
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23
24 68 5.0%. [3] Early and precise identification of neonatal sepsis is crucial for slowing the
25
26
27 69 progression of the disease and decreasing mortality. [4] Notwithstanding, there are
28
29
30 70 many clinical biomarkers in the clinic for the diagnosis of neonatal sepsis, and due to
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32
33 71 the long time consumption, low diagnostic performance, and the rapid progress of the
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35
36 72 disease, missed identification of neonatal sepsis delays diagnosis and treatment,
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39 73 increasing the risk of death. [5]
40
41
42 74 The accurate identification of neonatal sepsis is critical to provide sufficient treatment
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45 75 time and improve clinical outcomes. In contrast, the NLR is an independent predictor
46
47
48 76 in the clinic that has been widely used in various diseases, such as immune system
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51 77 diseases, tumours, and cancers. [6] Many studies have shown that the NLR is more
52
53
54 78 reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts
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56
57 79 alone. Nevertheless, there is still a dispute about diagnosing the effectiveness of
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60 80 neonatal sepsis. [7, 8]

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4 81 We assessed the accuracy as a biomarker for diagnosing neonatal sepsis in newborns
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7 82 by performing a systematic literature review and a meta-analysis, comparing the
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10 83 predictive value, and providing a reference for the clinical diagnosis of neonatal sepsis.
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16 85 **Methods**

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18 86 The present meta-analysis was conducted and reported according to the Preferred
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20 87 Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA).
21
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23 88 For details, see PRISMA-DTA for abstracts and PRISMA-DTA.
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25

26 89 **Patient and Public Involvement**

27
28 90 No patients were involved.
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31 91 **Data source**

32
33 92 We searched the Cochrane, PubMed, Embase, Web of Science, CNKI, Wanfang,
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36 93 China Biomedical Literature Database, and VIP Database for studies on the diagnostic
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39 94 accuracy of neonatal sepsis published before June 2022. We used a combination of
40
41
42 95 subject words and free words to search the study and the following keywords:
43
44 96 "Neutrophil and lymphocyte ratio," "Infant," "Newborn," "Neonate," "sepsis,"
45
46
47 97 "septicemia," "Neonatal Sepsis. "In addition, we checked the reference lists of each
48
49
50 98 of the primary studies to identify additional publications. The retrieval format is shown
51
52
53 99 in (Additional file 1).
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55 100 **Study eligibility**

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4 101 Inclusion criteria: (1). The purpose of the study was to evaluate or explore the
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7 102 diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case
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10 103 group included newborns with confirmed neonatal sepsis, and the control group
11
12 104 included newborns with neonates without sepsis. The diagnostic gold standard is
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14
15 105 blood culture (4). It can directly or indirectly obtain the true positive, false positive,
16
17
18 106 true negative, and false negative values of the neutrophil-lymphocyte ratio in the
19
20 107 diagnosis of neonatal sepsis. The language is English or Chinese.

21
22
23 108 Exclusion criteria: (1) Being able to be extracted from the full text (2) Reviews,
24
25
26 109 conference reports, individual cases, and animal experiments; (3) A duplicated study.

27 28 110 **Data extraction and quality assessment**

29
30
31 111 Two authors(XY, SYS) independently conducted the literature screening, data
32
33
34 112 extraction, and quality evaluation. In case of disagreement, the third author (MWJ)
35
36
37 113 decided. extracted data from the included literature, including the year of publication,
38
39
40 114 country of origin, study design, author, publication year, newborn birth situation,
41
42
43 115 study location, sample size, case and control numbers, cut-off value, true positive
44
45
46 116 value, false-positive value, false-negative value, true negative value, sensitivity, and
47
48
49 117 specificity. We assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2)
50
51
52 118 checklist. We used Review Manager (version 5.3) for quality assessment.

53 119 **Statistical analyses**

54
55
56 120 The heterogeneity of the included studies was evaluated by the Cochrane Q test and I²
57
58
59 121 statistic. I² could be calculated from the Formula of $I^2=100\% \times (Q - df)/Q$. If I² was <50%

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4 122 or the p value was >0.1 , a fixed effects model was used for pooling the data; whereas,
5
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7 123 if I^2 was $>50\%$ or the p value was <0.1 , then there is more heterogeneity among studies,
8
9
10 124 and a bivariate random effects model was used for pooling the data; if I^2 was $<50\%$ or
11
12 125 the p value was <0.1 , a fixed effects model could be used; if I^2 was $>50\%$ or the p value
13
14
15 126 was >0.1 , a bivariate random effects model could be used. If there was heterogeneity
16
17
18 127 between the studies, the source of the heterogeneity was further explored, and
19
20 128 threshold effect and nonthreshold effect analyses were carried out. Meta Disc1.4
21
22
23 129 software was used to analyze the threshold effect heterogeneity. For heterogeneity
24
25
26 130 caused by non-threshold effects, we performed meta-regression analysis and
27
28
29 131 sensitivity analysis to find the source of heterogeneity. At the same time, we
30
31
32 132 performed subgroup analyses by cut-off value, neonatal birth status, and type of sepsis
33
34
35 133 to assess the stability of the results. The combined sensitivity, combined specificity,
36
37 134 combined diagnostic odds ratio (DOR), combined positive likelihood ratio (LR^+),
38
39 135 combined negative likelihood ratio (LR^-), and its 95% confidence interval (95% CI)
40
41
42 136 were determined using Stata 16.0. Simultaneously, a combined receiver operating
43
44
45 137 characteristic curve (SROC) fitting analysis was performed. All studies are presented
46
47
48 138 as a circle and plotted with the SROC curve. The summary point is represented by a
49
50
51 139 dot which was surrounded by a 95% confidence region. The area under the SROC
52
53
54 140 curve was calculated. At the same time, we assessed the bias of included studies by
55
56 141 contour-enhanced funnel plots. If there was bias, we judged the stability of the results
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4 142 by the cut-and-fill method. We used Stata (version 16.0) and MetaDiSc (version 1.4)
5
6
7 143 to perform the analyses.
8

9 144 **Results**

12 145 **Identification of studies**

15 146 After checking duplicates and reading abstracts and excluding relevant literature
16
17 147 according to the exclusion criteria, a final total of 14 studies were used for the current
18
19
20 148 meta-analysis. [9-22] The specific process is shown in Fig 1. Of these, 783 neonates
21
22
23 149 in the sepsis group and 716 neonates in the nonsepsis group were studied and evaluated.
24
25
26 150 (Additional file 2) shows the significant characteristics of the selected studies. The
27
28
29 151 baseline information included the following parameters: the number of patients,
30
31
32 152 gestational age, regions, types of sepsis, disease diagnosis methods, study design, and
33
34 153 NLR cut-off value.
35

36 154 **Quality of studies**

39 155 We imported the literature into Review Manager 5.3 and used the QUADAS-2 tool to
40
41
42 156 evaluate the quality of the 14 included references. According to the methodological
43
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45 157 evaluation results, the gold standard for the diagnosis of all patients is blood culture.
46
47
48 158 For patient selection, three references were considered high risk. Since most studies
49
50
51 159 do not specify a threshold in advance, there may be a risk of bias. Most articles did
52
53
54 160 not mention whether the interpretation of the experimental results to be evaluated was
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57 161 performed without knowing the results of the gold standard, indicating that it is not
58
59 162 clear whether the interpretation of the results will produce a risk of bias. (Figs. 2, 3)
60

163 **Heterogeneity exploration**

164 Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly
165 composed of threshold effect heterogeneity and nonthreshold effect heterogeneity.

166 Through the combination of data, we found that the sensitivity and specificity of I^2
167 were 91.62% and 92.54%, respectively. This indicates that there is considerable
168 heterogeneity. We first conducted a threshold effect test. By using metadisc1.4, we
169 found that the Spearman correlation coefficient was -0.037 ($p= 0.899$) ($p>0.05$). It
170 shows no threshold effect heterogeneity, so to further find the source of heterogeneity,
171 we carried out meta-regression and sensitivity analysis. In the meta-regression
172 analysis, we used the publication year (with 2019 as the cut-off), region, study type,
173 and neonatal birth status as variables for analysis. The meta-regression results show
174 that articles in prospective studies are the main source of heterogeneity($p=0.01$)
175 (Additional file 3). Sensitivity analysis removes non-Asian, preterm, and late-onset
176 sepsis research results and shows that the region is the main source of heterogeneity.
177 (Additional file 4).

178 **Data synthesis and Subgroup analysis**

179 With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity and specificity of
180 the NLR in the diagnosis of neonates were 0.74 (95% CI 0.61-0.83) and 0.88 (95% CI
181 0.73-0.95), respectively; LR^+ was 6.35 (95% CI 2.5-15.47), LR^- was 0.30 (95% CI
182 0.19-0.46), DOR was 21.27 (95% CI 6.98-64.84), and area under the curve (AUC)
183 was 0.87 (95% CI 0.84-0.89) (Figs. 4, 5, 6, 7).

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4 184 The results of the EOS subgroup analysis showed that the pooled sensitivity and
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6
7 185 specificity of the NLR in the diagnosis of neonatal sepsis were 0.75 (95% CI 0.47-
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10 186 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
11
12 187 (95% CI 0.10-0.63), DOR was 247 (95% CI 16-3785), and the area under the curve
13
14
15 188 (AUC) was 0.97 (95% CI 0.95-0.98). The results of the LOS subgroup analysis
16
17
18 189 showed that the pooled sensitivity and specificity of the NLR in the diagnosis of
19
20
21 190 neonatal sepsis were 0.60 (95% CI 0.53-0.67) and 0.85 (95% CI 0.80-0.90); LR⁺ was
22
23 191 3.71 (95% CI 2.73-5.02), LR⁻ was 0.41 (95% CI 0.08-1.94), DOR was 11.14 (95% CI
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25
26 192 6.54-18.98), and the area under the curve (AUC) was 0.85. Cut-off value: 0-2, pooled
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28
29 193 sensitivity and specificity were 0.74(95% CI 0.69-0.78) and 0.90(95% CI 0.71-0.97),
30
31
32 194 respectively; LR⁺ was 7.1(95% CI 2.3-21.8), LR⁻ was 0.29(95% CI 0.23-0.36), DOR
33
34 195 was 25 (95% CI 7-88), the area under the curve (AUC) was 0.77. Cut-off value: 2-4,
35
36
37 196 pooled sensitivity and specificity were 0.79(95% CI 0.72-0.85) and 0.62(95% CI 0.54-
38
39
40 197 0.70); LR⁺ was 2.21(95% CI 1.24-3.92), LR⁻ was 0.33(95% CI 0.23-0.46), DOR was
41
42 198 6.73(95% CI 2.81-16.14) The area under the curve (AUC) was 0.85. Cut-off value: >4,
43
44
45 199 pooled sensitivity and specificity were 0.60(95% CI 0.53-0.67) and 0.91(95% CI 0.85-
46
47
48 200 0.95); LR⁺ was 9.0(95% CI 0.3-270.24), LR⁻ was 0.29(95% CI 0.03-2.68), DOR was
49
50
51 201 31.51(95% CI 0.81-1229.29) The area under the curve (AUC) was 0.95.(Additional
52
53 202 file 5)

203 **Publication bias exploration**

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4 204 The contour-enhanced funnel plot results suggested that there was publication bias,
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6
7 205 and after our cut-and-fill method, the results showed that the stability of our meta-
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10 206 analysis results was not affected.. (Fig. 8)

11 12 207 **Discussion**

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15 208 The early identification of neonatal sepsis remains challenging in the clinic, and the
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17
18 209 NLR is broadly used in diagnosing immune system diseases, tumours, and cancers.
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20
21 210 However, the accurate diagnosis of neonatal sepsis is still questionable. [23,24,25] For
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23
24 211 the first time, we conducted a meta-analysis and systematic review of the diagnostic
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27 212 performance of NLR in neonatal sepsis, which may provide a better reference value
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30 213 for the early diagnosis of neonatal sepsis and for NLR to diagnose neonatal sepsis,
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33 214 providing evidence-based evidence.. The meta-analysis included all 14 studies from 7
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36 215 nations, including 1499 patients with neonatal sepsis. Moreover, the results revealed
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39 216 that the combined AUC of the NLR in the diagnosis of neonatal sepsis was 0.874 (95%
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41
42 217 CI=0.84, 0.89), showing that the NLR is a helpful indicator for the diagnosis of early
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44
45 218 neonatal sepsis.

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48 219 Omran A et al. found that NLR is closely related to neonatal sepsis. Within a few
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51 220 hours after neonatal sepsis, NLR can rapidly increase in a short time compared to CRP.
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53
54 221 The use of NLR makes it possible to identify neonatal sepsis early [26] can be used as
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56
57 222 an auxiliary diagnostic index for the diagnosis of neonatal sepsis, [27] timely diagnosis
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60 223 and early appropriate antibiotic treatment. Seymour CW et al. showed that in the ROC
224 curve analysis of bacterial sepsis according to the Sepsis-2 standard, NLR showed a

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4 225 moderate AUC (0.68), which was significantly higher than that of CRP, lactate and
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6
7 226 PCT, [28, 29] suggesting that NLR has better diagnostic performance. Mahmoud
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9
10 227 NMSA et al. found that when the cut-off value was 0.1, NLR showed the best
11
12 228 specificity and negative predictive value for neonatal sepsis (SPE was 99%, NPV was
13
14
15 229 75%), compared with CRP and PCT, NLR showed higher specificity with better
16
17
18 230 diagnostic power. [18] A study by Alkan Ozdemir S et al. in the diagnosis of late-
19
20 231 onset neonatal sepsis showed that NLR had a high sensitivity, specificity, and
21
22
23 232 accuracy of 0.73, 0.78, and 0.76 respectively, with an NLR cut-off value of 1.77.[10]
24
25
26 233 In the study of Goldberg O, it was found that the cut-off value of NLR was 1.5, and
27
28 234 NLR could be used as a single laboratory index to diagnose neonatal sepsis, [12]
29
30
31 235 indicating that NLR could be a valuable indicator to exclude neonatal sepsis.
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34 236 Subgroup analysis indicated that pooled sensitivity and specificity were higher for
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36
37 237 detecting the NLR in a group of early-onset neonatal sepsis. The results express the
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40 238 stability of the results. Neonatal early-onset sepsis mainly emphasizes that the bacteria
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43 239 originate from intrauterine tissue and during delivery, and the spectrum of pathogenic
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46 240 bacteria is relatively concentrated. [30, 31] Streptococcus B and Escherichia coli are
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49 241 the most common pathogens of early-onset neonatal sepsis. In the future, more
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52 242 research can be incorporated to further verify the accuracy of the NLR diagnosis of
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55 243 early-onset sepsis.
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57
58 244 Our study included homogeneous research as much as possible, but the included
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60 245 studies still had heterogeneity in which nonthreshold effects can be explained to partial

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4 246 heterogeneity. The results of the meta-regression analysis indicated that the study type
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7 247 may be the main sources of heterogeneity. (Additional file 3). The sensitive analysis
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10 248 results also indicate that the non-Asian region is the primary source of heterogeneity
11
12 249 (Additional file 4). However, after removing all non-Asian articles, heterogeneity still
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14
15 250 existed, indicating this study's heterogeneity is for other reasons.

16
17 251 In addition, several limitations of this study should be noted. (1). Although it is
18
19
20 252 homogeneous to reduce the choice of bias applications, heterogeneity is still in the
21
22
23 253 inclusive research. (2). The diagnosis of newborns will also have differences due to
24
25
26 254 different researchers, resulting in false positive and false negative results for the
27
28
29 255 diagnosis of neonatal sepsis, which leads to bias. (3). A part of the included research
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31 256 was a retrospective study, so there may be a selection of research objects. (4). The
32
33
34 257 included research comes from different countries, and newborns have different
35
36
37 258 immunity for different races and sexes. Therefore, it is necessary to carry out the same
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40 259 race, large sample, multicentre prospective clinical study to determine value of the
41
42 260 NLR in diagnosing neonatal sepsis in the future.

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46 47 262 **Conclusion**

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51 263 In summary, our findings suggest that the neutrophil to lymphocyte ratio is a helpful
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54 264 indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined
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57 265 with other laboratory tests and specific clinical manifestations. However, it is limited
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60 266 to the research site and research type. Further research is needed to carry out

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4 267 multicentre prospective studies with multiple samples to verify the accuracy of
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7 268 neutrophil to lymphocyte ratio (NLR) diagnosis and improve neonatal sepsis
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10 269 prognosis.

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14 15 271 **Abbreviations**

16
17
18 272 NLR: neutrophil to lymphocyte ratio; QUADAS-2: Quality Assessment of Diagnostic
19
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21 273 Accuracy Studies-2; CI: confidence interval; SEN: sensitivity; SPE: specificity; LR:
22
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24 274 negative likelihood ratio; LR⁺: positive likelihood ratio; DOR: diagnostic odds ratio;
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27 275 TP: true positive; FP: false positive; TN: true negative; FN: false negative; EOS: early-
28
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30 276 onset sepsis; LOS: late-onset sepsis; AUC: area under the curve; SROC: summary
31
32 277 receiver operating characteristic.

33 34 278 **Contributors**

35
36
37 279 XY wrote the manuscript. LHX, ZYX, and MWJ performed the literature review. XY
38
39
40 280 and SYS performed the statistical analysis. MWJ and WCS revised the text. All
41
42
43 281 authors read and approved the final manuscript.

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1
2
3
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5

6
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8

9
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11

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13

14
15 291 **Ethics approval and consent to participate:** Not applicable.
16

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18

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20 293
21

22
23 294 **Reference**
24

25
26 295 [1] Du Lizhong.Challenges in diagnosis and prevention of neonatal sepsis, *Chin J*
27
28 296 *Pediatr*,2019 ; 57(04): p. 241-243.
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46 385 **Figure legends:**

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49 386 Figure 1: Flowchart of study selection, inclusion, and exclusion for the meta-analysis
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52 387 Figure 2: Risk of bias and applicability concerns summary
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55 388 Figure 3: Risk of bias and applicability concerns graph
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58 389 Figure 4: Forest plot of the pooled sensitivity and specificity
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60 390 Figure 5: Forest plot of the pooled diagnostic odds ratio

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4 391 Figure 6: Forest plot of the pooled positive LR and negative LR
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7 392 Figure 7: SROC of the neutrophil to lymphocyte ratio for the diagnosis of sepsis
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9 393 Figure 8: Contour-enhanced funnel plot of studies included in the meta-analysis
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15 395 **Additional file legends:**
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17 396 Additional file 1: Detailed literature search strategy
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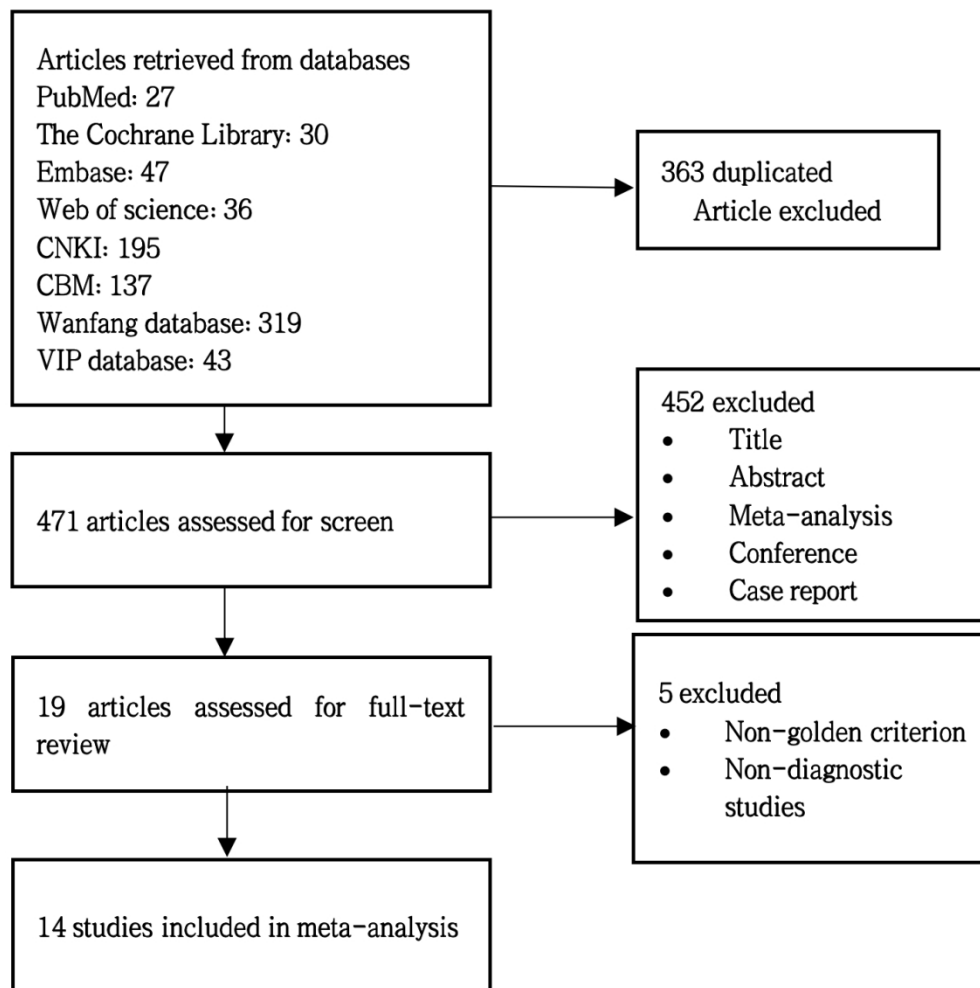
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20 397 Additional file 2: Characteristics of the included 14 studies
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23 398 Additional file 3: The result of meta-regression.
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28 400 Additional file 5: Subgroup analysis of neutrophil-to-lymphocyte ratio in the diagnosis
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Flowchart of study selection, inclusion, and exclusion for the meta-analysis

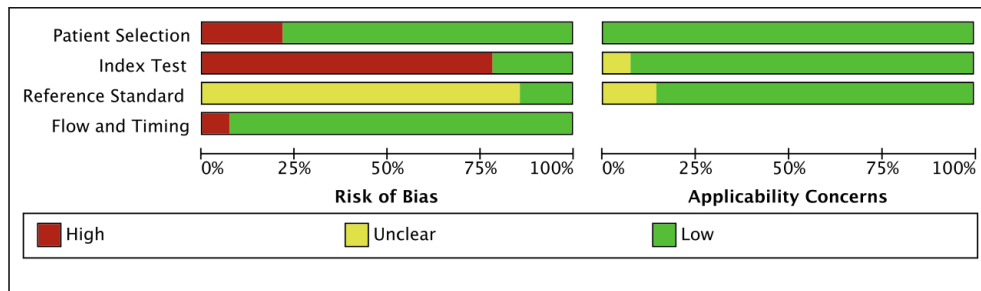
254x253mm (144 x 144 DPI)

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

High
 Unclear
 Low

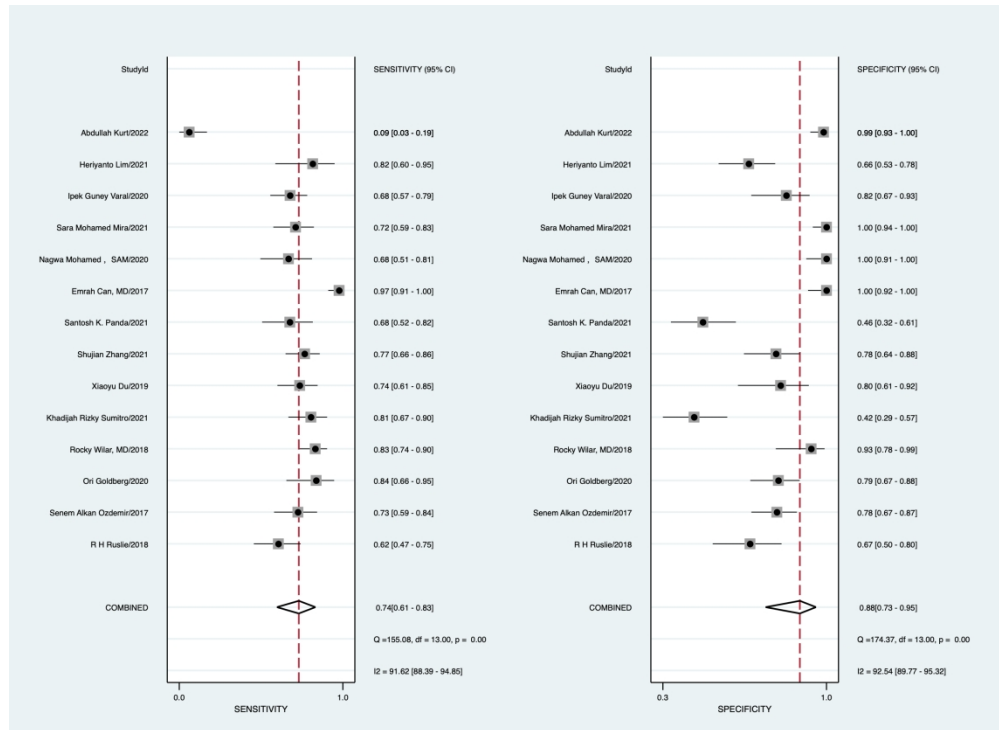
Risk of bias and applicability concerns summary

228x309mm (144 x 144 DPI)



Risk of bias and applicability concerns graph

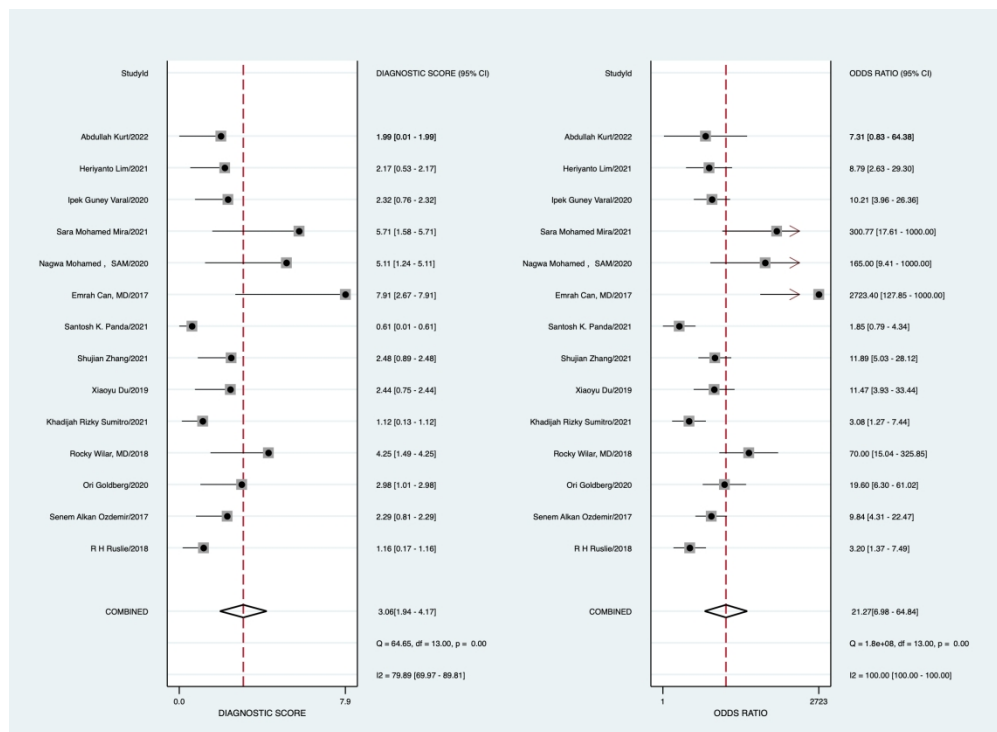
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Forest plot of the pooled sensitivity and specificity

445x323mm (144 x 144 DPI)

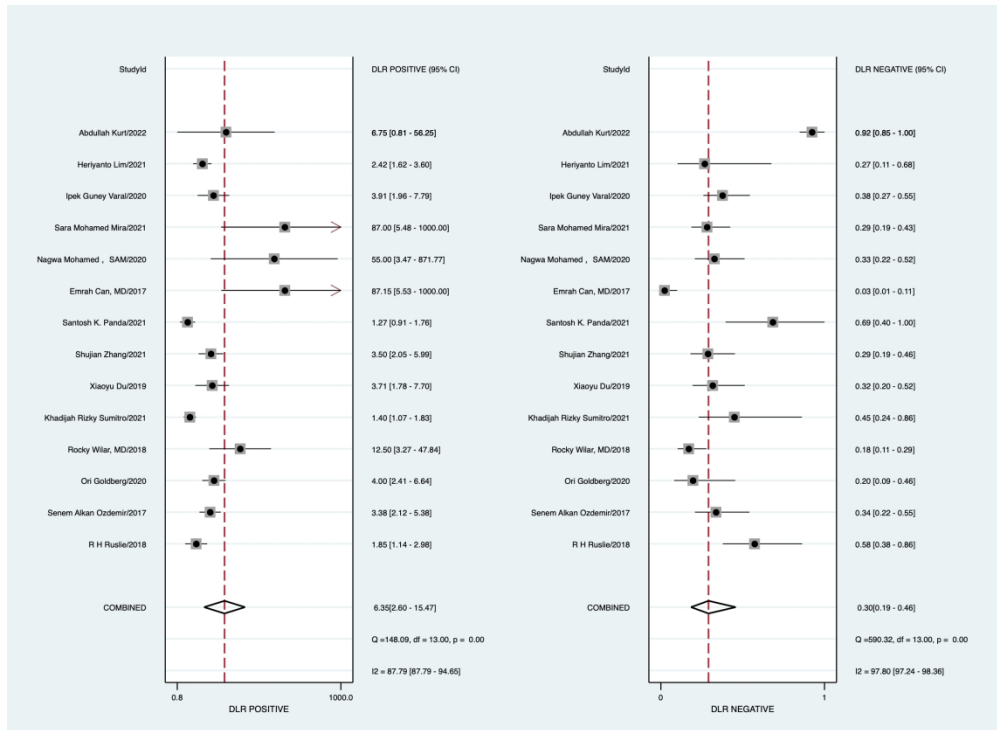
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Forest plot of the pooled diagnostic odds ratio

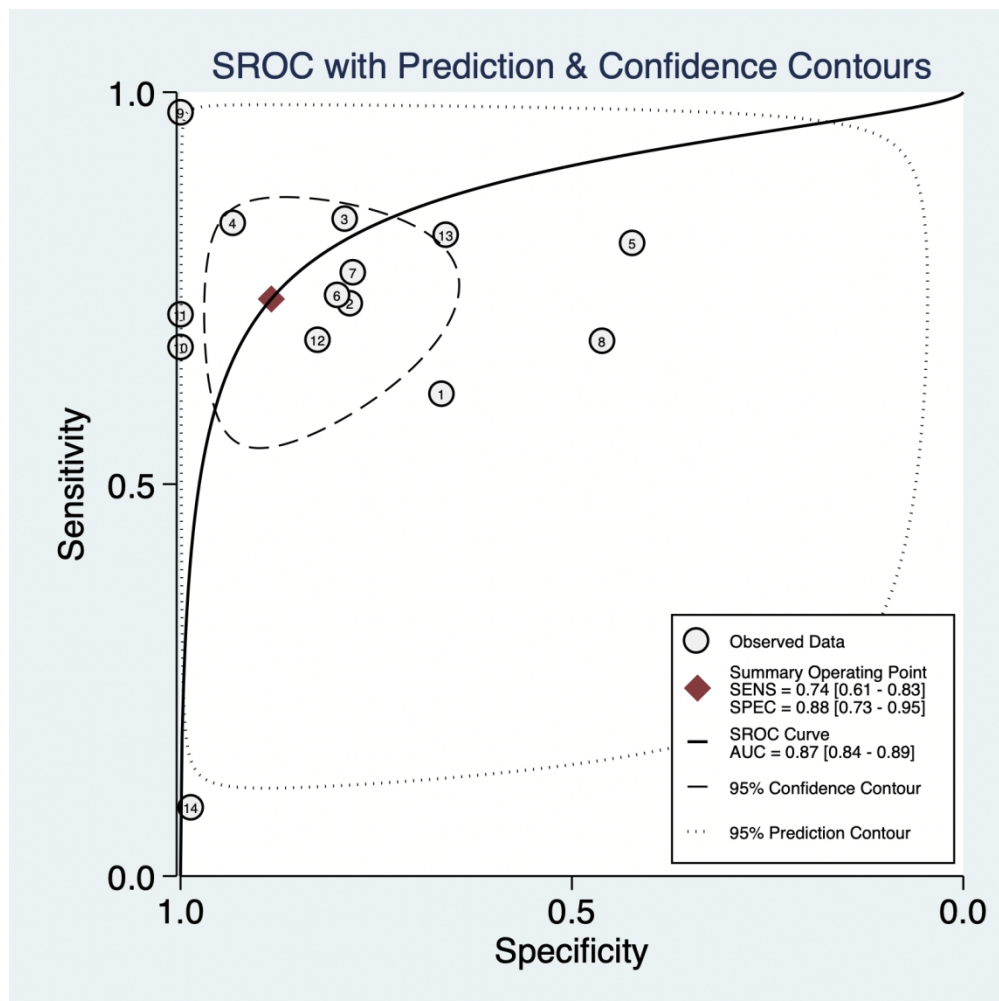
445x323mm (144 x 144 DPI)

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Forest plot of the pooled positive LR and negative LR

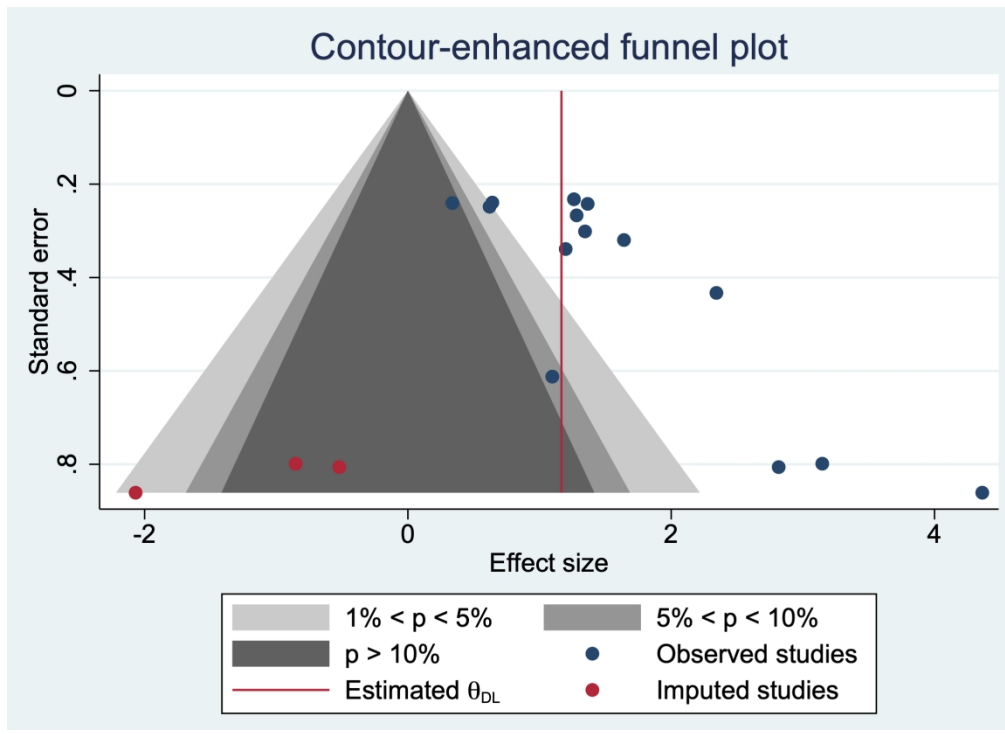
445x323mm (144 x 144 DPI)



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

288x287mm (144 x 144 DPI)

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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 sepsis':ab,ti #22 : 'neonatal sepsis':ab,ti #21 : 'newborn sepsis':ab,ti #20 : 'newborn sepsis'/exp #19 : #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 #18 : 'severe sepsis':ab,ti #17 : 'poisoning, blood':ab,ti #16 : 'septicemia':ab,ti #15 : 'pyohemia':ab,ti #14 : 'pyohemia':ab,ti #13 : 'bloodstream infection':ab,ti #12 : 'sepsis':ab,ti

	<p>#11 : 'sepsis'/exp #10 : #5 OR #6 OR #7 OR #8 #9 : 'neonate':ab,ti #8 : 'newborn':ab,ti #7 : 'newborn infant':ab,ti #6 : 'newborn':ab,ti #5 : 'newborn'/exp #4 : #1 OR #2 OR #3 #3 : 'nlr':ab,ti #2 : 'neutrophil to lymphocyte ratio':ab,ti #1 : 'neutrophil and lymphocyte ratio':ab,ti</p>																																							
Database	Web of science																																							
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Search details	<p>#1 (((((((((((TS=(Neonatal Sepsis)) OR TS=(Neonatal sepsis)) OR TS=(Sepsis, Neonatal Late-Onset)) OR TS=(Early Onset Sepsis)) OR TS=(Sepsis, Neonatal Early-Onset)) OR TS=(los)) OR TS=(eos)) OR TS=(sepsis)) OR TS=(Bloodstream Infection)) OR TS=(pyohemic)) OR TS=(pyaemic)) OR TS=(Septicemia)) OR TS=(Poisoning, Blood)) OR TS=(Severe Sepsis) #2 TS=(Neutrophil and lymphocyte ratio) or TS=(Neutrophil to lymphocyte ratio) or TS=(nlr) #3 (((TS=(Infant, Newborn)) OR TS=(Newborn Infant)) OR TS=(Newborn)) OR TS=(Neonate) #1 and #2 and #3</p>																																							
Database	Cochrane																																							
Website	https://www.cochrane.org																																							
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Results	30																																							
Search details	<table border="1"> <thead> <tr> <th>ID</th> <th>Search</th> <th>Hits</th> </tr> </thead> <tbody> <tr> <td>#1</td> <td>MeSH descriptor: [Neonatal Sepsis] explode all trees</td> <td>86</td> </tr> <tr> <td>#2</td> <td>(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)</td> <td>2151</td> </tr> <tr> <td>#3</td> <td>(LOS):ti,ab,kw OR (EOS):ti,ab,kw (Word variations have been searched)</td> <td>15529</td> </tr> <tr> <td>#4</td> <td>#1 or #2 or #3</td> <td>17494</td> </tr> <tr> <td>#5</td> <td>MeSH descriptor: [Sepsis] explode all trees</td> <td>4918</td> </tr> <tr> <td>#6</td> <td>(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)</td> <td>13925</td> </tr> <tr> <td>#7</td> <td>(Poisoning, Blood):ti,ab,kw OR (Severe Sepsis):ti,ab,kw (Word variations have been searched)</td> <td>4942</td> </tr> <tr> <td>#8</td> <td>#5 or #6 or #7</td> <td>16646</td> </tr> <tr> <td>#9</td> <td>#4 or #8</td> <td>31666</td> </tr> <tr> <td>#10</td> <td>MeSH descriptor: [Infant, Newborn] explode all trees</td> <td>17498</td> </tr> <tr> <td>#11</td> <td>(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)</td> <td>40837</td> </tr> <tr> <td>#12</td> <td>#10 or #11</td> <td>40928</td> </tr> </tbody> </table>	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
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#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 (<i>Chinese database</i>)
Website	https://www.cnki.net
Time	database building - 2022.06.28
Results	195
Search detail	(主题=脓毒症 + 败血症 + 新生儿败血症 + 血流感染 + 早发性败血症 + 迟发性败血症 + 血液中毒 + 新生儿脓毒症) AND (主题=中性粒淋巴细胞比 + nlr)
Database	Wanfang (<i>Chinese database</i>)
Website	https://www.wanfangdata.com.cn/index.html
Time	database building - 2022.06.28
Results	319
Search details	检索表达式(中英文扩展&主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)
Database	China Biomedical Literature Database (<i>Chinese database</i>)
Website	http://www.sinomed.ac.cn/index.jsp
Time	database building - 2022.06.28
Results	137
Search details	((("中性粒淋巴细胞比值"[常用字段:智能] OR "nlr"[常用字段:智能])) AND (("脓毒症"[常用字段:智能] OR "败血症"[常用字段:智能] OR "新生儿脓毒症"[常用字段:智能] OR "新生儿败血症"[常用字段:智能] OR "早发性败血症"[常用字段:智能] OR "迟发性败血症"[常用字段:智能] OR "血流感染"[常用字段:智能]))
Database	VIP Database (<i>Chinese database</i>)
Website	http://qikan.cqvip.com
Time	database building - 2022.06.28
Results	43
Search details	检索表达式(主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)

Table 1 characteristics of the included 14 studies.

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

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

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

Reference

- [1] Ruslie R H, Tjipta D G, Samosir C T, et al. Bacterial pattern, and role of laboratory parameters as marker for neonatal sepsis[C]/IOP Conference Series: Earth and Environmental Science. *IOP Publishing*, 2018, 125(1): 012057.
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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 ² lo	I ² hi
Asia	Yes	2.74	0.25	27	0	100
	No					
Year (2019)	Yes (≥ 2019)	1.82	0.40	0	0	100
	No (< 2019)					
Preterm	Yes	0.31	0.86	0	0	100
	No					
Prospective	Yes	5.28	0.07	62	15	100
	No					

Table 3 The results of sensitivity analysis

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

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

Reference

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

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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

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Registration	12	Prospero: CRD42021278881	
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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.

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For peer review only



PRISMA-DTA Checklist

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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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6



PRISMA-DTA Checklist

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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

Page 1 of 2

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

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Additional analysis	23	<p>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)</p> <p>(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).</p> <p>(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).</p> <p>(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).</p>	7-8
DISCUSSION			
Summary of evidence	24	<p>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.</p>	8-9
Limitations	25	<p>(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.</p>	9
Conclusions	26	<p>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.</p>	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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1 **The accuracy of the neutrophil to lymphocyte ratio for the diagnosis of neonatal**
2 **sepsis: a systematic review and meta-analysis**

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14 23 **Abstract**
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16 24 **Objectives:** The purpose of this study was systematically and quantitatively to assess
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18 25 the value of the neutrophil to lymphocyte ratio (NLR) for the diagnosis of neonatal
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20 26 sepsis by systematic review and meta-analysis.
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24 27 **Design:** Systematic review and meta-analysis.
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28 28 **Methods:** Eight major databases, including The Cochrane, PubMed, Embase, Web of
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30 29 Science, CNKI, Wanfang, China Biomedical Literature Database, and VIP Database,
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32 30 were systematically searched for neutrophil to lymphocyte ratio diagnoses of neonatal
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34 31 sepsis from inception to June 2022. Two investigators independently conducted the
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36 32 literature search, screening, data extraction. And quality evaluation with the
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38 33 QUADAS-2 checklist. Statistical analysis was performed using Review Manager 5.3,
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40 34 Stata 16.0, R(version 3.6.0) and Meta-DISC1.4.
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48 35 **Results:** A total of 14 studies comprising 1499 newborns were included in this meta-
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50 36 analysis. With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity of the
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52 37 neutrophil to lymphocyte ratio in the diagnosis of neonatal sepsis was 0.74 (95%
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54 38 confidence interval [CI]: 0.61-0.83), the pooled specificity was 0.88 (95% CI 0.73-
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56 39 0.95), the positive likelihood ratio was 6.35(95% CI 2.6-15.47), the negative
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4 40 likelihood ratio was 0.30(95% CI 0.19-0.46), the diagnostic odds ratio was 12.88 (95%
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7 41 CI 4.47-37.08), area under the curve (AUC) was 0.87(95% CI 0.84-0.89). In the
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10 42 subgroup analysis of early-onset neonatal sepsis, the pooled sensitivity was 0.75 (95%
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12 43 CI 0.47-0.91), the pooled specificity was 0.99 (95% CI 0.88-1.00), the positive
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14 44 likelihood ratio was 63.3 (95% CI 5.7-696.8), the negative likelihood ratio was 0.26
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17 45 (95% CI 0.10-0.63), the diagnostic odds ratio was 247(95% CI 16-3785), and the area
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20 46 under the curve (AUC) was 0.97 (95% CI 0.95-0.98).

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23 47 **Conclusions:** Our findings suggest that the neutrophil to lymphocyte ratio is a helpful
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26 48 indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined
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29 49 with other laboratory tests and specific clinical manifestations.

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32 50 **Keywords:** Sepsis, Newborn, Neutrophil to lymphocyte ratio, Meta-analysis
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36 37 52 **Strengths and limitations**

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40 53 ● We conducted a comprehensive search of each literature database and formulated
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42 54 detailed inclusion and ranking criteria to ensure the quantity and quality of the
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44 55 included literature.
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47 56 ● Subgroup analyses were performed according to sepsis type, study area, and cut-
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49 57 off value as described in the methodology section of this study.
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52 58 ● Our included articles lack more multicentre and large sample studies.
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55 59 ● There may be other clinical and statistical heterogeneity in the included studies.
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62 Background

63 Neonatal sepsis is a systemic inflammatory response syndrome caused by a bacterial
64 infection in the neonatal stage. The clinical manifestations gradually surface in the
65 whole body of the inflammatory response and finally progress into organ failure,
66 leading to death. [1] Studies have shown that the morbidity of neonatal sepsis is 1 - 20
67 % in newborns and is also the third highest after premature delivery and neonatal
68 encephalopathy (perinatal asphyxia and trauma). [2] At present, neonatal sepsis is
69 faced with insufficient diagnostic methods, resulting in the inability to guide clinical
70 treatment in a timely manner, thereby affecting its therapeutic effect.

71 According to a survey, the global mortality rate of neonatal sepsis reached 1.0% to
72 5.0%. [3] Early and precise identification of neonatal sepsis is crucial for slowing the
73 progression of the disease and decreasing mortality. [4] Notwithstanding, there are
74 many clinical biomarkers in the clinic for the diagnosis of neonatal sepsis, and due to
75 the long time consumption, low diagnostic performance, and the rapid progress of the
76 disease, missed identification of neonatal sepsis delays diagnosis and treatment,
77 increasing the risk of death. [5]

78 The accurate identification of neonatal sepsis is critical to provide sufficient treatment
79 time and improve clinical outcomes. In contrast, the NLR is an independent predictor
80 in the clinic that has been widely used in various diseases, such as immune system
81 diseases, tumours, and cancers. [6] Many studies have shown that the NLR is more

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4 82 reliable for diagnosing neonatal sepsis than neutrophil counts or lymphocyte counts
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7 83 alone. Nevertheless, there is still a dispute about diagnosing the effectiveness of
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10 84 neonatal sepsis. [7, 8]

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12 85 We assessed the accuracy as a biomarker for diagnosing neonatal sepsis in newborns
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15 86 by performing a systematic literature review and a meta-analysis, comparing the
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18 87 predictive value, and providing a reference for the clinical diagnosis of neonatal sepsis.
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23 89 **Methods**

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26 90 The present meta-analysis was conducted and reported according to the Preferred
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29 91 Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA).

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31 92 For details, see PRISMA-DTA for abstracts and PRISMA-DTA.
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33 93 **Patient and Public Involvement**

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36 94 No patients were involved.
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39 95 **Data source**

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42 96 We searched the Cochrane, PubMed, Embase, Web of Science, CNKI, Wanfang,
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45 97 China Biomedical Literature Database, and VIP Database for studies on the diagnostic
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48 98 accuracy of neonatal sepsis published before June 2022. We used a combination of
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51 99 subject words and free words to search the study and the following keywords:
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54 100 "Neutrophil and lymphocyte ratio," "Infant," "Newborn," "Neonate," "sepsis,"
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57 101 "septicemia," "Neonatal Sepsis. "In addition, we checked the reference lists of each
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4 102 of the primary studies to identify additional publications. The retrieval format is shown
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7 103 in (Additional file 1).

104 **Study eligibility**

105 Inclusion criteria: (1). The purpose of the study was to evaluate or explore the
106 diagnostic value of the neutrophil to lymphocyte ratio in neonatal sepsis. The case
107 group included newborns with confirmed neonatal sepsis, and the control group
108 included newborns with neonates without sepsis. The diagnostic gold standard is
109 blood culture (4). It can directly or indirectly obtain the true positive, false positive,
110 true negative, and false negative values of the neutrophil-lymphocyte ratio in the
111 diagnosis of neonatal sepsis. The language is English or Chinese.

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

114 **Data extraction and quality assessment**

115 Two authors(XY, SYS) independently conducted the literature screening, data
116 extraction, and quality evaluation. In case of disagreement, the third author (MWJ)
117 decided. extracted data from the included literature, including the year of publication,
118 country of origin, study design, author, publication year, newborn birth situation,
119 study location, sample size, case and control numbers, cut-off value, true positive
120 value, false-positive value, false-negative value, true negative value, sensitivity, and
121 specificity. We assess the quality of the Diagnostic Accuracy Studies-2 (QUADAS-2)
122 checklist. We used Review Manager (version 5.3) for quality assessment.

123 **Statistical analyses**

124 Statistical heterogeneity was assessed using forest plots with 95% prediction interval,
125 the tau-squared (τ^2) value and I^2 statistic. The 95% prediction interval was applied to
126 estimate the effect size range in further studies^[9]. If there was heterogeneity between
127 the studies, the source of the heterogeneity was further explored, and threshold effect
128 and nonthreshold effect analyses were carried out. Meta Disc1.4 software was used to
129 analyze the threshold effect heterogeneity. For heterogeneity caused by non-threshold
130 effects, we performed meta-regression analysis and sensitivity analysis to find the
131 source of heterogeneity. At the same time, we performed subgroup analyses by cut-
132 off value, neonatal birth status, and type of sepsis to assess the stability of the results.
133 The combined sensitivity, combined specificity, combined diagnostic odds ratio
134 (DOR), combined positive likelihood ratio (LR+), combined negative likelihood
135 ratio(LR-), and its 95% confidence interval (95% CI) were determined using Stata
136 16.0. Simultaneously, summary receiver operating characteristic (SROC) curve
137 analysis was performed. All studies are presented as a circle and plotted with the
138 SROC curve. The summary point is represented by a dot which was surrounded by a
139 95% confidence region. The area under the SROC curve was calculated. At the same
140 time, we assessed the bias of included studies by contour-enhanced funnel plots. If
141 there was bias, we judged the stability of the results by the cut-and-fill method. We
142 used Stata (version 16.0), R(version 3.6.0) and MetaDiSc (version 1.4) to perform the
143 analyses.

144 **Results**

145 **Identification of studies**

146 After checking duplicates and reading abstracts and excluding relevant literature
147 according to the exclusion criteria, a final total of 14 studies were used for the current
148 meta-analysis. [10-23] The specific process is shown in Fig 1. Of these, 783 neonates
149 in the sepsis group and 716 neonates in the nonsepsis group were studied and evaluated.
150 (Additional file 2) shows the significant characteristics of the selected studies. The
151 baseline information included the following parameters: the number of patients,
152 gestational age, regions, types of sepsis, disease diagnosis methods, study design, and
153 NLR cut-off value.

154 **Quality of studies**

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

163 **Heterogeneity exploration**

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4 164 Since the heterogeneity of diagnostic meta-analysis is widespread, it is mainly
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7 165 composed of threshold effect heterogeneity and nonthreshold effect heterogeneity.
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10 166 Through the combination of data, by combining the data we found that the results were
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12 167 highly heterogeneous, We first conducted a threshold effect test. By using metadisc1.4,
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15 168 we found that the Spearman correlation coefficient was -0.037 ($p= 0.899$) ($p>0.05$). It
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18 169 shows no threshold effect heterogeneity, so to further find the source of heterogeneity,
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21 170 we carried out meta-regression and sensitivity analysis. In the meta-regression
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24 171 analysis, we used the publication year (with 2019 as the cut-off), region, study type,
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27 172 and neonatal birth status as variables for analysis. The meta-regression results show
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30 173 that articles in prospective studies are the main source of heterogeneity($p=0.01$)
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32 174 (Additional file 3). Sensitivity analysis removes non-Asian, preterm, and late-onset
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34 175 sepsis research results and shows that the region is the main source of heterogeneity.
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37 176 (Additional file 4).

177 **Data synthesis and Subgroup analysis**

178 With a cut-off value ranging from 0.1 to 9.4, the pooled sensitivity and specificity of
179 the NLR in the diagnosis of neonates were 0.74 (95% CI 0.61-0.83) and 0.88 (95% CI
180 0.73-0.95), respectively; LR^+ was 6.35 (95% CI 2.5-15.47), LR^- was 0.30 (95% CI
181 0.19-0.46), DOR was 12.88 (95% CI 4.47-37.08), and area under the curve (AUC)
182 was 0.87 (95% CI 0.84-0.89) (Figs. 4, 5, 6, 7).

183 The results of the EOS subgroup analysis showed that the pooled sensitivity and
184 specificity of the NLR in the diagnosis of neonatal sepsis were 0.75 (95% CI 0.47-

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4 185 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
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7 186 (95% CI 0.10-0.63), DOR was 247 (95% CI 16-3785), and the area under the curve
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10 187 (AUC) was 0.97 (95% CI 0.95-0.98). The results of the LOS subgroup analysis
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12 188 showed that the pooled sensitivity and specificity of the NLR in the diagnosis of
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15 189 neonatal sepsis were 0.60 (95% CI 0.53-0.67) and 0.85 (95% CI 0.80-0.90); LR⁺ was
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18 190 3.71 (95% CI 2.73-5.02), LR⁻ was 0.41 (95% CI 0.08-1.94), DOR was 11.14 (95% CI
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20 191 6.54-18.98), and the area under the curve (AUC) was 0.85. Cut-off value: 0-2, pooled
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23 192 sensitivity and specificity were 0.74(95% CI 0.69-0.78) and 0.90(95% CI 0.71-0.97),
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26 193 respectively; LR⁺ was 7.1(95% CI 2.3-21.8), LR⁻ was 0.29(95% CI 0.23-0.36), DOR
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28 194 was 25 (95% CI 7-88), the area under the curve (AUC) was 0.77. Cut-off value: 2-4,
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31 195 pooled sensitivity and specificity were 0.79(95% CI 0.72-0.85) and 0.62(95% CI 0.54-
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34 196 0.70); LR⁺ was 2.21(95% CI 1.24-3.92), LR⁻ was 0.33(95% CI 0.23-0.46), DOR was
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37 197 6.73(95% CI 2.81-16.14) The area under the curve (AUC) was 0.85. Cut-off value: >4,
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40 198 pooled sensitivity and specificity were 0.60(95% CI 0.53-0.67) and 0.91(95% CI 0.85-
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42 199 0.95); LR⁺ was 9.0(95% CI 0.3-270.24), LR⁻ was 0.29(95% CI 0.03-2.68), DOR was
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45 200 31.51(95% CI 0.81-1229.29) The area under the curve (AUC) was 0.95.(Additional
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48 201 file 5)

202 **Publication bias exploration**

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

206 Discussion

207 The early identification of neonatal sepsis remains challenging in the clinic, and the
208 NLR is broadly used in diagnosing immune system diseases, tumours, and cancers.
209 However, the accurate diagnosis of neonatal sepsis is still questionable. [24,25,26] For
210 the first time, we conducted a meta-analysis and systematic review of the diagnostic
211 performance of NLR in neonatal sepsis, which may provide a better reference value
212 for the early diagnosis of neonatal sepsis and for NLR to diagnose neonatal sepsis,
213 providing evidence-based evidence.. The meta-analysis included all 14 studies from 7
214 nations, including 1499 patients with neonatal sepsis. Moreover, the results revealed
215 that the combined AUC of the NLR in the diagnosis of neonatal sepsis was 0.874 (95%
216 CI=0.84, 0.89), showing that the NLR is a helpful indicator for the diagnosis of early
217 neonatal sepsis.

218 Omran A et al. found that NLR is closely related to neonatal sepsis. Within a few
219 hours after neonatal sepsis, NLR can rapidly increase in a short time compared to CRP.
220 The use of NLR makes it possible to identify neonatal sepsis early [27] can be used as
221 an auxiliary diagnostic index for the diagnosis of neonatal sepsis, [28] timely diagnosis
222 and early appropriate antibiotic treatment. Seymour CW et al. showed that in the ROC
223 curve analysis of bacterial sepsis according to the Sepsis-2 standard, NLR showed a
224 moderate AUC (0.68), which was significantly higher than that of CRP, lactate and
225 PCT, [29, 30] suggesting that NLR has better diagnostic performance. Mahmoud
226 NMSA et al. found that when the cut-off value was 0.1, NLR showed the best

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4 227 specificity and negative predictive value for neonatal sepsis (SPE was 99%, NPV was
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7 228 75%), compared with CRP and PCT, NLR showed higher specificity with better
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10 229 diagnostic power. [19] A study by Alkan Ozdemir S et al. in the diagnosis of late-
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12 230 onset neonatal sepsis showed that NLR had a high sensitivity, specificity, and
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15 231 accuracy of 0.73, 0.78, and 0.76 respectively, with an NLR cut-off value of 1.77.[11]
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18 232 In the study of Goldberg O, it was found that the cut-off value of NLR was 1.5, and
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20 233 NLR could be used as a single laboratory index to diagnose neonatal sepsis, [13]
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23 234 indicating that NLR could be a valuable indicator to exclude neonatal sepsis.
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26 235 Subgroup analysis indicated that pooled sensitivity and specificity were higher for
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28 236 detecting the NLR in a group of early-onset neonatal sepsis. The results express the
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31 237 stability of the results. Neonatal early-onset sepsis mainly emphasizes that the bacteria
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34 238 originate from intrauterine tissue and during delivery, and the spectrum of pathogenic
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37 239 bacteria is relatively concentrated. [31, 32] Streptococcus B and Escherichia coli are
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40 240 the most common pathogens of early-onset neonatal sepsis. In the future, more
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42 241 research can be incorporated to further verify the accuracy of the NLR diagnosis of
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45 242 early-onset sepsis.
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48 243 Our study included homogeneous research as much as possible, but the included
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50 244 studies still had heterogeneity in which nonthreshold effects can be explained to partial
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53 245 heterogeneity. The results of the meta-regression analysis indicated that the study type
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56 246 may be the main sources of heterogeneity. (Additional file 3). The sensitive analysis
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59 247 results also indicate that the non-Asian region is the primary source of heterogeneity
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4 248 (Additional file 4). However, after removing all non-Asian articles, heterogeneity still
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7 249 existed, indicating this study's heterogeneity is for other reasons.

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9 250 In addition, several limitations of this study should be noted. (1). Although it is
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12 251 homogeneous to reduce the choice of bias applications, heterogeneity is still in the
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15 252 inclusive research. (2). The diagnosis of newborns will also have differences due to
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18 253 different researchers, resulting in false positive and false negative results for the
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21 254 diagnosis of neonatal sepsis, which leads to bias. (3). A part of the included research
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24 255 was a retrospective study, so there may be a selection of research objects. (4). The
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27 256 included research comes from different countries, and newborns have different
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30 257 immunity for different races and sexes. Therefore, it is necessary to carry out the same
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33 258 race, large sample, multicentre prospective clinical study to determine value of the
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36 259 NLR in diagnosing neonatal sepsis in the future.

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38 39 261 **Conclusion**

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43 262 In summary, our findings suggest that the neutrophil to lymphocyte ratio is a helpful
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46 263 indicator for the diagnosis of early neonatal sepsis, but it still needs to be combined
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49 264 with other laboratory tests and specific clinical manifestations. However, it is limited
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52 265 to the research site and research type. Further research is needed to carry out
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55 266 multicentre prospective studies with multiple samples to verify the accuracy of
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58 267 neutrophil to lymphocyte ratio (NLR) diagnosis and improve neonatal sepsis
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60 268 prognosis.

269

270 Abbreviations

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

277 Contributors

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

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

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4 290 **Availability of data and materials:** No data are available.
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7 291 **Consent for publication:** Not applicable.
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10 292 **Ethics approval statement:** No animal or human participant was involved in this
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13 293 study.
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17 294 **Funding:** None.
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21
22 296 **Reference**
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49 387 **Figure legends:**

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52 388 Figure 1: Flowchart of study selection, inclusion, and exclusion for the meta-analysis

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55 389 Figure 2: Risk of bias and applicability concerns summary

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58 390 Figure 3: Risk of bias and applicability concerns graph

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391 Figure 4: Forest plot of the pooled sensitivity and specificity

392 Figure 5: Forest plot of the pooled diagnostic odds ratio

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

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

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

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397 **Additional file legends:**

398 Additional file 1: Detailed literature search strategy

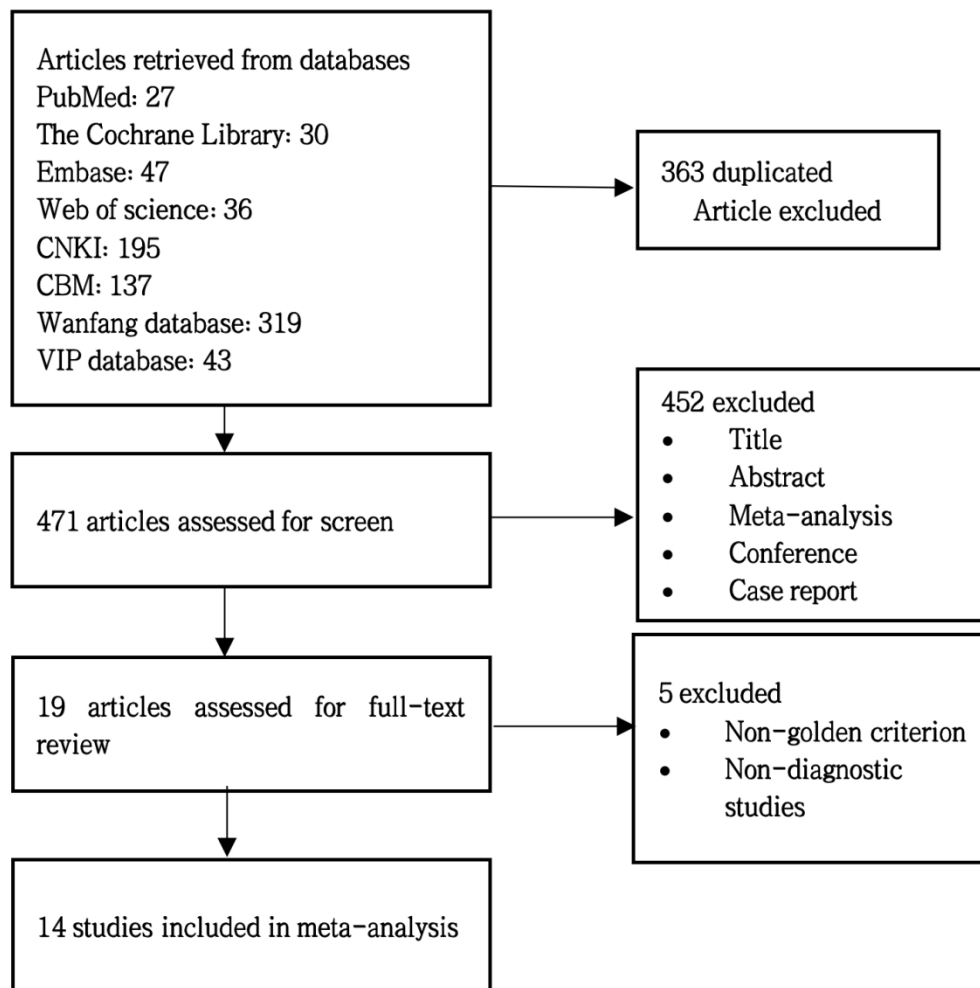
399 Additional file 2: Characteristics of the included 14 studies

400 Additional file 3: The result of meta-regression.

401 Additional file 4: The results of sensitivity analysis.

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


403 of neonatal sepsis



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

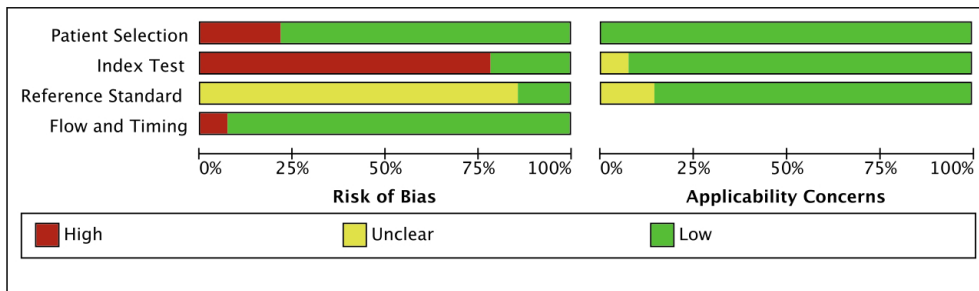
254x253mm (144 x 144 DPI)

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

 High	 Unclear	 Low
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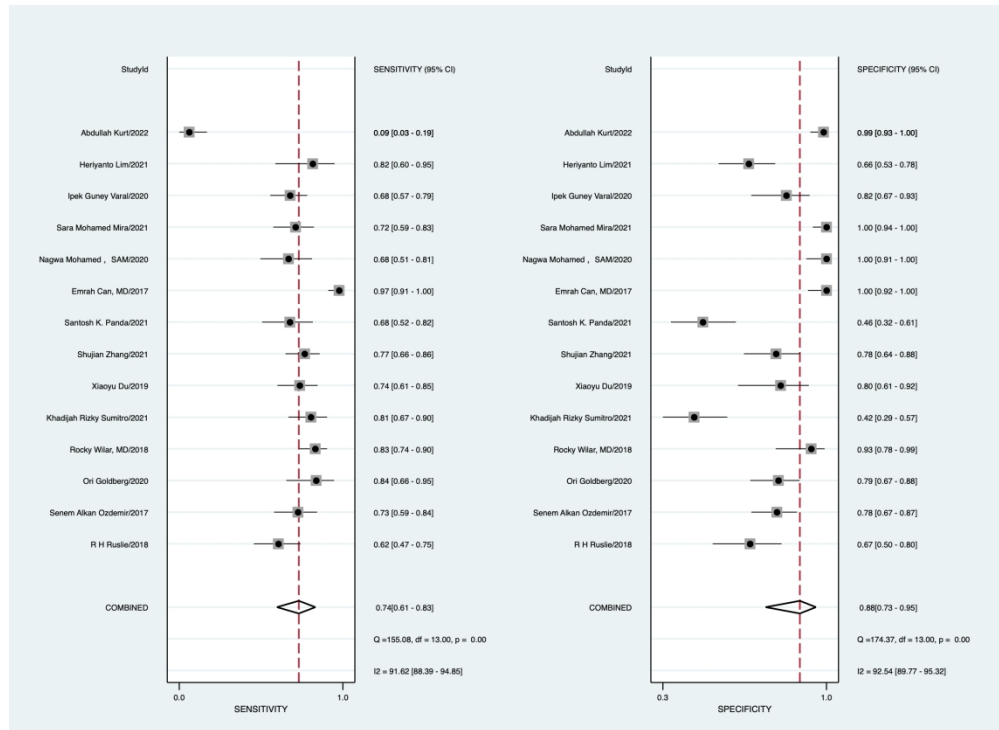
Risk of bias and applicability concerns summary

228x309mm (144 x 144 DPI)



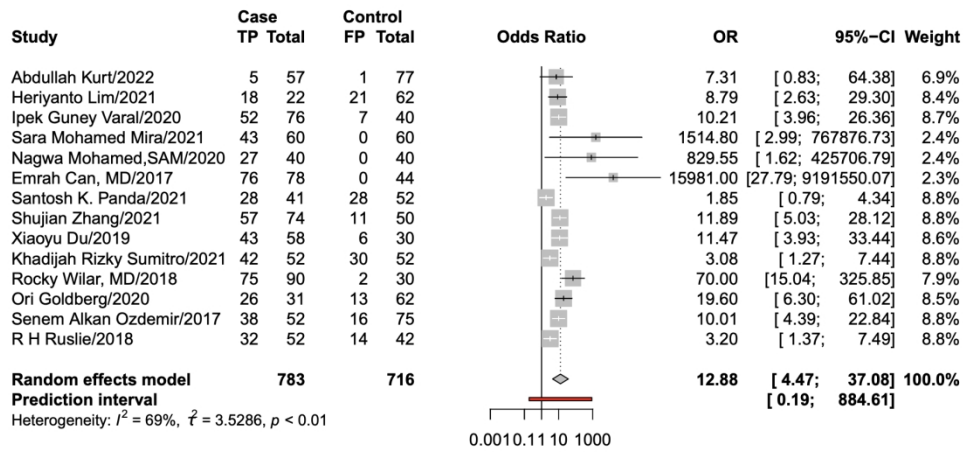
Risk of bias and applicability concerns graph

229x70mm (144 x 144 DPI)



Forest plot of the pooled sensitivity and specificity

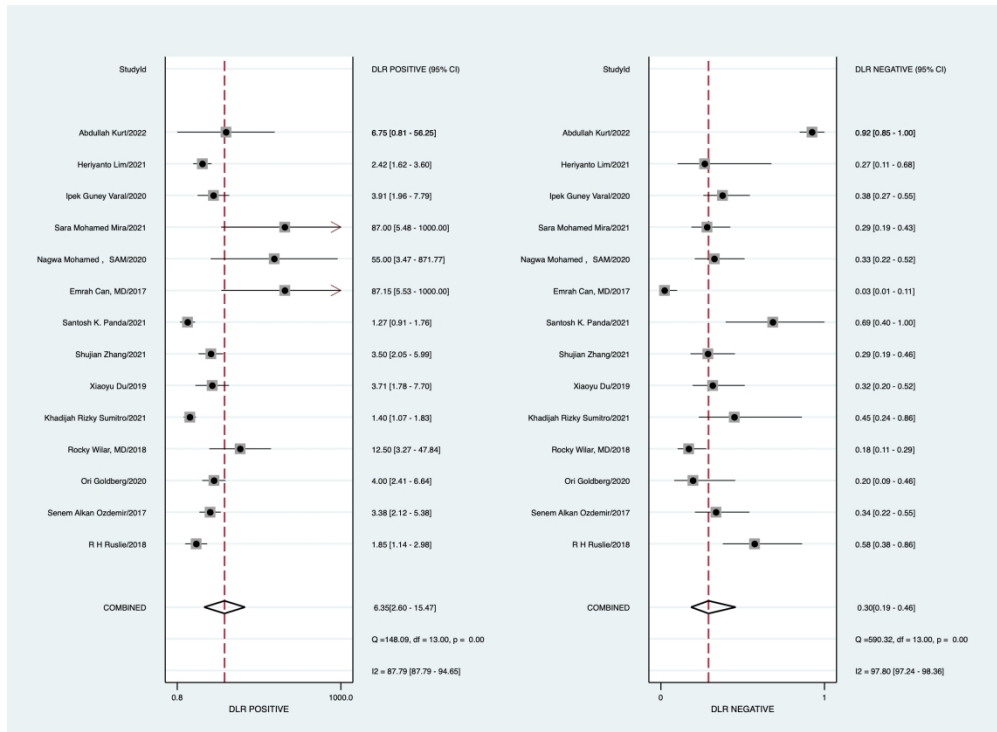
445x323mm (144 x 144 DPI)



Forest plot of the pooled diagnostic odds ratio

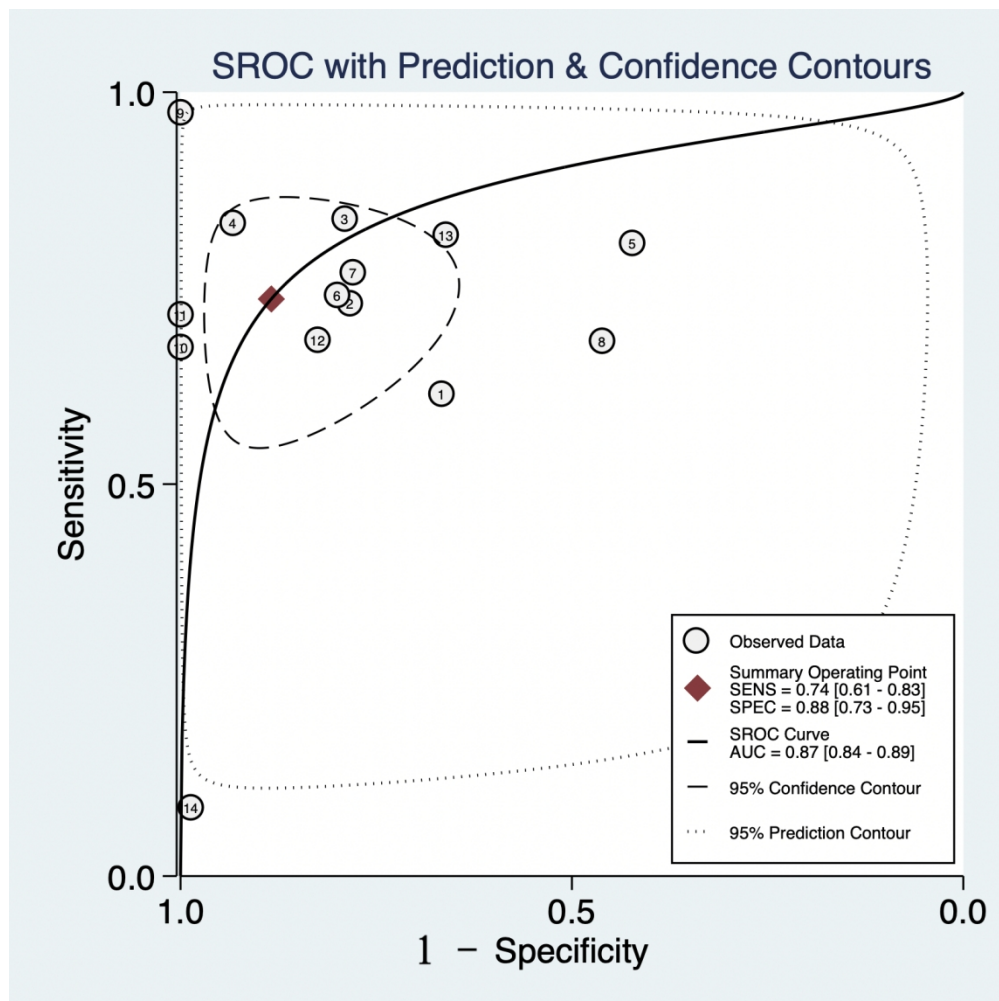
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Forest plot of the pooled positive LR and negative LR

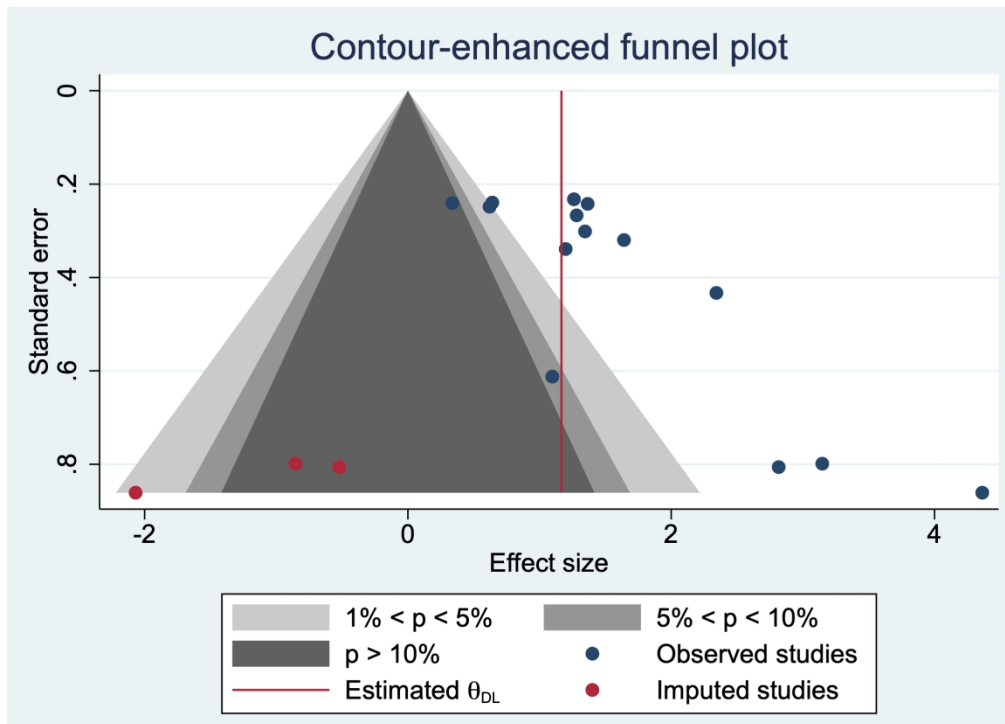
445x323mm (144 x 144 DPI)



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

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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	<p>No. Query</p> <p>#33: #10 AND #30 AND #32</p> <p>#32: #1 OR #2 OR #3 OR #31</p> <p>#31 : 'neutrophil lymphocyte ratio'/exp</p> <p>#30: 'neutrophil lymphocyte ratio'/exp</p> <p>#29 : #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28</p> <p>#28 : 'eos':ab,ti</p> <p>#27 : 'los':ab,ti</p> <p>#26 : 'sepsis, neonatal early-onset':ab,ti</p> <p>#25 : 'early onset sepsis':ab,ti</p> <p>#24 : 'sepsis, neonatal late-onset':ab,ti</p> <p>#23 : 'neonatal sepsis':ab,ti</p> <p>#22 : 'neonatal sepsis':ab,ti</p> <p>#21 : 'newborn sepsis':ab,ti</p> <p>#20 : 'newborn sepsis'/exp</p> <p>#19 : #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18</p> <p>#18 : 'severe sepsis':ab,ti</p> <p>#17 : 'poisoning, blood':ab,ti</p> <p>#16 : 'septicemia':ab,ti</p> <p>#15 : 'pyohemia':ab,ti</p> <p>#14 : 'pyohemia':ab,ti</p> <p>#13 : 'bloodstream infection':ab,ti</p> <p>#12 : 'sepsis':ab,ti</p>

	<p>#11 : 'sepsis'/exp #10 : #5 OR #6 OR #7 OR #8 #9 : 'neonate':ab,ti #8 : 'newborn':ab,ti #7 : 'newborn infant':ab,ti #6 : 'newborn':ab,ti #5 : 'newborn'/exp #4 : #1 OR #2 OR #3 #3 : 'nlr':ab,ti #2 : 'neutrophil to lymphocyte ratio':ab,ti #1 : 'neutrophil and lymphocyte ratio':ab,ti</p>																																							
Database	Web of science																																							
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Results	36																																							
Search details	<p>#1 (((((((((((TS=(Neonatal Sepsis)) OR TS=(Neonatal sepsis)) OR TS=(Sepsis, Neonatal Late-Onset)) OR TS=(Early Onset Sepsis)) OR TS=(Sepsis, Neonatal Early-Onset)) OR TS=(los)) OR TS=(eos)) OR TS=(sepsis)) OR TS=(Bloodstream Infection)) OR TS=(pyohemic)) OR TS=(pyaemic)) OR TS=(Septicemia)) OR TS=(Poisoning, Blood)) OR TS=(Severe Sepsis) #2 TS=(Neutrophil and lymphocyte ratio) or TS=(Neutrophil to lymphocyte ratio) or TS=(nlr) #3 (((TS=(Infant, Newborn)) OR TS=(Newborn Infant)) OR TS=(Newborn)) OR TS=(Neonate) #1 and #2 and #3</p>																																							
Database	Cochrane																																							
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Search details	<table border="1"> <thead> <tr> <th>ID</th> <th>Search</th> <th>Hits</th> </tr> </thead> <tbody> <tr> <td>#1</td> <td>MeSH descriptor: [Neonatal Sepsis] explode all trees</td> <td>86</td> </tr> <tr> <td>#2</td> <td>(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)</td> <td>2151</td> </tr> <tr> <td>#3</td> <td>(LOS):ti,ab,kw OR (EOS):ti,ab,kw (Word variations have been searched)</td> <td>15529</td> </tr> <tr> <td>#4</td> <td>#1 or #2 or #3</td> <td>17494</td> </tr> <tr> <td>#5</td> <td>MeSH descriptor: [Sepsis] explode all trees</td> <td>4918</td> </tr> <tr> <td>#6</td> <td>(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)</td> <td>13925</td> </tr> <tr> <td>#7</td> <td>(Poisoning, Blood):ti,ab,kw OR (Severe Sepsis):ti,ab,kw (Word variations have been searched)</td> <td>4942</td> </tr> <tr> <td>#8</td> <td>#5 or #6 or #7</td> <td>16646</td> </tr> <tr> <td>#9</td> <td>#4 or #8</td> <td>31666</td> </tr> <tr> <td>#10</td> <td>MeSH descriptor: [Infant, Newborn] explode all trees</td> <td>17498</td> </tr> <tr> <td>#11</td> <td>(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)</td> <td>40837</td> </tr> <tr> <td>#12</td> <td>#10 or #11</td> <td>40928</td> </tr> </tbody> </table>	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
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	#13 (Neutrophil and lymphocyte ratio):ti,ab,kw OR (Neutrophil to lymphocyte ratio):ti,ab,kw OR (nlr):ti,ab,kw (Word variations have been searched) 915 #14 #9 or #12 68896 #15 #14 and #13 30
Database	CNKI (<i>Chinese database</i>)
Website	https://www.cnki.net
Time	database building - 2022.06.28
Results	195
Search detail	(主题=脓毒症 + 败血症 + 新生儿败血症 + 血流感染 + 早发性败血症 + 迟发性败血症 + 血液中毒 + 新生儿脓毒症) AND (主题=中性粒淋巴细胞比 + nlr)
Database	Wanfang (<i>Chinese database</i>)
Website	https://www.wanfangdata.com.cn/index.html
Time	database building - 2022.06.28
Results	319
Search details	检索表达式(中英文扩展&主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)
Database	China Biomedical Literature Database (<i>Chinese database</i>)
Website	http://www.sinomed.ac.cn/index.jsp
Time	database building - 2022.06.28
Results	137
Search details	((("中性粒淋巴细胞比值"[常用字段:智能] OR "nlr"[常用字段:智能])) AND (("脓毒症"[常用字段:智能] OR "败血症"[常用字段:智能] OR "新生儿脓毒症"[常用字段:智能] OR "新生儿败血症"[常用字段:智能] OR "早发性败血症"[常用字段:智能] OR "迟发性败血症"[常用字段:智能] OR "血流感染"[常用字段:智能]))
Database	VIP Database (<i>Chinese database</i>)
Website	http://qikan.cqvip.com
Time	database building - 2022.06.28
Results	43
Search details	检索表达式(主题词扩展): 主题:(新生儿败血症 or 败血症 or 新生儿脓毒症 or 脓毒症 or 早发性败血症 or 迟发性败血症 or 血流感染) and 主题:(中性粒淋巴细胞比值 or nlr)

Table 1 characteristics of the included 14 studies.

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

5							EOS、	57/77	5	1	52	76	8.8	98.7	4.79	
6	Abdullah Kurt [14]	2022	2016-2018	Retrospective	Blood culture	Turkey	LOS									NA
8							EOS	20/77	3	1	17	76	15	98.7	4.79	
9							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.
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Table 2 The result of meta-regression**Sensitivity and Specificity**

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

Joint Model

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

Table 3 The results of sensitivity analysis

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

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

Reference

- [1] Ruslie R H, Tjipta D G, Samosir C T, et al. Bacterial pattern, and role of laboratory parameters as marker for neonatal sepsis[C]//IOP Conference Series: Earth and Environmental Science. *IOP Publishing*, 2018, 125(1): 012057.
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Table 4 Subgroup analysis of neutrophil-to-lymphocyte ratio in the diagnosis of neonatal sepsis.

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

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

Reference

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

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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	



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Registration	12	Prospero: CRD42021278881	
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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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For peer review only



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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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6



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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

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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



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Additional analysis	23	<p>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)</p> <p>(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).</p> <p>(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).</p> <p>(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).</p>	7-8
DISCUSSION			
Summary of evidence	24	<p>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.</p>	8-9
Limitations	25	<p>(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.</p>	9
Conclusions	26	<p>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.</p>	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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