Diagnostic value of neutrophil CD64 combined with CRP for neonatal sepsis: A meta-analysis

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**Abstract**

**Background:** Sepsis is the leading cause of morbidity and mortality in newborns. CD64 combined with c-reactive protein (CRP) could improve the sensitivity and specificity of neonatal sepsis diagnosis, but the results were still controversial. Therefore, this meta-analysis was conducted to clarify the importance of CD64 combined with CRP in the diagnosis of neonatal sepsis.

**Methods:** The researches published as of December 24, 2018 were comprehensively searched in PubMed, Embase (included Embase and Medline), the Cochrane Library and Web of Science. Totally, 8 articles were included, involving 1114 objects. Statistical calculations were performed using Stata14.0 and Review Manager 5.3.

**Results:** The diagnostic accuracy of all included studies was pooled as follows: sensitivity, 0.95 (95% CI: 0.86–0.98); specificity, 0.86 (95% CI: 0.74–0.93); positive likelihood ratio (PLR), 6.8 (95% CI: 3.50–13.20); negative likelihood ratio (NLR), 0.06 (95% CI: 0.02–0.18); diagnostic odds ratio (DOR), 118.0 (95% CI: 25.00–549.00), and the area under the curve (AUC) was 0.96 (95% CI: 0.94–0.97). It was found that heterogeneity was not caused by threshold effect \( P = 0.16 \), but the results of sensitivity \( (I^2 = 87.57\%) \) and specificity \( (I^2 = 89.07\%) \) analyses indicated significant heterogeneity between studies.

**Conclusions:** The combined application of CD64 and CRP improved the accuracy of neonatal sepsis diagnosis.

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2.2. Selection criteria

If the following inclusion criteria were met, relevant studies were included: 1) To investigate the diagnostic value of nCD64 combined with CRP in neonatal sepsis; 2) providing the golden standard of blood culture; 3) the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) can be obtained by calculation. The exclusion criteria in this study were as follows: 1) Eliminated the conference abstract or report, review or meta-analysis, and republished articles; 2) studies with insufficient data to extract were also excluded.

2.3. Data extraction and quality assessment

Two independent authors performed the initial search, imported EndNote and deleted the duplicate record automatically or manually, screened the titles and abstract, recognized the potentially studies, and got the full text. The two authors independently determined the included references and extracted the data, and the differences were resolved by a third author. The following data were extracted from each study: surname of the first author, publication year, country, number of infected and non-infected groups, the type of sepsis, nCD64 analysis method, analysis cutoff, sensitivity, specificity, TP, FP, FN, TN. The quality assessment of diagnostic research methodologies was conducted in accordance with QUADAS-2 tool guidelines [17].

2.4. Statistical analysis

STATA 14.0 and Review Manager 5.3 were used to perform the meta-analysis. In the diagnostic meta-analysis, considering that the combined CD64 test and the single CD64 test may have different diagnostic effects on neonatal sepsis, and the single test has been studied [15,16], we collected the individual data of CD64 combined CRP

Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Infected/noninfected</th>
<th>Diagnosis standard</th>
<th>Type of sepsis</th>
<th>Infants</th>
<th>nCD64 analysis</th>
<th>Analysis cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
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<tr>
<td>Qin</td>
<td>2017</td>
<td>China</td>
<td>37/21</td>
<td>Clinical or proven</td>
<td>c</td>
<td>N</td>
<td>FCM</td>
<td>2.58 CD64 index</td>
<td>97.29</td>
<td>76.19</td>
<td>31</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Shimi</td>
<td>2016</td>
<td>Egypt</td>
<td>60/60</td>
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<td>c</td>
<td>Preterm + term</td>
<td>FCM</td>
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<td>b</td>
<td>Preterm + term</td>
<td>FCM</td>
<td>2.5 CD64 index</td>
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<td>Clinical</td>
<td>a</td>
<td>Preterm</td>
<td>FCM</td>
<td>1010 PE-molecules bound/cell</td>
<td>77.27</td>
<td>90</td>
<td>68</td>
<td>7</td>
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<td>63</td>
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<tr>
<td>Genel</td>
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<td>Turkey</td>
<td>49/35</td>
<td>Clinical or proven</td>
<td>c</td>
<td>Preterm + term</td>
<td>FCM</td>
<td>3.05 MFI</td>
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<td>71</td>
<td>44</td>
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<td>USA</td>
<td>35/74</td>
<td>Clinical or proven</td>
<td>c</td>
<td>Preterm + term</td>
<td>FCM</td>
<td>4.93 CD64 index</td>
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<td>FCM</td>
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NOTE: a, early-onset; b, late-onset; c, early and late-onset; FCM, flow cytometric technology; MFI, mean fluorescence intensity; TP, true positive; FP, false positive; TN, true negative; FN, false negative.
diagnostic markers from the included studies. Therefore, we calculated the pooled sensitivity, specificity, PLR, NLR, DOR and 95% CI of CD64 combined CRP diagnosis using a bivariable meta-analysis model [18]. We constructed the symmetric receiver operator characteristic curve (SROC), calculated the area under the SROC curve, and evaluated the overall performance of CD64 combined with CRP in the diagnosis of neonatal sepsis. Spearman correlation coefficient was used to test the inter-study heterogeneity caused by threshold effect [19]. The Cochran Q test and I² statistics have always been used to evaluate non-threshold effects [20]. Fagan's nomogram was used to investigate the clinical value of CD64 combined with CRP in the detection of neonatal sepsis. The Deek's funnel plot method was used to explore publication bias (P<0.05) [21]. The sensitivity analysis was performed by excluding one study at a time and recalculating the risk effect.

3. Results

A total of 293 studies were found through literature search, of which 127 studies were excluded due to duplicates and 134 studies were excluded after we reviewed the retrieved literature's titles and abstracts. After reading the full-text of the remaining 32 studies, we further eliminated 24 studies, of which 23 were identified as CD64 alone and one as non-CD64 combined with CRP. Finally, 8 studies were included in this meta-analysis [22-29]. The flow chart of the meta-analysis is presented in Fig. 1. The basic information and quality evaluation results included in the study are shown in Table 1 and Fig. 2.

3.1. Diagnostic accuracy of CD64 + CRP for neonatal sepsis

The pooled results for diagnostic accuracy of all included studies were as follows: sensitivity, 0.95 (95% CI: 0.86-0.98); specificity, 0.86 (95% CI: 0.74-0.93); PLR, 6.8 (95% CI: 3.50-13.20); NLR, 0.06 (95% CI: 0.02-0.18); and DOR, 118.0 (95% CI: 25.00-549.00), and the AUC was 0.96, (95% CI: 0.94–0.97) (Figs. 3 and 4).

3.2. Heterogeneity and publication bias

It was found that heterogeneity was not caused by threshold effect (P = 0.16), but the results of sensitivity (I² = 87.57%) and specificity
(I² = 89.07%) analysis indicated significant heterogeneity between studies (Fig. 3). In addition, Deeks’ funnel plot showed no significant publication bias in our study (P = 0.960) (Fig. 6).

3.3. Sensitivity analysis

An outlier study was found through the sensitivity analysis and outlier detection (Fig. 7A, B). After the abnormal study was excluded, the combined results were sensitivity 0.92 (95% CI: 0.85–0.96), specificity 0.82 (95% CI: 0.74–0.88), PLR 5.20 (95% CI: 3.50–7.60), NLR 0.09 (95% CI: 0.05–0.18), DOR 56.00 (95% CI: 27.00–115.00), AUC 0.93 (95% CI: 0.91–0.95), however, the results were a change from previous results. Further analysis found that there was still outlier in the study, and the combined results after elimination had minimal changes: sensitivity 0.91 (95% CI: 0.83–0.95), specificity 0.80 (95% CI: 0.72–0.86), PLR 4.60 (95% CI: 3.30–6.40), NLR 0.11 (95% CI: 0.06–0.20), DOR 41.00 (95% CI: 24.00–71.00), AUC 0.91 (95% CI: 0.89–0.94). The heterogeneity was reduced after removing the literature one by one (sensitivity I² = 81.95%, specificity I² = 81.21%; sensitivity I² = 79.35%, specificity I² = 72.94%).

4. Discussion

Neonatal sepsis is one of the important causes of high neonatal mortality. Therefore, accurate diagnosis and appropriate medicine are particularly important for improving adverse outcomes. However, numerous studies have shown that clinical signals, non-specificity, and laboratory tests, including blood cultures, are not always reliable [30]. Up to now, many markers for the diagnosis of neonatal sepsis have been proposed, such as c-reactive protein, PCT, IL-6, etc. However, the identification of NS by a single biomarker is not reliable enough at present. More researchers focused on the combination of different biomarkers in different clinical environments, hoping to obtain clearer conclusions [31,32]. Thus, we conducted this meta-analysis to investigate the important role of CD64 combined with CRP in the diagnosis of neonatal sepsis. The main finding of this meta-analysis was that CD64 combined with CRP could improve the accuracy of neonatal sepsis diagnosis.

A meta-analysis of the diagnostic value of CD64 in the independent diagnosis of neonatal sepsis was performed in the two studies, and a large difference was found between the results of the two studies, which may be caused by the different inclusion and exclusion criteria of the two studies. The integrated sensitivity, specificity, PLR, NLR, DOR and AUC of Dai’s and Shi’s studies were 80% (95% CI: 69–88%), 83% (95% CI: 71–90%), 4.6 (95% CI: 2.5–8.6), 0.24 (95% CI: 0.14–0.41), 19 (95% CI: 6–57), 0.88 (95% CI: 0.85–0.91); 0.77 (95% CI: 0.74–0.79), 0.74 (95% CI: 0.72–0.75), 3.58 (95% CI: 2.85–4.49), 0.29 (95% CI: 0.22–0.37), 15.18 (95% CI: 9.75–23.62), respectively [15,16]. Our study found that the value of CD64 combined with CRP in the diagnosis of neonatal sepsis was superior.
References


Conflict of interests

All authors declare that they have no conflict of interests.

Acknowledgments

None.

Fig. 7. Influence analysis and outlier detection. A and B, (a) goodness of fit, (b) bivariate normality, (c) influence analysis, and (d) outlier detection.


