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ORIGINAL ARTICLE

A meta-analysis of interleukin-6 as a valid and accurate index in diagnosing early neonatal sepsis

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We aimed to systematically assess the overall value of interleukin 6 (IL-6) in diagnosing neonates with sepsis. A systematic literature search was conducted using the following electronic databases: PubMed, Embase, and Cochrane, to identify eligible studies through the index words updated till November 2018. Cross-sectional studies, as well as prospective cohort studies, were included in the above-mentioned group of eligible studies. We also searched the literature sources that had a link to the present study, which were further assessed by heterogeneity through the use of a proper-effects model to calculate pooled weighted specificity, sensitivity, and diagnostic odds ratio (DOR). We also conducted summary receiver operating characteristic (SROC) analyses for neonatal sepsis. In the present meta-analysis, there were 31 studies exploring IL-6 for the diagnostic accuracy of neonatal sepsis. The global specificity and sensitivity of IL-6 for neonatal sepsis were as follows: 88% (95% confidence interval [CI]: 83%-92%) and 82% (95% CI: 77%-86%), respectively. The global positive and negative likelihood ratio of IL-6 in diagnosing neonatal sepsis were 7.03 (95% CI: 4.81-10.26) and 0.20 (95% CI: 0.15-0.26), respectively. The global DOR was 29.54 (95%CI: 18.56-47.04) of IL-6. In addition, the area under the SROC was high for IL-6 (AUC = 0.92; 95% CI: 0.89-0.94). In this study, we performed a systematic review and meta-analysis to assess the diagnostic accuracy studies of IL-6 in diagnosing neonatal sepsis. Our results suggested that IL-6 is a valid and accurate index in diagnosing early neonatal sepsis, but it still needs to be combined with other laboratory tests and specific clinical manifestations.

KEYWORDS

diagnostic accuracy, IL-6, meta-analysis, neonatal sepsis

1 | INTRODUCTION

Sepsis is a medical emergency and is usually associated with high mortality and morbidity among newborn infants. Blood culture has been regarded as the gold standard for sepsis diagnosis. Nevertheless, it is difficult for definitive and early diagnosis of neonatal sepsis because of the non-specific clinical signs and symptoms of the disease; 48 to 72 hours or longer are needed for blood culture, not to mention the possibility of false negative results. Currently, the following parameters have been used frequently to aid sepsis diagnosis in newborns: immature/total leukocyte ratio (IT ratio); white blood cell (WBC) count; absolute leukocyte counts; and acute-phase reactants including procalcitonin (PC), C-reactive protein (CRP), and interleukin-6 (IL-6).[1–3] Nevertheless, the above-mentioned inflammatory markers could be affected by several factors, such as foetal or maternal non-infectious conditions. In addition, it has been challenging to definitively diagnose sepsis because of the different half-lives of inflammatory markers. Despite the fact that several laboratory approaches, such as molecular and cytokine analysis, have been proposed and further utilised to identify

microorganisms, cost-effective issues still exist. Several reports with samples from newborns, children, and adults indicated morphological changes in leukocytes during infection. The conductivity (MNC, MMC), mean neutrophil and monocyte volume (MNV, MMV), volume distribution width (NDW, MDW), and scattering (MNS, MMS) obtained through mathematical analysis of morphological changes were used in diagnosing sepsis.[4–9] Given the above-mentioned background, we collected updated evidence available to assess IL-6 in diagnosing neonatal sepsis based on qualified studies in the present meta-analysis.

Key Messages

- the overall value of interleukin-6 (IL-6) in diagnosing neonates harbouring sepsis was investigated
- thirty-one studies exploring IL-6 in diagnostic accuracy of neonatal sepsis were included for meta-analysis
- IL-6 is a valid and accurate index in diagnosing early neonatal sepsis

2 | METHODS

2.1 | Literature search

An electronic literature search was conducted for all the eligible trials through the use of Embase, Cochrane, and PubMed databases, updated till November 2018, for studies on the accuracy of IL-6 in diagnosing neonatal sepsis. In addition, we also searched associated publications as well as reference materials. The following search terms were used: newborn, neonatal, infant, sepsis, pyohemia, pyaemia, IL-6, and interleukin-6. These terms were used in combination with "AND" or "OR." The search process was carried out separately by two reviewers. Any differences were settled through the aid of a third party.

2.2 | Selection criteria

To be included in the current meta-analysis, studies should meet the following criteria: (a) cross-sectional or cohort study; (b) study patients were neonates harbouring suspected sepsis without other serious illnesses and neonates in the control group were without sepsis; (c) sepsis was diagnosed by IL-6 and another golden standard; (d) false positive (FP), true positive (TP), true negative (TN), and false negative (FN) were included as data across the study; and (e) the publications were only available in English.

Studies that met the following criteria should be excluded: (a) duplicate publication or shared result or content; (b) case report, expert comment, systematic review, conference report, meta-analysis, theoretical research, and economic analysis; and (c) irrelevant outcomes.

All the present studies were hand-screened separately by two reviewers for evaluation of eligibility. Any arising disagreements were then settled through the help of a third reviewer.

2.3 | Data extraction

The authors extracted data from included studies. The present study consisted of basic information and main outcomes. Basic information included the following parameters: the author's name, sample size, percentage of male, gestational age, test method, and the cut-off value of IL-6. The second part contained clinical outcomes. For each selected study, we constructed a 2 × 2 contingency table, of which the results through the application of the gold standard and magnetic resonance imaging were negative or positive. The data included TP, FP, FN, and TN. In the 2 × 2 contingency table, a value of 0 in one single cell across the study represents the addition of 0.5 to all cells for further calculation. We also calculated the likelihood ratio, sensitivity, and specificity. The diagnostic odds ratio (DOR) was measured for diagnostic accuracy. A DOR value of 1 represents a test without discriminatory power; a higher DOR value indicates a greater degree of relevance of the assessed diagnostic test. The above-mentioned process was separately conducted by two investigators; any arising differences were resolved by discussion to reach a consensus.

2.4 | Statistics analysis

The meta-analysis was conducted using STATA 10.0 (Texas). Heterogeneity of the trial results was assessed using the χ^2 and I^2 tests to select the ideal analysis model (the random-effects model or the fixed-effects model): $I^2 > 50\%$ and χ^2 test $P \leq 0.05$ reflected a high heterogeneity, and the random-effects model was utilised; $I^2 \leq 50\%$ and χ^2 test $P > 0.05$ reflected an acceptable heterogeneity of the data when assessed using the fixed-effects model. To further investigate heterogeneity, we conducted a diagnostic threshold analysis on the basis of the correlation (Spearman's) for heterogeneity between the logit of sensitivity and [1 –specificity]. The specificity and sensitivity of the study exhibit a negative correlation (or a positive correlation between sensitivity and [1 –specificity]), with the presence of threshold effect. Hence, a strong positive correlation is accompanied by the threshold effect between sensitivity and [1 –specificity]. When there was heterogeneity because of the threshold effect, a summary receiver operating characteristic (SROC) curve was then plotted. This method was appropriate considering the overestimation of global sensitivity and specificity values. In such cases, the SROC curve was recommended for analysis plus ROC panel points. To identify publication bias, we also utilised Deeks' Funnel Asymmetry Plot.

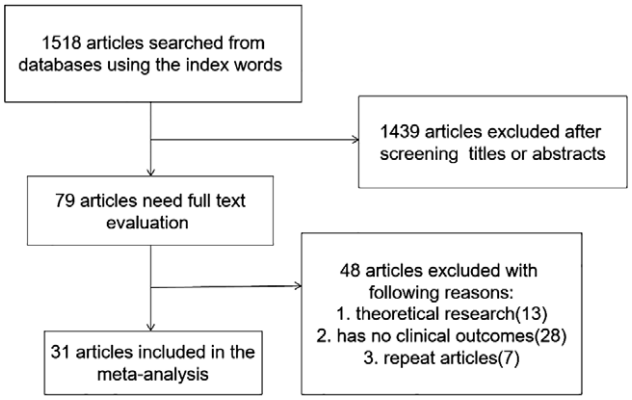

FIGURE 1 The flow diagram of the literature search and selection process

3 | RESULTS

3.1 | Study characteristics

Through the search of indexes, a total of 1518 publications were included. After title and abstract screening, 1439 publications were then excluded; thus, 79 publications were further assessed. During full-text screening, 48 publications were excluded because of: theoretical research,[10] lack of clinical outcomes,[11] and duplicate articles.[7] Therefore, a final total of 31 studies[10–15,17–40] were used for the current meta-analysis, of which 1448 neonates were studied and evaluated in the sepsis group

TABLE 1 The basic characteristics of included studies

Study	No. of patients		Gestational age		Gender		Test Method	Cut-off value (pg/mL)	TP	FP	FN	TN
	Sepsis	No sepsis	Sepsis	No sepsis	Sepsis	No sepsis						
Tunc et al[19]	30	20	37.5	38.5	11 M	12 M	—	7	29	1	1	19
Boskabadi et al[31]	41	43	35.6/35.89	36.12	—	—	ELISA	10.85	38	1	3	42
Prashant et al[33]	50	50	—	—	33 M	35 M	ELISA	16.35	39	11	11	39
Abdollahi et al[36]	49	16	—	—	—	—	ELISA	60	27	0	22	16
Oncel et al[38]	76	52	33.1	32.4	49 M	32 M	ELISA	26	64	1	12	51
Cekmez et al[37]	62	43	36.1	36	—	—	ELISA	15	58	2	4	41
Labenne et al[12]	31	182	28.4	29.3	19 M	105 M	ELISA	300	27	33	4	149
Celik et al[13]	232	50	30.6/30.8	31.7	125 M	30 M	ELISA	24.65	167	8	65	42
Dilli et al[14]	35	42	31.2	31.5	23 M	26 M	ELISA	24.9	28	3	7	39
Sarafidis et al[10]	31	21	—	—	—	—	ELISA	69.98	25	4	6	17
Bender et al[15]	29	94	39	37	14 M	54 M	CHIIA	12	17	6	12	88
Kocabaş et al[16]	26	29	35.8	37.3	16 M	16 M	ELISA	3.6	25	3	1	26
Ng et al[17]	44	111	28.5	28.8	24 M	48 M	ELISA	26.1	36	20	8	91
Verboon-Maciolek et al[18]	66	26	29	30	33 M	18 M	ELISA	60	45	6	21	20
Laborada et al[20]	48	57	31.4	30.6	25 M	22 M	ELISA	18	37	15	11	42
Resch et al[21]	41	27	—	—	—	—	ELISA	60	22	0	19	27
Reyes et al[22]	20	40	36	37	8 M	20 M	ELISA	30	12	8	8	32
Martin et al[23]	12	20	—	—	—	—	CHIIA	160	12	6	0	14
Mehr et al[24]	11	26	30.1	34	7 M	11 M	ELISA	32	9	2	2	24
Kallman et al[25]	30	28	32/37	39	—	—	ELISA	135	29	8	1	20
Silveira and Procianoy[26]	66	51	37.4/37.1/36.4	39.1	—	—	ELISA	32	59	28	7	23
Küster et al[27]	21	20	27.1	29.2	12 M	8 M	ELISA	25	30	1	1	19
Ng et al[28]	35	46	29.3	29.6	13 M	23 M	ELISA	31	31	2	4	44
Lusyati et al.[11]	25	34	34	34	13 M	11 M	CHIIA	28	20	13	5	21
	18	34	32	34	8 M	11 M	CHIIA	93	13	9	5	25
Basu et al[29]	32	32	—	—	—	—	ELISA	50	24	0	8	32
Hotoura et al[30]	17	40	30.6	30.5	—	—	ELISA	60	11	2	6	38
Hotoura et al[32]	25	50	—	—	—	—	ELISA	60	23	1	2	49
Gonzalez et al[34]	8	19	28.2	27.7	—	—	—	18	6	6	2	13
Canpolat et al[35]	32	42	—	—	—	—	—	7.6	30	1	2	41
Zhao et al[39]	49	61	39.3	39.3	35 M	35 M	ELISA	32	43	12	6	49
Çelik et al[40]	116	111	32.2	34.4	62 M	70 M	CLIA	12.55	28	29	12	82
	40	111	32.5	34.4	26 M	70 M	CLIA	15.4	26	32	14	79

Abbreviations: CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

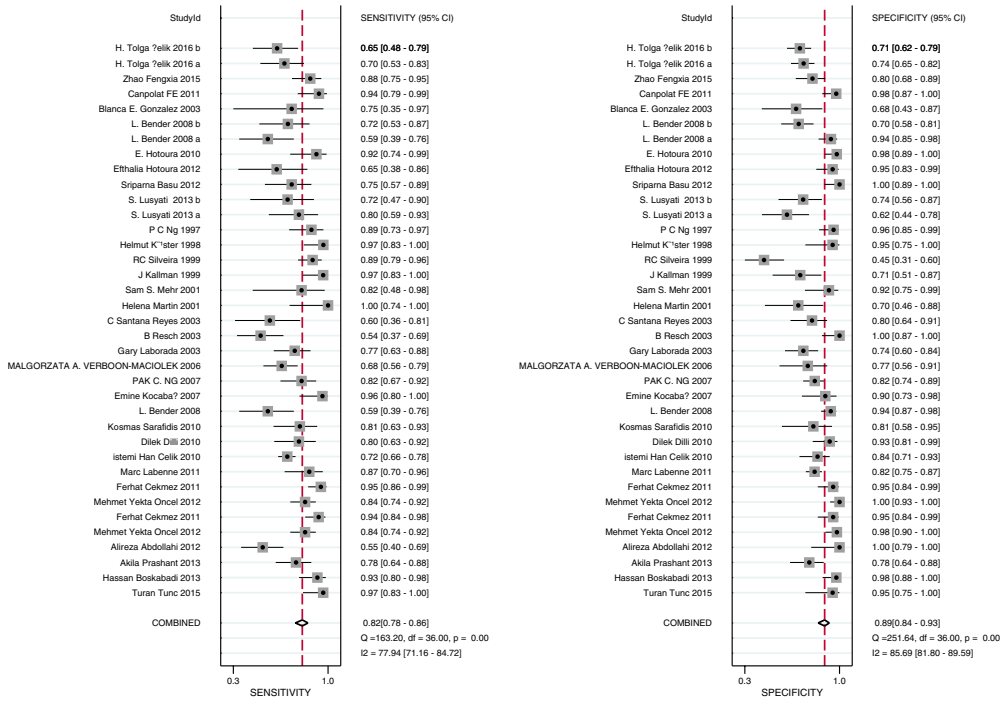

FIGURE 2 Forest plot showing the sensitivity and specificity values of interleukin-6 for neonatal sepsis

and 1628 neonates in the no-sepsis group (see Figure 1). Table 1 shows the major characteristics of the selected studies. The baseline information included the following parameters: the number of patients, gestational age, gender, test method, and the cut-off value of IL-6.

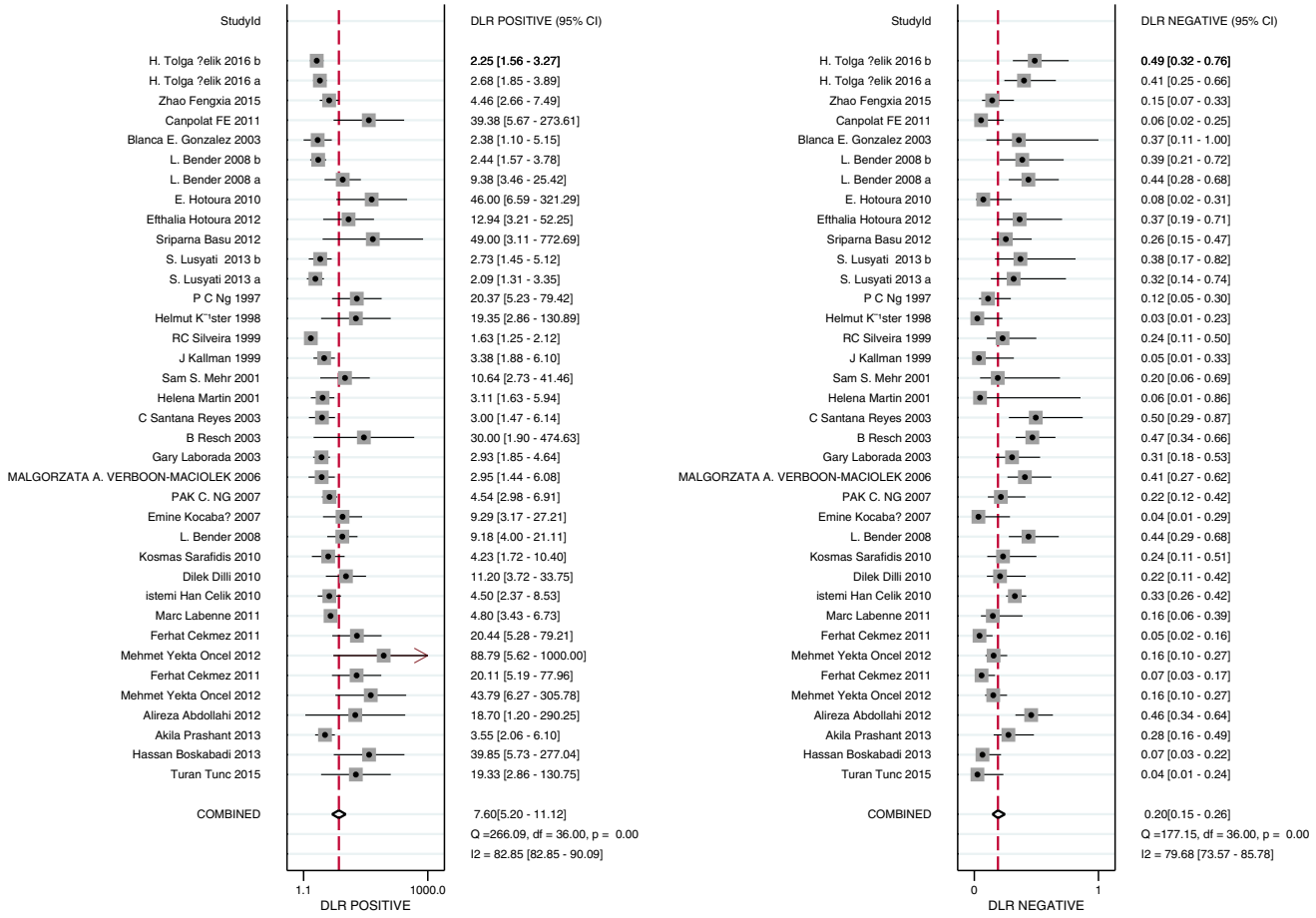

FIGURE 3 Forest plot showing the positive and negative likelihood ratio of interleukin-6 for neonatal sepsis

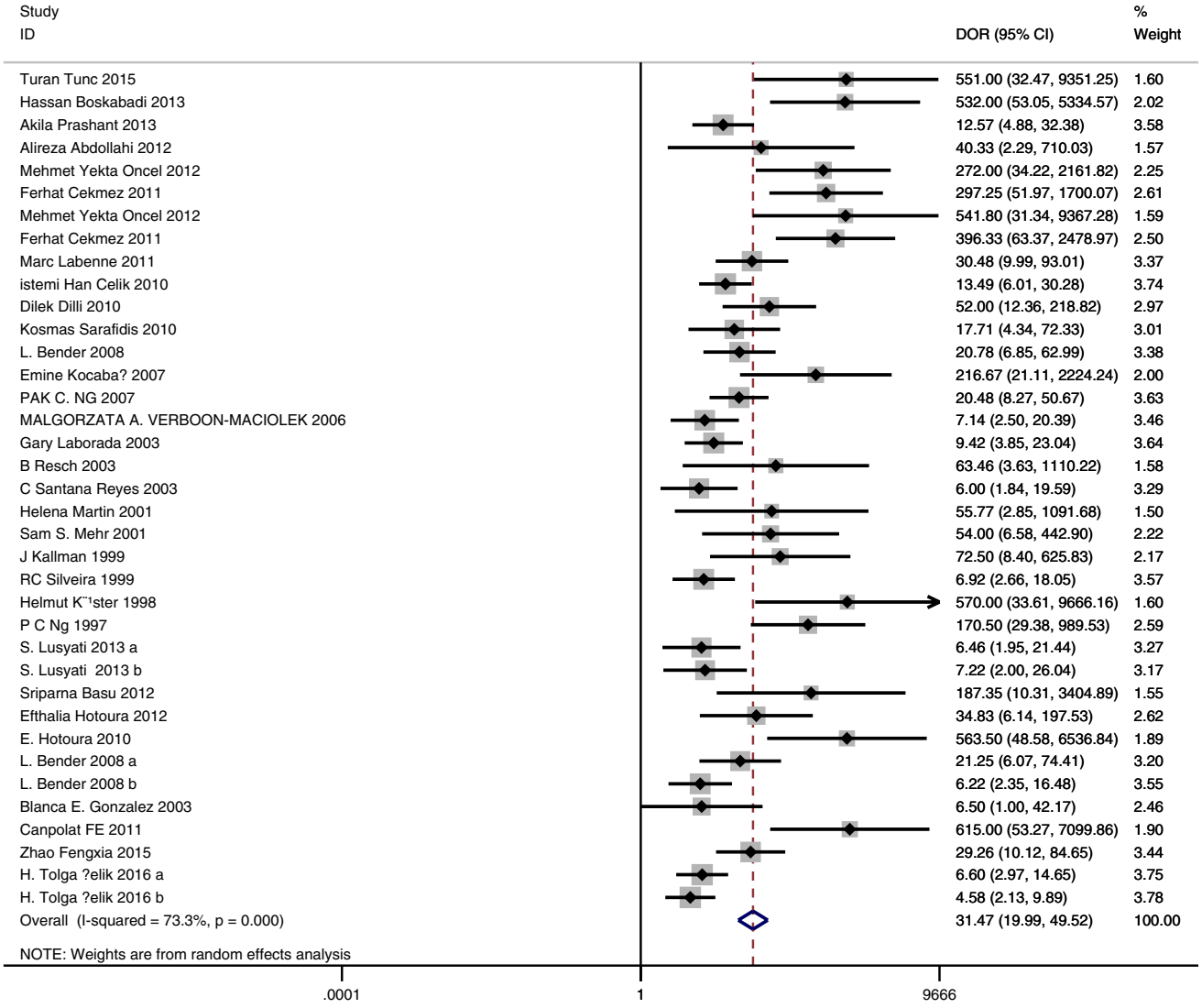

FIGURE 4 Forest plot showing the diagnostic odds ratio of interleukin-6 for neonatal sepsis

3.2 | Diagnostic accuracy

Overall, the accuracy of IL-6 for neonatal sepsis was shown across the study. According to the I^2 tests ($I^2 = 97\%$) and χ^2 test ($Q = 0.73.3$, $P = 0.000$), the random-effects model was applied for pooled analysis of DOR given that heterogeneity was considered to be high. There was no threshold effect on the basis of correlation (Spearman's $R = -0.2738$, $P = 0.1232$) between the logit of sensitivity and [1 – specificity].

The global sensitivity and specificity were 88% (95% CI: 83%-92%) and 82% (95% CI: 77%-86%), respectively. The global positive likelihood ratio was calculated to be 7.03 (95% CI: 4.81-10.26). Hence, a positive IL-6 result would be increased by 7.03-fold the odds of an accurate diagnosis of neonatal sepsis. Given a value of 0.20 (95% CI: 0.15-0.26) for the global negative likelihood ratio, it demonstrated the use of IL-6 considering the value was close to zero. Specifically, the odds of a false-positive result were only increased by a factor of 0.20. The global DOR was 29.54 (95%CI: 18.56-47.04); thus, the odds of a positive IL-6 result were 31.47-fold higher among newborns with sepsis in comparison with those without sepsis. There was a high area under the SROC (AUC = 0.92; 95% CI: 0.89-0.94). All the above results are presented in Figures 2–5.

3.3 | Quality assessment and potential bias

On the basis of predefined criteria, a total of 31 publications were analysed in the current meta-analysis. We applied Deeks' Funnel Asymmetry Plot for quality assessment as well as for potential bias. The funnel plot for DOR of medial meniscus tears in studies was associated with evident symmetry, indicating no significant publication bias (Figure 6, $P = 0.23$).

4 | DISCUSSION

As a matter of fact, there have been several other similar studies and meta-analyses concerning IL-6 in terms of diagnostic accuracy for neonatal sepsis. According to earlier

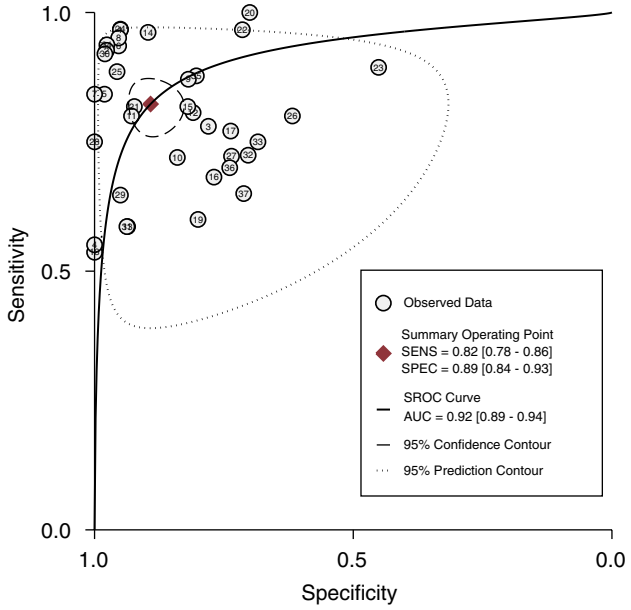

FIGURE 5 Summary of receiver operating characteristic plots for diagnostic accuracy of interleukin-6 for neonatal sepsis

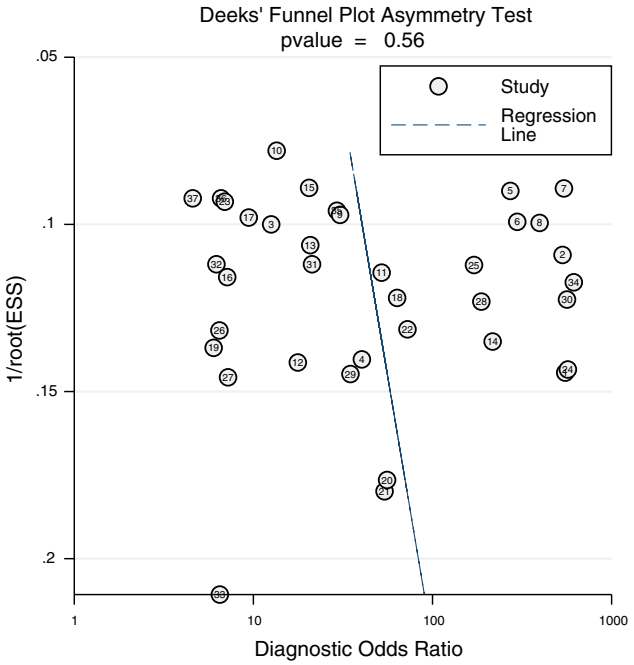

FIGURE 6 Funnel plot of studies included in the meta-analysis

studies by Jing et al,[41] 33 studies with a total of 3135 neonates showed that the specificity and sensitivity of IL-6 for the diagnosis of neonatal were calculated to be 0.83 (95% CI:0.81-0.85) and 0.79 (95% CI: 0.76-0.81), respectively, and the area under SROC curve was 0.89. The post-test probability was 5%, and the positive IL-6 was 60%. Chauhan et al[42] included six studies in which a total of 1323 infants with very-low birth weight (VLBW) were recruited. All were of reasonable methodological quality. There was no strong evidence for a significant association between IL-6 (2174C) polymorphism and VLBW infants with sepsis based on the data from a random-effects meta-analysis: pooled relative risk 0.90 (95% CI 0.62-1.31). No modest relation was present between IL-6 polymorphism and neonatal sepsis in VLBW infants on the basis of the available data, which also failed to support screening infants for this allele with an attempt to guide selective antimicrobial prophylaxis.

Neonatal sepsis is one of the greatest challenges to neonatal health. The diagnosis of neonatal sepsis has always been a worldwide problem because of the specificity of the patients and the complexity of the disease itself. Many researchers are studying and proposing diagnostic markers of neonatal sepsis. However, because of the differences in experimental conditions and race, the accuracy of diagnostic markers of neonatal sepsis in different individual studies vary, especially in the evaluation of some important biomarkers. The strengths of the present study include the systematic review of the published literature assessing the diagnostic efficacy of IL-6 in detecting neonatal sepsis. A total of 31 studies were included for final analysis. We evaluated and measured the publication bias through the use of Deeks' funnel plot, finding no significant publication bias of the included studies. As the change of neonatal sepsis is rapid, and different diagnostic markers all have a certain change cycle, we should try to measure a series of changes of markers to find the rule. In addition, studies further prove that no single marker can obtain satisfactory results in the diagnosis of neonatal sepsis, so we should pay attention to the study of combined diagnostic markers, especially the diagnostic accuracy at a specific time.

Admittedly, this study is also subject to several limitations: (a) differences in the predefined criteria for newborns; (b) the treatments and diseases of newborns were not available; (c) publications from this study were only available in English, being the source of bias; (d) difference of detection methods between studies; (e) difference in the IL-6 cut-off value; and (f) we used pooled data for analyses with unavailable individual data, which limited more comprehensive analyses.

Given the overall results from the present systematic review and meta-analysis, the present study offers moderate evidence to prove that IL-6 is a highly accurate diagnostic tool for detecting neonatal sepsis. In addition, there is no link to significant publication bias across the included studies.

CONFLICTS OF INTEREST

The authors declare there is no conflict of interest.

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