Original Article
Diagnostic performance of interleukin-6 and interleukin-8 for bacterial meningitis: a meta-analysis

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Abstract: This study aimed to summarize the overall diagnostic performance of interleukin-6 and interleukin-8 in cerebrospinal fluid for bacterial meningitis through meta-analysis due to inconclusive results reported. Literature search was performed in PubMed and Embase to identify eligible studies. Data were retrieved and sensitivity, specificity, positive likelihood ratio/negative likelihood ratio (PLR/NLR), and diagnostic odds ratio (DOR) were pooled. Summary receiver operating characteristic curve and the area under the curve (AUC) were calculated to evaluate their overall test performances. Thirteen studies were included for present meta-analysis. The summary estimates for interleukin-6 in diagnosing bacterial meningitis were: sensitivity, 0.91 (95% CI 0.81-0.96); specificity, 0.93 (95% CI 0.84-0.97); PLR, 12.38 (95% CI 5.42-28.29); NLR, 0.10 (95% CI 0.04-0.21); DOR, 129.76 (95% CI 41.48-405.88); and AUC 0.97 (95% CI 0.95-0.98). The corresponding summary performance estimates for interleukin-8 were as follows: sensitivity, 0.95 (95% CI 0.71-0.99); specificity, 0.89 (95% CI 0.77-0.95); PLR, 8.50 (95% CI, 3.83-18.86); NLR, 0.06 (95% CI 0.01-0.40); DOR, 154.25 (95% CI 14.56-1634.33); and AUC 0.95 (95% CI 0.93-0.97). Measurements of interleukin-6 and interleukin-8 play a valuable role in diagnosing bacterial meningitis. Nevertheless, their results should be interpreted in parallel with the results of routine tests and clinical symptoms.

Keywords: Bacterial meningitis, interleukin-6, interleukin-8, diagnosis, meta-analysis

Introduction

Bacterial meningitis remains a life-threatening disease that continues to inflict a heavy burden on patients [1, 2]. It was reported that the incidence of bacterial meningitis is about five cases per 100,000 adults per year in developed countries and may be ten times higher in less developed countries [3]. Bacterial meningitis is associated with high mortality and morbidity rates, with 20% and 50% of patients died in high and lower-income countries, respectively [3, 4]. In addition, patients with bacterial meningitis may often suffer serious sequelae, such as neurological sequelae, including hearing loss and neuropsychological impairment, occurring in about 50% of survivors [5]. Thus, to make an early diagnosis and timely administration of antibiotics will be of great importance in saving lives of bacterial meningitis patients [1, 4].

The diagnosis of bacterial meningitis is still a clinical challenge. The clinical features of bac-

terial meningitis are nonspecific, and the routine cerebrospinal fluid (CSF) examination doesn't supply satisfactory sensitivity and specificity for distinguishment of bacterial meningitis from other types of meningitis [6, 7]. While the empirical use of antibiotics for each suspected patients would lead to unnecessary hospitalization, needless antibiotic use, and increased cost for patients [8]. Therefore, it is of great importance to find novel and reliable CSF biomarkers that can increase diagnostic accuracy of bacterial meningitis when the current available CSF analysis is insufficient.

Growing studies suggest that cytokines involved in immune and inflammatory modulation, such as interleukin-6 (IL-6) or interleukin-8 (IL-8), are potential markers of meningeal inflammation [9, 10]. IL-6 has pro-inflammatory effects and it stimulates the growth of B lymphocytes that have differentiated into antibody producing cells [11, 12], and IL-8 acts as a chemoattractant for neutrophils to the site of inflammation [13], both play an important role in the patho-

genesis and clinical course of bacterial meningitis [9]. Both IL-6 and IL-8 in the CSF of bacterial meningitis patients were increased up to 48 hours after initiation of treatment, and elevated levels of IL-6 and IL-8 in CSF are good indicators of meningeal inflammation [12, 13]. A number of studies have investigated the diagnostic potential of IL-6 and IL-8 for bacterial meningitis, but with considerable varying results, to help gain more reliable conclusions, this study aimed to summarize the overall diagnostic accuracy of IL-6 and IL-8 for bacterial meningitis with standard methods recommended by the Cochrane Diagnostic Test Accuracy Working Group [14].

Method

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews, and this retrospective study didn't need institutional review board approval.

Search strategy and literature selection

A comprehensive literature search was performed in PubMed and Embase up to December, 2014 for studies that evaluated the diagnostic performance of CSF IL-6 or IL-8 for bacterial meningitis. The following search terms were used: "Interleukin-6 *or* IL-6 *or* Interleukin-8 *or* IL-8" AND "Bacterial meningitis" AND "Sensitivity or Specificity or Accuracy". In addition, we scanned the references of all studies and related review articles to identify potential studies.

Two independent reviewers screened the publications and defined the inclusion criteria as follows: (1) They were diagnostic studies that evaluated the diagnostic performance of IL-6 or IL-8 for bacterial meningitis on humans; (2) They used CSF as clinical samples; (3) They supplied enough data to calculate sensitivity and specificity; (4) They were published in English. To avoid selection bias, studies with less than 20 subjects were excluded, abstracts with limited information were also excluded.

Data extraction and quality assessment

For each of the included studies, two independent reviewers extracted data regarding the first author, publication year, country of origin,

IL-6 or IL-8 assay method, cut-off values and patient distribution between groups. For each study, we constructed 2 × 2 contingency tables in which all participants were classified as having positive or negative IL-8 or IL-6 results. Quality of included studies was assessed by use of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool based on 14 items, which was specifically developed for assessing quality of studies on diagnostic tests [15]. Any disagreements were adjudicated by a third investigator.

Statistical analysis

This meta-analysis was performed using a bivariate model [16]. First of all, we calculated pooled estimates of sensitivity and specificity, then, based on the pooled estimates of sensitivity and specificity, we calculated positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratios (DOR), which were used as major indexes of diagnostic accuracy. We summarized the performance of a diagnostic test based on the results of multiple studies with the summary receiver operating characteristic (SROC) curve. The area under the curve (AUC) represents the test's ability accurately to distinguish subjects with disease from those without disease; an AUC of 1.0 would represent perfect discriminatory ability [17]. Post-test probability was calculated using the overall prevalence of 20% with Fagan nomograms.

Cochran Q test and I^2 statistic were used to identify the potential heterogeneity, a P value of < 0.05 via the Cochran Q test or an I^2 values of > 50%, was considered as presence of significant heterogeneity. Deeks' funnel plot was used to detect potential publication bias [18]. The statistical analysis was performed using the "Midas" module in STATA 12.0 (Stata Corp., College Station, TX). All statistical tests were two-sided, with P values less than 0.05 taken as the threshold for statistical significance.

Results

After a systematic literature search and selection, a total of 13 studies regarding the usefulness of IL-6 or IL-8 to diagnose bacterial meningitis were included for present meta-analysis [19-31]. The main reason to rule out a study was: it didn't report sufficient data to re-con-
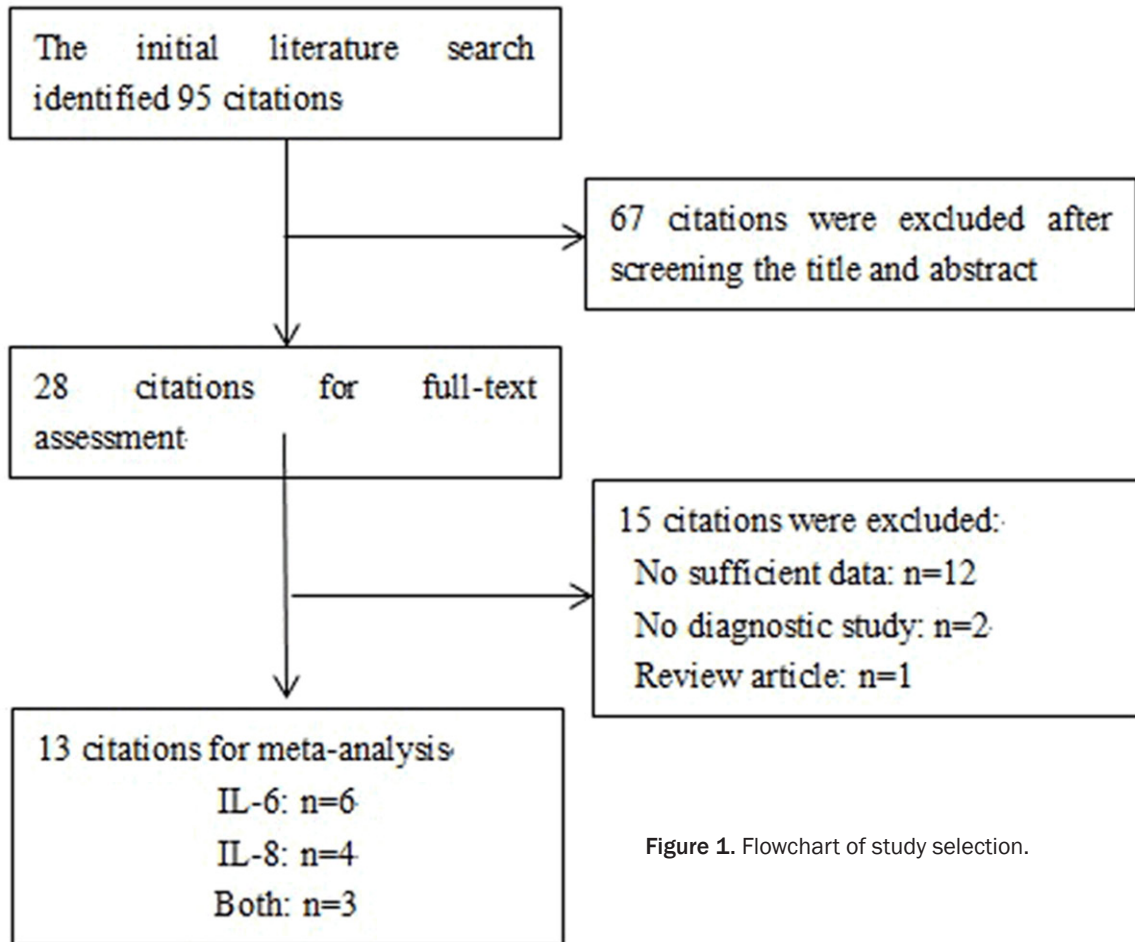
Figure 1. Flowchart of study selection.

struct 2 × 2 tables. **Figure 1** outlines the process of selecting studies.

Study characteristics report

There were nine studies examined the diagnostic performance of IL-6 for bacterial meningitis [19-27]. Including 315 bacterial meningitis patients and 510 controls. There were seven studies determined the diagnostic accuracy of IL-8 for bacterial meningitis [22, 24, 26, 28-31], including 241 bacterial meningitis patients and 233 controls. All the studies supplied the definition of bacterial meningitis based on CSF analysis, bacterial examinations and clinical information, which is widely accepted for diagnosing bacterial meningitis. All the studies described the methods of IL-6 and IL-8 measurement and most supplied cut-off values. Of the includes studies, 10 studies with QUADAS scores ≥ 10, suggesting the reliability of our results. The

detailed clinical characteristics and QUADAS scores of included studies were summarized in **Table 1**.
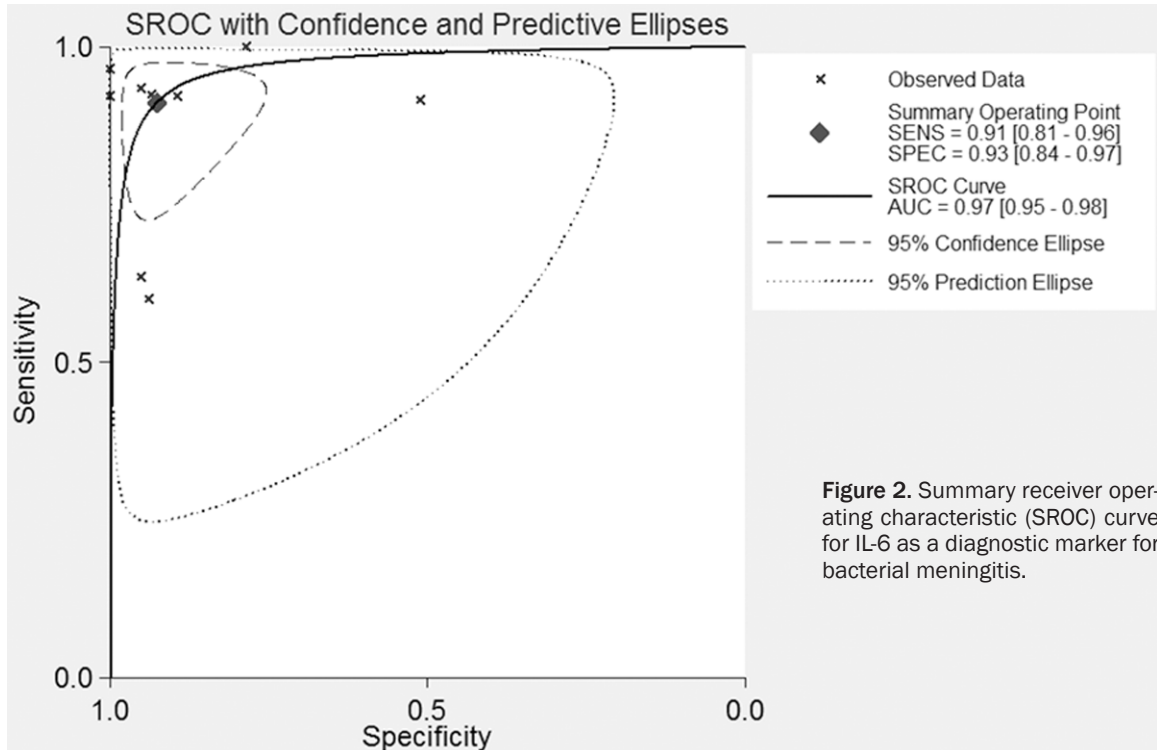
Diagnostic accuracy of IL-6

The pooled sensitivity of IL-6 was 0.91 (95% CI: 0.81-0.96); the specificity was 0.93 (95% CI: 0.84-0.97); the PLR was 12.38 (95% CI: 5.42-28.29); and the NLR was 0.10 (95% CI: 0.04-0.21); the DOR was 129.76 (95% CI: 41.48-405.88). **Figure 2** shows a plot of the rate of true positives as a function of the rate of false positives for individual studies, as well as the corresponding SROC curve. The AUC for IL-6 was 0.97 (95% CI: 0.95-0.98). Fagan's nomogram for likelihood ratios (**Figure 3**, left) indicated that using IL-6 to detect bacterial meningitis increased the post-probability to 76% when its results were positive and reduced the post-probability to 2% when the results were

Table 1. Clinical characteristics of studies included in the meta-analysis of diagnosis of bacterial meningitis using IL-6 and IL-8

| First author | Year | Country | Sample size | | Assay method | Cut-off value | TP | FP | FN | TN | QUADAS score |
			BM	non-BM							
IL-6											
Dulkerian SJ	1995	USA	20	42	ELISA	NA	20	9	0	33	8
Hashim IA	1995	UK	123	123	Radioimmunoassay	3.4 ng/mL	115	6	8	117	7
López-Cortés LF	1997	Spain	15	83	ELISA	10000 pg/mL	9	5	6	78	10
Kleine TO	2003	Germany	40	46	SPSCI	2500 ng/L	37	3	3	43	10
Hsieh CC	2009	China	12	41	ELISA	10 pg/mL	11	20	1	21	11
Chen Z	2012	China	22	61	Radioimmunoassay	51.6 ng/mL	14	3	8	58	12
Vázquez JA	2012	Argentina	13	27	ELISA	90 pg/dL	12	0	1	27	11
Prasad R	2014	India	57	30	ELISA	100 pg/mL	55	0	2	30	12
Takahashi W	2014	Japan	13	57	CLEIA	644 pg/mL	12	6	1	51	11
IL-8											
Ostergaard C	1996	Denmark	31	13	ELISA	3 ug/L	25	1	6	12	8
Kleine TO	2003	Germany	40	46	SPSCI	4000 ng/L	19	4	21	42	10
Pinto Junior VL	2011	Brazil	9	18	ELISA	1.685 ng/dL	9	1	0	17	11
Chen Z	2012	China	22	61	Radioimmunoassay	1.14 pg/mL	20	20	2	41	12
Bociąga-Jasik M	2012	Poland	42	25	ELISA	773.5 pg/mL	42	6	0	19	11
Prasad R	2014	India	57	30	ELISA	75 pg/mL	57	0	0	30	12
Abdelmoez AT	2014	Egypt	40	40	ELISA	3.6 ng/mL	33	6	7	34	11

CLEIA: Chemiluminescent enzyme immunoassay; ELISA: Enzyme-linked immunosorbent assay; FN: False negative; FP: False positive; NA: Not available; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; SPSCI: Solid phase sandwich chemoluminescence immunoassays; TN: True positive; TP: True positive.

Figure 2. Summary receiver operating characteristic (SROC) curve for IL-6 as a diagnostic marker for bacterial meningitis.

negative. All five performance indices showed high I² values: sensitivity, 78.22%; specificity, 92.43%; PLR, 88.78%; NLR, 80.02%; and DOR, 95.40% (all with P < 0.05 in Cochran Q test).
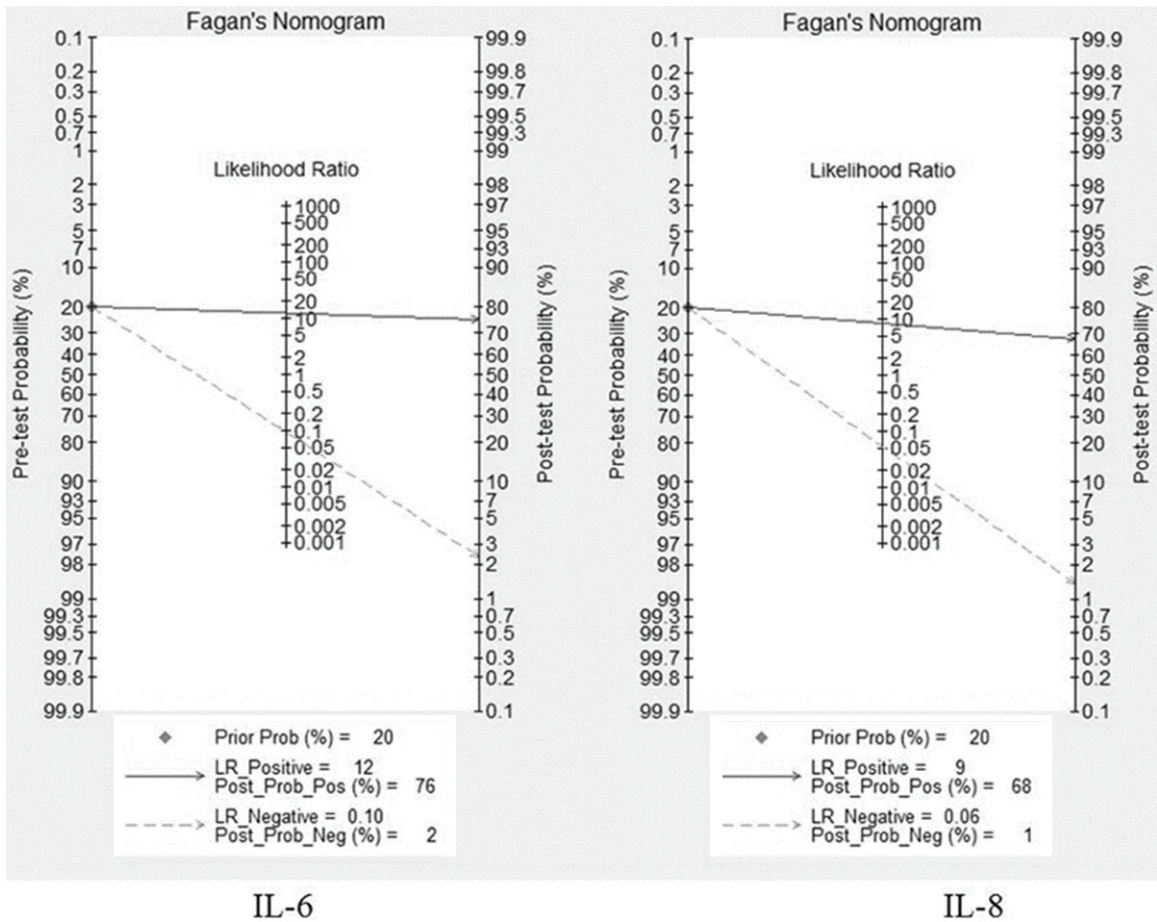
Figure 3. Fagan's nomogram for likelihood ratios and pre- and post-test probabilities for using IL-6 (Left) and IL-8 (Right) to diagnose bacterial meningitis.

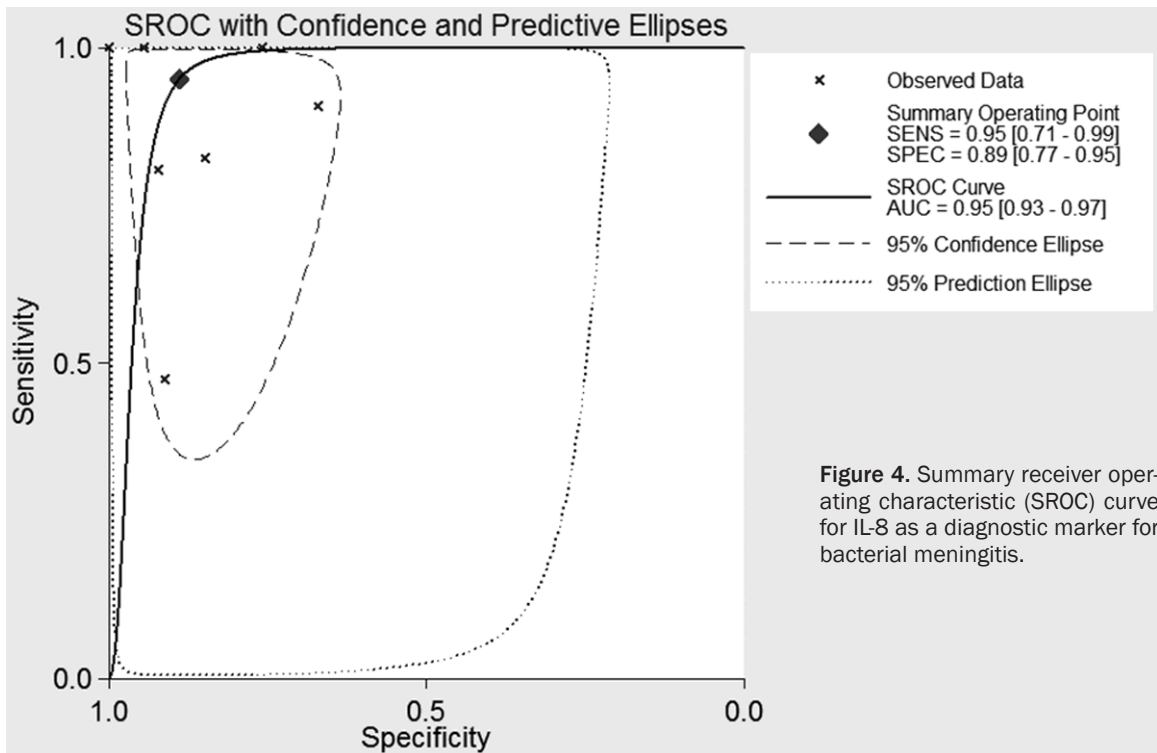**Table 2.** Summary characteristics of diagnostic performance of IL-6 and IL-8

Diagnostic index	IL-6	IL-8
Sensitivity	0.91	0.95
	(95 CI: 0.81-0.96)	(95 CI: 0.71-0.99)
Specificity	0.93	0.89
	(95 CI: 0.84-0.97)	(95 CI: 0.77-0.95)
PLR	12.38	8.5
	(95 CI: 5.42-28.29)	(95 CI: 3.83-18.86)
NLR	0.1	0.06
	(95 CI: 0.04-0.21)	(95 CI: 0.01-0.40)
DOR	129.76	154.25
	(95 CI: 41.48-405.88)	(95 CI: 14.56-1634.33)
PPP	76%	68%
PPN	2%	1%
AUC	0.97	0.95
	(95 CI: 0.95-0.98)	(95 CI: 0.93-0.97)

AUC: Area under the curve; DOR: Diagnostic odds ratios; NLR: Negative likelihood ratios; PLR: Positive likelihood ratios; PPN: Post-probability negative; PPP: Post-probability positive.

This suggests substantial heterogeneity among the studies.

Diagnostic accuracy of IL-8

For heterogeneity examination, all five performance indices of IL-8 showed high I^2 values: sensitivity, 92.94%; specificity, 88.07%; PLR, 80.85%; NLR, 94.25%; and DOR, 99.99% (all with $P < 0.05$ in Cochran Q test), suggesting significant heterogeneity among the studies. The summary estimates for IL-8 in the diagnosis of bacterial meningitis were: sensitivity 0.95 (95% CI: 0.71-0.99); specificity 0.89 (95% CI: 0.77-0.95); PLR 8.5 (95% CI: 3.83-18.86); NLR 0.06 (95% CI: 0.01-0.40); and DOR 154.25 (95% CI: 14.56-1634.33). **Table 2** summarized the pooled sensitivity, specificity, PLR, NLR, and DOR for the IL-8 in the diag-

Figure 4. Summary receiver operating characteristic (SROC) curve for IL-8 as a diagnostic marker for bacterial meningitis.

nosis of bacterial meningitis, and **Figure 4** shows the SROC curve. The AUC was 0.95 (95% CI: 0.93-0.97), suggesting high overall accuracy. Fagan's nomogram for likelihood ratios (**Figure 3**, Right) indicated that using IL-8 to detect bacterial meningitis increased the post-probability to 68% when the results were positive and reduced the post-probability to 1% when the results were negative.

Publication bias

Deeks' funnel plot asymmetry test was used to assess likelihood of publication bias in the final included studies. The slope coefficients were associated with a *P* value of 0.21 and 0.96 for IL-6 and IL-8, respectively, suggesting symmetry in the data and low likelihood of such bias (**Figure 5**).

Discussion

The prognosis of bacterial meningitis depends significantly on a rapid and accurate diagnosis, while the diagnosis of bacterial meningitis remains a clinical challenge. Since an overwhelming inflammatory reaction is one of the most important clinical characteristics of bacterial meningitis, growing studies have investi-

gated the diagnostic potential of IL-6 and IL-8, two of cytokines that regulating inflammation, for bacterial meningitis, but with considerable varying results [32, 33]. This study summarized the overall diagnostic performance of IL-6 and IL-8 for bacterial meningitis based on current available publications. To our best knowledge, this is the first study to summarize the overall diagnostic accuracy of IL-6 and IL-8 for bacterial meningitis.

Our results suggest that IL-6 plays a valuable role in the diagnosis of bacterial meningitis. Its pooled sensitivity is 0.91 and the pooled specificity is 0.93 indicating a low rate of missed diagnosis (9%), and a low rate of misdiagnosis (7%). The average PLR was 12.38, showing that there is a large likelihood of bacterial meningitis cases that are correlated with CSF IL-6 levels. The average NLR was 0.10, indicating that a negative CSF IL-6 result could almost rule out the possibility of bacterial meningitis. The average DOR was 129.76, suggesting a high diagnostic performance. The SROC curve was used to summarize the overall diagnostic accuracy of IL-6 with an AUC of 0.97, indicating that CSF IL-6 assays seemed to be helpful in the diagnosis of bacterial meningitis. And studies also showed that IL-6 is better than other CSF rou-
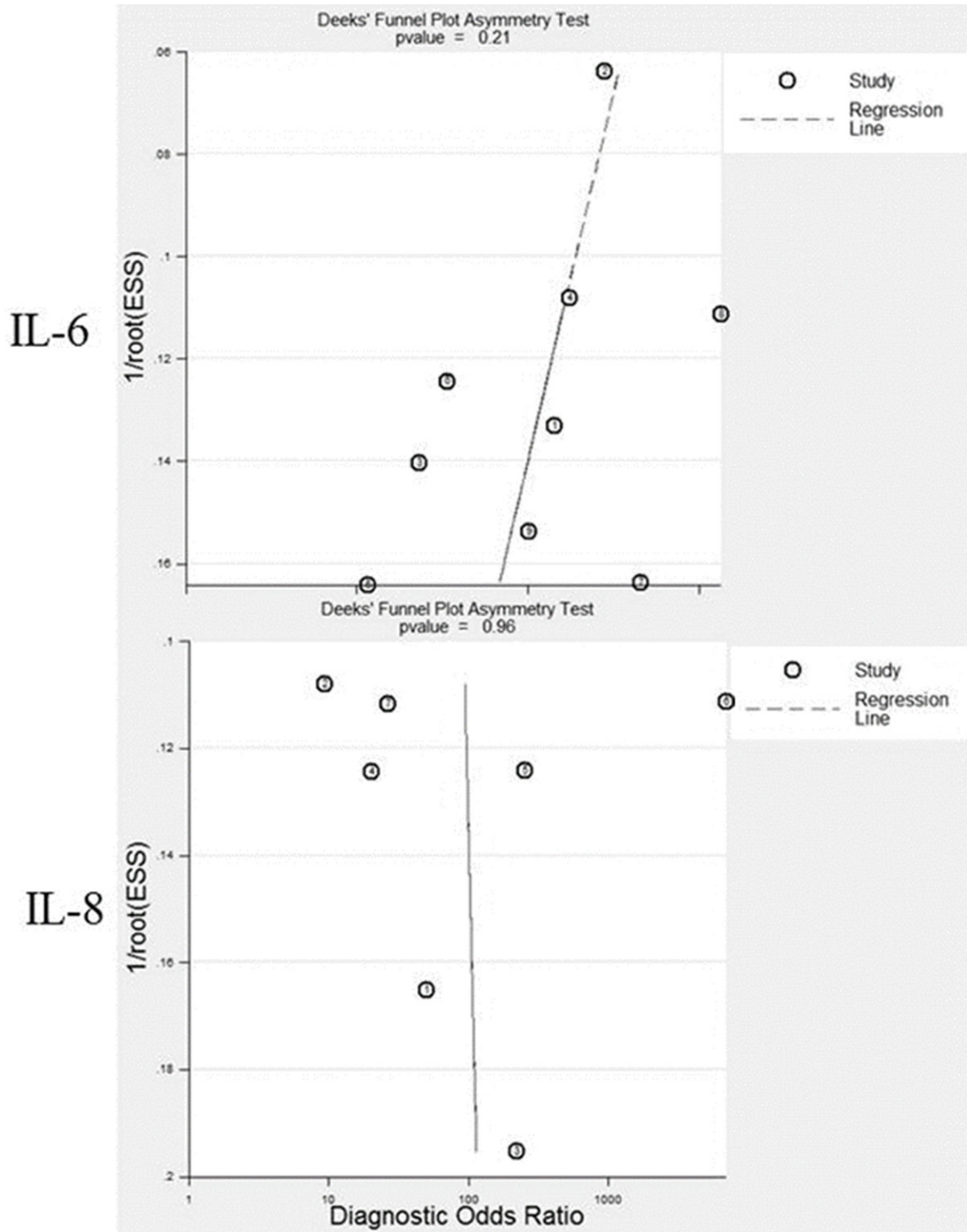
Figure 5. Deek's funnel plot to assess the likelihood of publication bias.

tine test markers, such as monocyte count, neutrophil count, protein level, glucose level [27]. The CSF IL-8 levels also play an important role in diagnosing bacterial meningitis, its sensitivity is higher than IL-6, but its specificity is lower than IL-6, revealing a relative high rate of misdiagnosis (11%). The pooled NLR was 0.06, which is low enough to rule out PH; while the PLR was 8.5, which was still lower than 10, considered the threshold for reliability. The pooled

DOR of IL-8 was 154.25 and the AUC of IL-8 was 0.95, both providing a high discriminatory ability. Our results reveal that both IL-6 and IL-8 play valuable role in the diagnosis of bacterial meningitis.

For clinical utility, we suggest that the results of IL-6 and IL-8 measurement should be interpreted in parallel with the results of traditional tests and clinical information. Chen et al reported that the combination of IL-6, IL-8 and other parameters such as leukocyte, glucose would increase the specificity, providing a better diagnostic accuracy [24]. We recommend that it should set up a diagnostic model that combining a panel of classic markers for bacterial meningitis. In addition, more studies performed in suitable models of meningitis are needed in order to establish the routine use of CSF IL-6 and IL-8 in the diagnosis of infectious diseases of the central nervous system [29]. The determination of CSF IL-6 and IL-8 not only plays a role in diagnosing bacterial meningitis, but also providing prognostic information. Prasad et al reported that in non-survivors of bacterial meningitis, the CSF levels of IL-6 and IL-8 were significantly increased, the authors proposed that higher concentrations of CSF IL-6 and IL-8 are associated with poor outcome in patients with bacterial meningitis [26]. Thus, CSF IL-6 and IL-8 measurement may be useful not only for diagnosing bacterial meningitis, but also for characterizing its clinical prognosis, which will be valuable for improving the comprehensive management of bacterial meningitis patients. Our meta-analysis also points out the need for investigating the effect of cut-off value on the diagnostic accuracy of IL-6 or IL-8 levels. This variation in cut-off value of IL-6 or IL-8 partly reflects differences in some clinical context: method of assay, age, and country of origin and so on. Further work should aim to identify the cut-off value under specific conditions that provides optimal diagnostic accuracy [29].

We should also pay attention to the several limitations in this meta-analysis, first of all, a relatively small final set of studies were included this study because of our strict inclusion criteria, which may not supply enough statistical power to draw definitive conclusions about the ability of CSF IL-6 and IL-8 levels to diagnose bacterial meningitis; the second, we identified significant heterogeneity among the studies, which may be caused by the year of publication,

IL-6 and IL-8 assay methods, age of patients, or the ethnicity difference, however, due to the limited included studies, we didn't to determine the covariates as possible sources of heterogeneity, further studies should pay attention to these covariates and avoid possible bias [34]. What's more, this meta-analysis only included studies published in English, which may cause language bias. Anyway, more studies at a large scale should be performed to discuss the diagnostic performance of IL-6 and IL-8 for bacterial meningitis.

Taken together, our results suggest that both CSF IL-6 and IL-8 play valuable role in the diagnosis of bacterial meningitis. Further studies are needed to validate our findings and investigate the role of IL-6 and IL-8 in the management of bacterial meningitis patients.

Acknowledgements

Disclosure of conflict of interest

None.

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