Systematic Review and Meta-Analysis

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Diagnostic accuracy of interleukin-33 for tuberculous pleural effusion

A systematic review and meta-analysis

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Abstract

Background: The detection of interleukin 33 (IL-33) in pleural effusion may be more sensitive in diagnosing tuberculous pleural effusion (TPE). The present study aimed to assess the accuracy of pleural IL-33 for the diagnosis of TPE by means of meta-analysis and systematic review of relevant studies.

Method: After retrieving the published studies, the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and a summary receiver operating characteristic curve were assessed to estimate the usefulness of pleural IL-33 in diagnosing TPE using meta-analysis with a random-effects model. We also performed meta-regression and subgroup analysis.

Results: A total of 639 patients from 6 studies were analyzed. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.87 (95% confidence interval [CI], 0.82–0.91), 0.76 (95% CI, 0.72–0.80), 6.54 (95% CI, 2.65–16.15), 0.17 (95% CI, 0.10–1.27), and 45.40 (95% CI, 12.83–160.70) respectively. The area under the curve was 0.94. The composition of the included population was the main cause of heterogeneity and subgroup analysis showed that pleural IL-33 had a higher specificity (0.93, 95% CI 0.87–0.96) when used for differential diagnosis between TPE and malignant pleural effusion.

Conclusion: The detection of IL-33 alone in pleural effusion seems to not be an efficient diagnostic marker for TPE but may serve as a novel biomarker to differentiate between TPE and malignant pleural effusion.

Abbreviations: CI = confidence interval, IL-33 = interleukin 33, MPE = malignant pleural effusion, NLR = negative likelihood ratio, OR = odds ratio, PLR = positive likelihood ratio, SROC = summary receiver operating characteristic, TPE = tuberculous pleural effusion.

Keywords: interleukin 33, meta-analysis, tuberculous pleural effusion

1. Introduction

Tuberculosis is a global public health problem. Tuberculosis still accounts for the highest mortality from any infectious disease in the world, disproportionately affecting lower-income populations and killing 1.5 million people in 2018.[1] Tuberculous pleural effusion (TPE) is one of the most common sites of extrapulmonary tuberculosis. TPE usually appears 3 to 6 months after the initial infection with *Mycobacterium tuberculosis* and is a severe delayed hypersensitivity caused by subpleural *M tuberculosis* infection.[2,3] There is a need for accurate diagnosis and prompt treatment of TPE as almost two-thirds of patients with spontaneously resolved TPE develop active tuberculosis at extrapleural sites at a later time.[4] However, due to non-specific clinical manifestation and the nature of laboratory testing, the diagnosis of TPE is still challenging.

According to Light's criteria, pleural effusion is always divided into transudate and exudate forms. Tuberculosis and cancer represent the 2 most frequent causes of exudative pleural fluid with predominantly lymphocytes in pleural fluid and similar results of biochemistry and routine examination. In light of the large gap between therapy and prognosis, diagnosing TPE in time and differentiating TPE from malignant pleural effusion (MPE) is of great importance. However, the diagnosis of TPE and differential diagnosis of TPE from pleural effusion from other etiologies, especially MPE, is always a challenge for clinicians. The gold standard for diagnosing TPE is the detection of *M tuberculosis* from either pleural effusion or pleural biopsy

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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specimens. This method has a 100% diagnostic specificity, but usually takes several weeks, leading to a delay in diagnosis and an increased risk of loss of follow-up. Moreover, pleural biopsy is an invasive procedure and relies strongly on an individual's biopsy skills.[5] Thus, more studies are highlighting less invasive and more convenient diagnostic biomarkers.[6–8]

Interleukins (ILs) are secreted proteins that bind to specific receptors and help mediate communication among leukocytes, which can promote various types of inflammatory responses.[9] Many studies showed that some ILs elevated in TPE have led researchers to explore their potential values for diagnosing TPE and differentiating TPE from other types of pleural effusion.[10,11] Some ILs, such as IL-18 and IL-27, seem to have higher accuracy than adenosine deaminase in diagnosing TPE. Interleukin 33 (IL-33) is an IL-1 family cytokine expressed in lung tissue and acts intracellularly as a nuclear factor and extracellularly as a cytokine. It induces helper T cells, mast cells, eosinophils, and basophils to display pro-T helper type 2 functions and is involved in allergic inflammation and asthma.[12–14] Some investigations demonstrated that IL-33 expression increased in the pleural space of patients with TPE, which was induced by interferon-γ and tumor necrosis factor α.[15,16] The detection of IL-33 in pleural effusion has the potential to have a higher sensitivity for the diagnosis of TPE. However, the sensitivity and specificity of IL-33 varies among relevant studies. Therefore, we evaluated the overall accuracy of IL-33 in pleural effusion for the diagnosis of TPE and the differential diagnosis between TPE and MPE, which has not been explored and summarized using meta-analysis before.

2. Materials and methods

2.1. Study selection

Two investigators searched the EMBASE, PUBMED, Wanfang, Weipu, and CNKI databases for pertinent articles up to March 31, 2020. The search key words were "interleukin-33/IL-33," "tuberculosis pleural effusion/fluid." The inclusion criteria of publications were as follows: TPE was diagnosed on the basis of the presence of positive staining or culture for *M tuberculosis* in pleural fluid, sputum, or pleural biopsy specimen or typical caseation granulomas on pleural biopsy; publications provided complete data for 2×2 tables. The exclusion criteria of publications were as follows: articles in the form of reviews, chapters, patents, guidelines, case reports, editorials, or letters; non-human studies; studies had no data for 2×2 tables. When the same sample group of people were analyzed in several publications, the results were accounted for only once. All of the related articles were scrutinized by 2 reviewers to judge their eligibility. A third investigator made the final decision on disagreements and examined whether any additional studies had been neglected. The whole process is shown in Fig. 1.

2.2. Data extraction and quality assessment

Data extracted from the publications included authors, publication year, test method, number of patients, cutoff values, data for 2×2 tables, sensitivity, specificity, and quality scores. When such data were not provided definitely, we used the specific mathematical formulas to calculate them from the related data on sensitivity, specificity, and positive and negative predictive values (PLR and NLR, respectively) or contacted the authors directly. We used 2 tools to assess the quality of publications: the QUADAS (quality assessment for studies of diagnostic accuracy, maximum score 14) tool[17] (i.e., empirical evidence, expert opinion, and formal consensus to assess the quality of primary studies of diagnostic accuracy) and the STARD (standards for reporting the accuracy of a diagnostic test, maximum score 25) initiative[18] (i.e., guidelines that aim to improve the quality of reporting in diagnostic studies). This study was approved by the ethics committee at Beijing Chao-Yang Hospital.

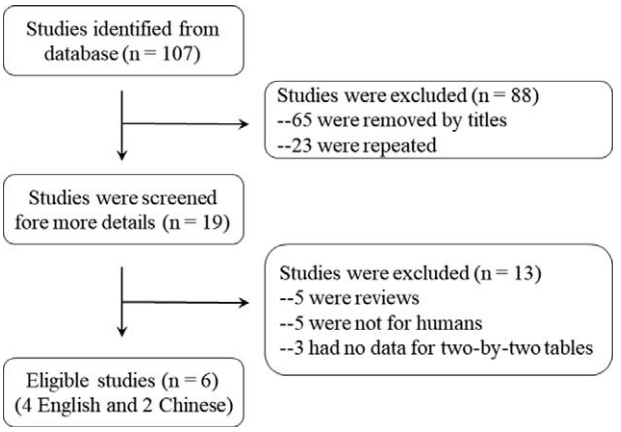

Figure 1. Flowchart demonstrating the algorithm for identifying suitable papers for inclusion.

2.3. Data analysis

We performed the present meta-analysis for the diagnostic accuracy of IL-33 in pleural effusion for TPE by estimating the overall sensitivity, specificity, PLR, NLR, and diagnostic odds ratio (OR) and assessed the summary receiver operating characteristic (SROC) curve. We classified patients into 2 groups (TPE and non-TPE) and conducted 2×2 table analysis. Inconsistency (I^2) was computed to indicate significant heterogeneity between studies. If $I^2 > 25\%$, this indicated significant heterogeneity. When significant heterogeneity was present, the pooled results (with corresponding 95% confidence intervals [CI]) were derived using the DerSimonian–Laird method (random-effects model).[19] The SROC curve (Fig. 2) represents the relationship between sensitivity and specificity across studies. The area under the curve[20] was calculated in order to judge the overall diagnostic performance. Moreover, meta-regression was used to explore the potential causes of heterogeneity in terms of

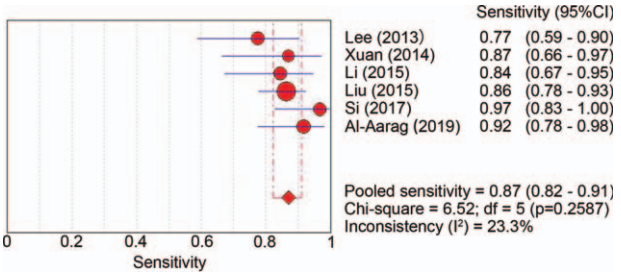

Figure 2. Summary receiver operating characteristic curve for IL-33 for the diagnosis of TPE. IL-33 = interleukin 33, TPE = tuberculous pleural effusion.

Table 1

Baseline characteristics of studies included in the meta-analysis.

Study							Number of patients		Test results				Quality scores	
First author, Year	Country	Language	Method	Cutoff, ng/L	Age of TPE patients (median)	Non-TPE contains only MPE or not	TPE	Non-TPE	TP	FP	FN	TN	QUADAS	STARD
Lee KS, 2013	Korean	English	ELISA	10	55	No	60	160	24	66	7	123	11	17
Xuan WX, 2014	China	English	ELISA	19.86	45	Yes	23	21	20	2	3	19	10	15
Li D, 2015	China	English	ELISA	68.3	56	No	32	55	27	16	5	39	11	17
Liu J-Q, 2015	China	Chinese	Luminex	19.31	39	Yes	95	52	82	5	13	47	10	14
Si Q, 2017	China	Chinese	ELISA	17.08	NA	Yes	30	42	29	3	1	39	10	14
Al-Aarag AH, 2019	Egypt	English	ELISA	19.16	44	Yes	36	33	33	1	3	32	10	15

FN = false-negative result, FP = false-positive result, MPE = malignant pleural effusion, QUADAS = the quality assessment for studies of diagnostic accuracy (maximum score 14), STARD = standards for reporting the accuracy of a diagnostic test (maximum score 25), TN = true-negative result, TP = true-positive result, TPE = tuberculous pleural effusion.

country, race, method, and inclusion group. Publication bias is a concern for meta-analysis of diagnostic studies. We examined the potential presence of publication bias using Deeks test. A P value $<.05$ was considered to indicate statistical significance. All analyses were performed using Meta-Disc version 1.4 (Meta-Disc, Unit of Clinical Biostatistics, Ramony, Cajal Hospital, Madrid, Spain) and Stata version 15.0 (StataCorp, College Station, TX).

3. Results

3.1. Eligible studies and quality assessment

Following an independent review, we eventually pooled 6 publications for analysis,[21–26] including 276 patients with TPE and 363 patients with non-TPE. The characteristics and quality scores of these studies are outlined in Table 1. In all selected studies, TPE patients were diagnosed based on bacteriological or histological results or clinical course. As shown in Table 1, the quality of research accuracy and reporting diagnostic accuracy of most studies were relatively good, as all studies had high QUADAS scores (≥10) and STARD scores (≥14).

3.2. Sensitivity, specificity, PLR, NLR, diagnostic OR, and SROC curve

Six studies were included in the current study. As shown in the forest plots (Figs. 3–7), the pooled sensitivity was 0.87 (95% CI, 0.82–0.91), whereas the pooled specificity was 0.76 (95% CI, 0.72–0.80). The pooled PLR and NLR were 6.54 (95% CI, 2.65–16.15) and 0.17 (95% CI, 0.10–1.27) respectively. The diagnostic OR was 45.40 (95% CI, 12.83–160.70). As shown in Fig. 2, the area under the curve was 0.94.

3.3. Post-test probability

When the pre-test prevalence of TPE was set to 10% (an assumptive low-risk value) and the IL-33 result was positive, the estimated post-test probability was 43% (Fig. 8), whereas a negative test result nearly excluded TPE (post-test probability, 2%). For a patient with 50% pre-test risk, a positive IL-33 result could increase the probability to 87% (Fig. 9); on the contrary, the post-test probability was 13% with negative IL-33 results.

3.4. Test of heterogeneity

The shape of the SROC curve suggested that variability in diagnostic thresholds across studies could not explain the heterogeneity. Cochran Q value was 23.83 ($P<.05$), indicating significant heterogeneity caused by other factors. Meta-regression (Table 2) was used to explore the source of heterogeneity in terms of region (Asian or non-Asian), method (enzyme-linked immunosorbent assay or Luminex), language (English or Chinese), and inclusion group (non-TPE contains only MPE or not). The results showed that the composition of the included population was the main cause of heterogeneity ($P=.0117$). The subgroup analysis (Table 3) showed that the heterogeneities were eliminated in pooled estimates and the pooled specificity was 0.93 and diagnostic OR was 102.34, which were much higher than the former ones.

3.5. Publication bias

Deeks test for publication bias showed $P=.47$ for IL-33, indicating that there was no significant publication bias (Table 4; Fig. 10).

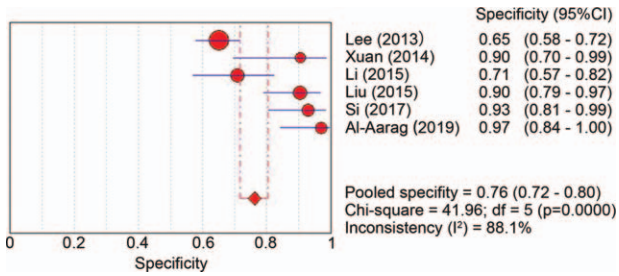

Figure 3. Forest plot of the meta-analysis of sensitivity for the diagnosis of TPE using IL-33. IL-33 = interleukin 33, TPE = tuberculous pleural effusion.

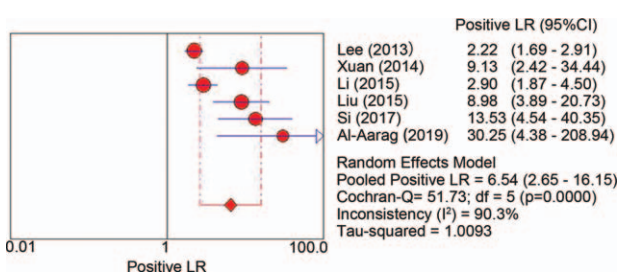

Figure 4. Forest plot of the meta-analysis of specificity for the diagnosis of TPE using IL-33. IL-33 = interleukin 33, TPE = tuberculous pleural effusion.

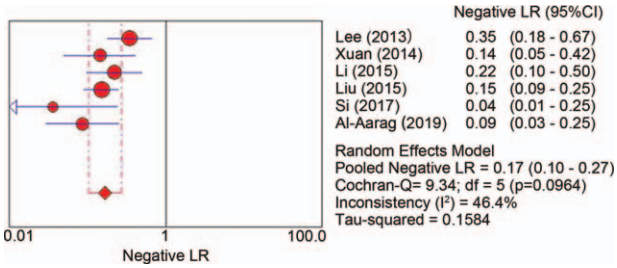

Figure 5. Forest plot of the meta-analysis of PLR for the diagnosis of TPE using IL-33. IL-33 = interleukin 33, PLR = positive likelihood ratio, TPE = tuberculous pleural effusion.

4. Discussion

The diagnosis of TPE is still a clinical challenge, since TPE and non-TPE have similar clinical or laboratory manifestations and sometimes lack pathological or etiological evidence. Researchers have struggled to identify new convenient and effective diagnostic markers to solve this problem. It has been suggested that IL-33 has a role in the pathogenesis of pleural inflammation and formation of pleural effusion.

There are many studies demonstrating that IL-33 is involved in the pathogenesis of the inflammatory response, and the conflicting hypotheses raise questions about the IL-33 response in pleural disease.[27–30] These studies are highlighted by the fact that TPE has a more polarized T helper type 1 reaction and IL-33 is more specifically associated with the pathophysiology of TPE than with other types of pleural effusion. The studies of Xuan et al[22] and Lee et al[21] found that the pleural IL-33 level was much higher than the serum IL-33 level in patients with TPE, and pleural and serum IL-33 levels were higher in patients with TPE compared with those with other types of pleural effusion.

Previous meta-analysis results suggest that assessing pleural levels of certain ILs (including IL-33) may assist in diagnosing TPE, although no single IL is likely to show adequate sensitivity or specificity on its own.[7] The current study focused on IL-33 and analyzed its diagnostic value for TPE in a more detailed way. The result showed that IL-33 in pleural effusion was not an effective biomarker for the diagnosis of TPE (sensitivity 0.87 and specificity 0.76), although significant heterogeneity existed between the studies. In meta-analysis, it is an important goal to explore the cause of heterogeneity, rather than calculate summary measures. The meta-regression results showed that the composition of the inclusion group was related with the pooled results. In the subgroup analysis, in terms of the inclusion group

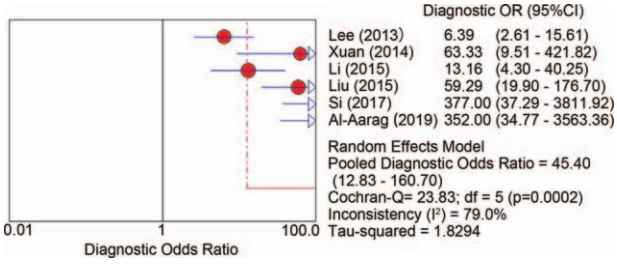

Figure 6. Forest plot of the meta-analysis of NLR for the diagnosis of TPE using IL-33. IL-33 = interleukin 33, NLR = negative likelihood ratio, TPE = tuberculous pleural effusion.

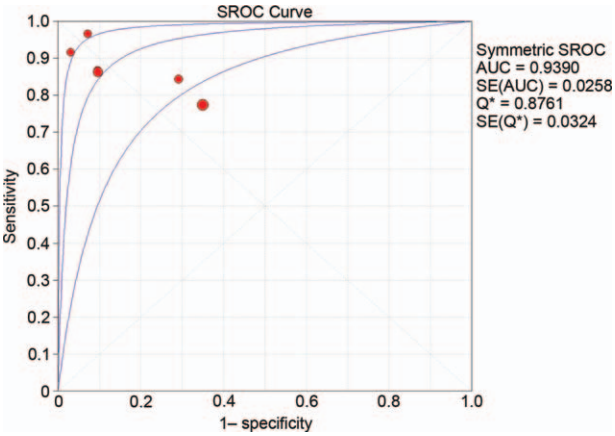

Figure 7. Forest plot of the meta-analysis of diagnostic OR for the diagnosis of TPE using IL-33. IL-33 = interleukin 33, OR = odds ratio, TPE = tuberculous pleural effusion.

(non-TPE group contained only MPE or not), the pooled specificity was significantly increased to 0.93, meaning that IL-33 could be a good marker for differentiating TPE from MPE.

On the one hand, the interpretation of this conclusion is limited by the fact that only 4 articles focused on the accuracy of IL-33 in the differential diagnosis between TPE and MPE. Given that the differential diagnosis of TPE from MPE is always a diagnostic

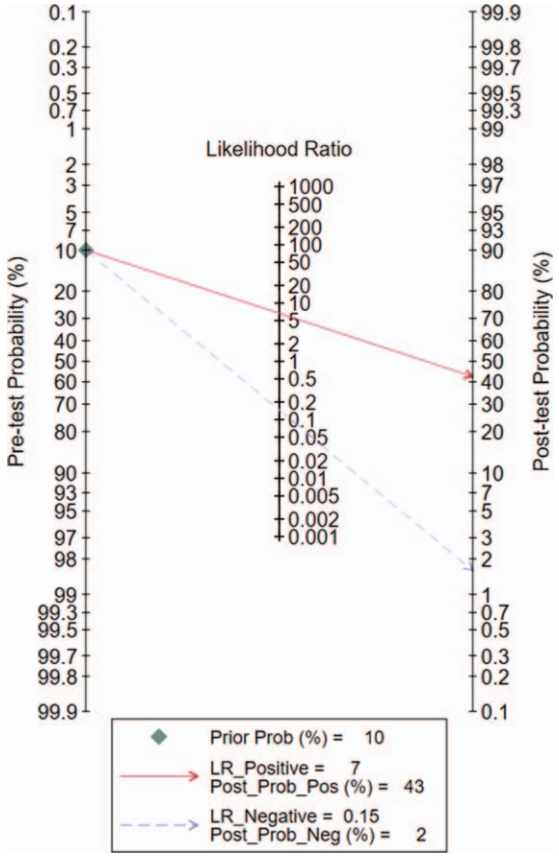

Figure 8. Fagan's nomogram for post-test probability of tuberculous pleural effusion at 10% pre-test probability.

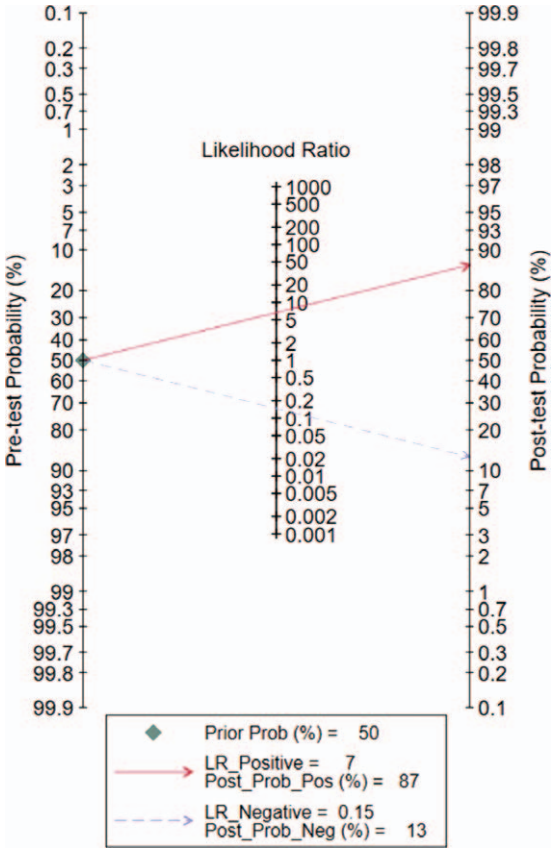

Figure 9. Fagan's nomogram for post-test probability of tuberculous pleural effusion at 50% pre-test probability.

Table 2

Meta-regression for the potential source of heterogeneity.

Study characteristic	RDOR	*P* value	95% CI
Region (Asian or non-Asian)	0.09	.2804	(0.00;18.06)
Method (ELISA or Luminex)	0.77	.8994	(0.00;150.49)
Language (English or Chinese)	1.74	.7363	(0.02;124.81)
Inclusion group (non-TPE contains only MPE or not)	11.17	.0117	(2.43;51.30)

CI = confidence interval, MPE = malignant pleural effusion, RDOR = relative diagnostic odds ratio, TPE = tuberculous pleural effusion.

challenge, it is of great interest to investigate the possible use of IL-33 as a novel pleural marker to make a definite diagnosis between TPE and MPE. On the other hand, it makes sense to investigate the level of IL-33 in pleural effusion in cases other than

Table 3

Subgroup analysis.

Pooled results	Pooled value	95% CI	*P* value	I^2 value (%)
Sensitivity	0.89	(0.84, 0.93)	.3297	12.6%
Specificity	0.93	(0.87, 0.96)	.6505	0.0%
Positive LR	11.17	(6.33 19.72)	.6770	0.0%
Negative LR	0.13	(0.08, 0.20)	.3560	7.4%
Diagnostic OR	102.32	(10.39, 259.18)	.3210	14.2%

CI = confidence interval, I^2 = inconsistency, LR = likelihood ratio, OR = odds ratio.

Table 4

Deeks test for publication bias.

yb	Coefficient	SE	*t*	*P* > |*t*|	95% confidence interval
Bias	17.3584	37.8306	0.46	.666	(–79.88825, 114.605)
Intercept	1.724574	4.189152	0.41	.698	(–9.043983, 12.49313)

yb, a general designation of a mathematical statistical model coefficient.

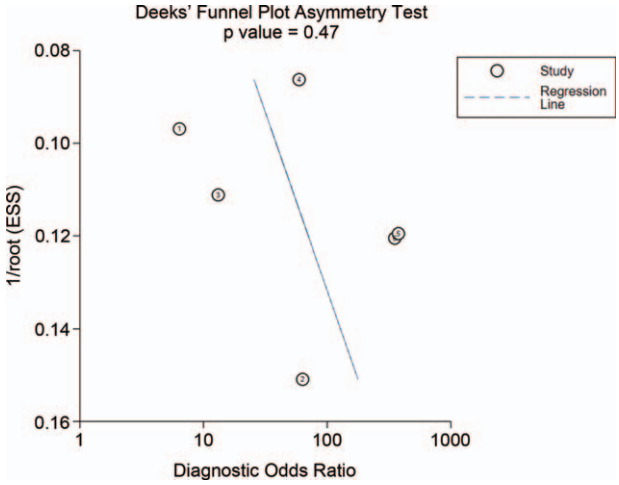

Figure 10. Deeks graph for the assessment of potential publication bias in IL-33. IL-33 = interleukin 33.

TPE or MPE and to investigate what causes such a difference in the accuracy of IL-33.

There are still some limitations in our study. This meta-analysis included relatively few eligible studies. It seems inevitable that some missing and unpublished data may still exist. In addition, the inclusion of non-TPE patients differed among the included studies, which was the main source of heterogeneity. Moreover, the combination of IL-33 and adenosine deaminase may serve as efficient diagnostic strategies in the management of pleural infection by *M tuberculosis*.[23] Unfortunately, there were few studies of the applications of IL-33 along with other biomarkers, and further studies focused on this issue are needed.

5. Conclusion

In conclusion, our study suggests that the detection of IL-33 in pleural effusion alone seems to not be an efficient diagnostic marker for TPE but could serve as a novel biomarker to differentiate between TPE and MPE and may help avoid more invasive diagnostic procedures.

Author contributions

Conceptualization: Xin-Yu Shi.
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Formal analysis: Xue-Bin Pei, Shu-Feng Dong.
Funding acquisition: Feng-Shuang Yi.
Investigation: Shu-Feng Dong.
Methodology: Feng-Shuang Yi, Xin Qiao.
Software: Xin Qiao, Shu-Feng Dong.
Supervision: Xin-Yu Shi.
Validation: Xin-Yu Shi, Xin Qiao.

Writing – original draft: Xin-Yu Shi, Xue-Bin Pei.

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