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Diagnostic accuracy of tumor necrosis factor-alpha assay for tuberculous pleurisy

A PRISMA-compliant meta-analysis

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Abstract

Background: The diagnosis of tuberculous pleurisy is difficult and traditional methods are not always helpful. Many studies have focused on the tumor necrosis factor-alpha (TNF-α) assay in pleural effusion for the diagnosis of tuberculous pleurisy, but the results remain controversial. This meta-analysis was conducted to determine the overall diagnostic accuracy of TNF-α.

Methods: Relevant studies were searched from PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), Wangfang, and Weipu. We pooled the published results and computed the accuracy measures, including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Receiver operating characteristic curves (SROC) and the area under the curve (AUC) were used to summarize the overall test performance.

Results: Twelve studies with 1022 patients met the inclusion criteria. The pooled sensitivity and specificity were 0.85 (95%CI, 0.81–0.89) and 0.80 (95% CI, 0.77–0.83) respectively. The area under the SROC curve was 0.89.

Conclusions: The results of meta-analysis suggested that the TNF-α assay plays a vital role in the diagnosis of tuberculous pleurisy, whereas other test results or clinical findings should be interpreted together with the TNF-α assay to improve the overall diagnostic accuracy.

Abbreviations: CNKI = Chinese National Knowledge Infrastructure, DOR = diagnostic odds ratio, ELISA = enzyme linked immunosorbent assay, NLR = negative likelihood, PLR = positive likelihood ratio, SROC = summary receiver operating characteristic curve, TB = tuberculosis, TNF-α = tumor necrosis factor-alpha, TPE = tuberculous pleural effusion.

Keywords: diagnostic accuracy, meta-analysis, pleural effusions, tuberculous pleurisy, tumor necrosis factor-alpha

1. Introduction

Pleural effusion is widely found in patients with a variety of diseases. Pleural tuberculosis (TB) is one of the most important and common causes of pleural effusion, especially in the regions with high prevalence. Nevertheless, the establishment of tuberculous pleural effusion (TPE) diagnosis is difficult and challenging. Traditionally, it is based on the isolation of *Mycobacterium tuberculosis* from the pleural fluid or pleural biopsy specimens or the demonstration of caseating granulomas on histological examination by obtaining biopsy. These methods are far from perfection; they are either insufficient or too invasive. Only 10% to 35% of cultures and 20% to 81% of molecular tests reveal *mycobacteria* in pleural fluid.[1] Pleural biopsy and culture of biopsy material provide a relative high sensitivity, but these procedures are invasive and may not be well accepted by all the patients.[2] Therefore, some new effective and efficient methods should be identified to aid the diagnosis of tuberculous pleurisy.

TNF-α is an important pro-inflammatory cytokine which is synthesized by lymphocytes and macrophages.[3] Previous study showed the diagnostic value of TNF-α assays in many diseases. Kleine et al[4] evaluated the diagnostic value of TNF-α assay in cerebrospinal fluid for bacterial meningitis, which reached a sensitivity of 85% and a specificity of 91.3%. Surbatovic and Padkovic study showed the correlation between TNF-α and severe acute pancreatitis (SAP). In patients with SAP, the lower level of TNF-α indicated higher probability to develop multiple organ dysfunction syndrome (MODS), with a sensitivity and specificity of 83% and 77.4% respectively.[5] Tebruegge et al[6] investigated the diagnostic value of peripheral blood TNF-α assay to differentiate between TB-uninfected and TB-infected children (up to 18 year), the results showed that the assay achieved an excellent diagnostic value, with a sensitivity of 95.5% and a specificity of 88.0%. Related studies proved that *mycobacterial* proteins can cause the secretion of TNF-α and it can reach high localized concentrations in pleural effusion to eliminate the bacilli and granuloma formation.[7] Therefore,

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various studies focused on whether TNF-α can be used as a diagnostic tool for tuberculous pleurisy. Some studies detected a high level of TNF-α in the tuberculous pleural effusion and many of them consider TNF-α assay can be used for the differential diagnosis of tuberculous pleural effusion. Several other studies, however, showed that there is no difference of TNF-α level between TB pleural effusion and Non-TB pleural effusion.[8–10] Due to the controversial results of the previous studies, this meta-analysis established the overall accuracy of pleural TNF-α test in the diagnosis of tuberculous pleurisy.

2. Methods

2.1. Search strategy and study selection

Multiple data base including Medline (using PubMed as the search engine), Embase, Web of Science, CNKI, Wangfang and Weipu (up to December 30, 2015) were searched using the following search strings: "tumor necrosis factor," "tuberculosis," "pleurisy/pleuritis," "pleural effusion/pleural fluid," "tuberculosis," "sensitivity and specificity," and "accuracy" to identify relevant literatures. References listed in the selected articles were also examined. The languages were limited to English or Chinese. Conference abstracts and letters to the journal editors were excluded because of limited information and data. A study providing both sensitivity and specificity of TNF-α was incorporated into the meta-analysis. Each included study was reviewed independently by 2 authors (ML and WZ). Disagreement was resolved by consensus. Ethical approval is not required because meta-analysis is based on the published articles.

2.2. Data extraction and quality assessment

The included literatures were evaluated independently by 2 reviewers (ML and WZ). The reviewers were blinded to publication to retrieve the data, including: the author, publication year, the country, patient number, test method, cut-off value, sensitivity, specificity, and methodological quality. To assess the trial methodology, we used the QUADAS-2(quality assessment for studies of diagnostic accuracy) tool to evaluate the quality of diagnostic accuracy of the primary studies we used.[11]

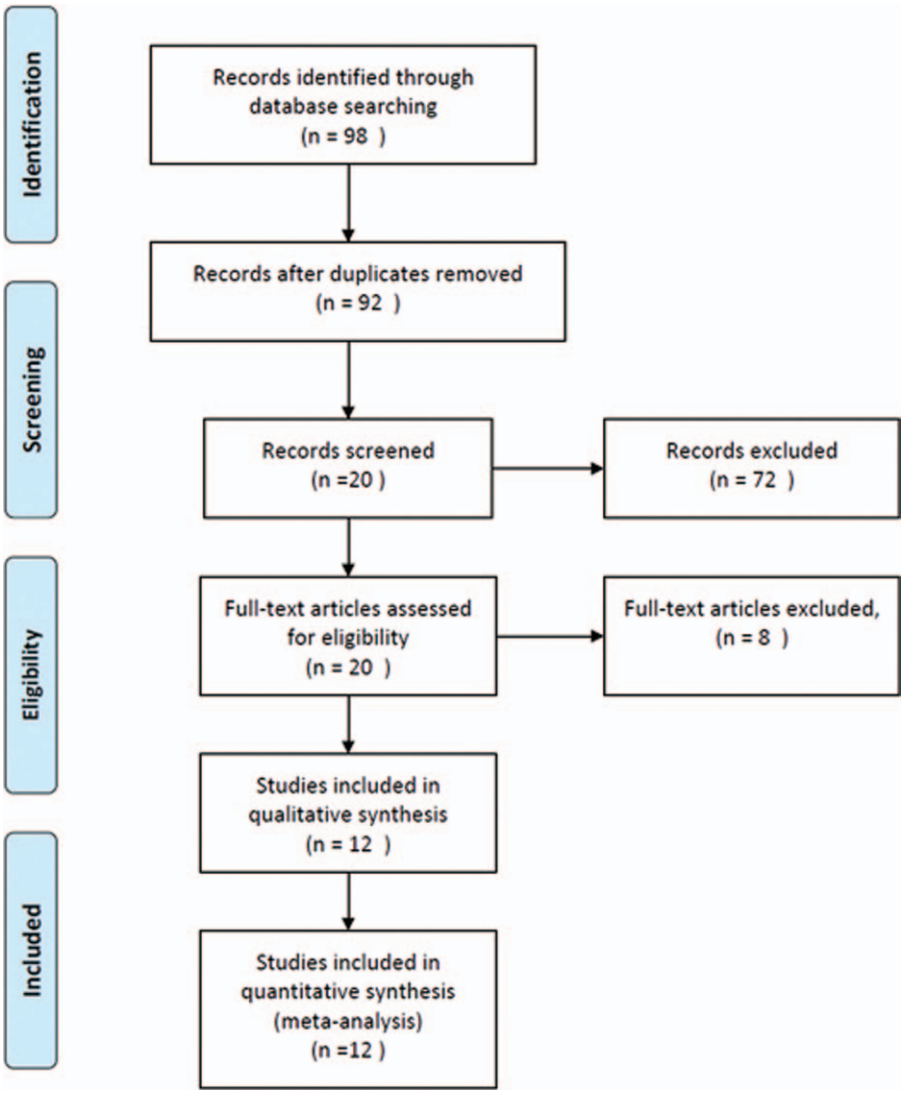

Figure 1. Flow chart of literature research.

Table 1

Summary of included studies.

Study/year	Country	Patients no	Assay method	Cutoff	Test results				Reference standard
					TP	FP	FN	TN	
Orphanidou/1996	Greece	97	RIA	40.4 pg/mL	23	10	4	60	His/Bac
Ogawa/1997	Japan	50	ELISA	60 pg/mL	16	6	2	26	His/Bac
Wang/2000	China	127	ELISA	70 pg/mL	57	7	8	55	His/Bac or Clin
Jin/2002	China	64	ELISA	75 pg/mL	29	5	5	25	His/Bac or Clin
Momi/2002	Japan	127	ELISA	55 pg/mL	29	21	12	65	His/Bac
Tahhan/2003	Turkey	62	ELISA	8 pg/mL	21	9	3	29	His/Bac
Wong/2003	Hongkong	66	ELISA	4 pg/mL	29	7	3	27	His/Bac or Clin
Huang/2005	China	63	ELISA	35 mg/L	26	10	3	24	His/Bac or Clin
Xu/2007	China	82	ELISA	9 pg/mL	38	14	6	24	His/Bac or Clin
Kiropoulos/2007	Greece	124	ELISA	88.1 pg/mL	24	7	1	92	His/Bac
Ciledag/2010	Turkey	70	ELISA	13.3 pg/mLl	10	19	4	37	His/Bac
Li/2014	China	90	ELISA	103.65 ng/L	38	9	8	35	His/Bac

Bac = bacteriology, Clin = clinical course, ELISA = enzyme-linked immunosorbent assay, FN = false negative, FP = false positive, His = histology, QUADAS = quality assessment for studies of diagnostic accuracy, RIA = radioimmunoassay, STARD = standards for reporting diagnostic accuracy, TN = true negative, TP = true positive.

2.3. Statistical analysis

We used standard methods recommended for the diagnostic accuracy of meta-analyses and followed the Preferred Reporting Items for Systemic Reviews and Meta-analysis (PRISMA) criteria.[12,13] We computed the following indices of test accuracy: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR).

The sensitivity and specificity of each single test were used to plot a summary ROC (SROC).[14,15] Spearman's rank correlation was performed as a test for the threshold effect. Heterogeneity among the primary studies was detected with Chi-squared and Fisher's exact tests. The average sensitivity, specificity, and other related measurements of the studies were calculated by random-effects model or fixed-effects model.[16,17] If there were enough studies, subgroup analyses were performed to explore potential between-study heterogeneity. Meta-regression analysis was conducted to explore the possible reasons for the heterogeneity. We also assessed the potential publication bias by using Deeks's funnel plots.[18]

The analysis was performed by 2 kinds of statistical software: Stata, version 11 (Stata Corporation; College Station, TX) and Meta-Disc for Windows (XI Cochrane Colloquium; Barcelona, Spain). All statistical tests were 2-sided, with P values of 0.05 denoting statistical significance.

3. Results

3.1. Studies included in the meta-analysis

After literature review, 20 studies were selected. Among them, 7 were excluded because sensitivity and specificity of TNF-α test could not be estimated with the data provided by the

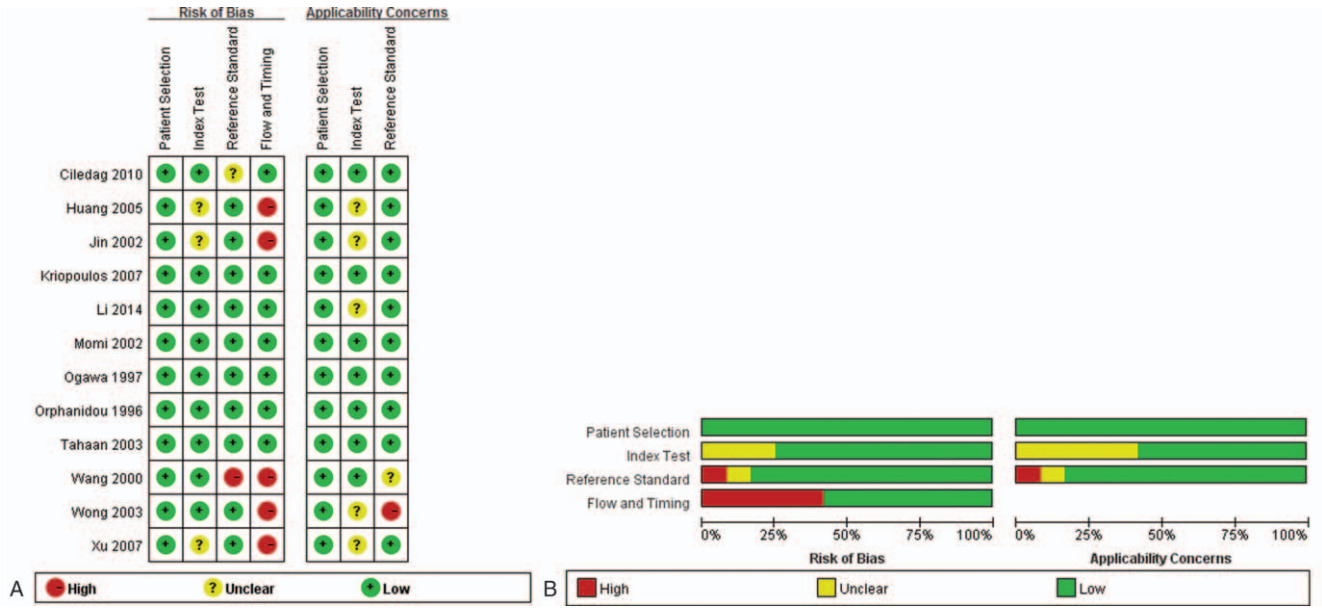

Figure 2. Methodological quality assessment of studies of the TNF-αassay. (A) Graph of risk of bias and applicability concerns. (B) Summary of risk bias and applicability concerns. TNF-α = tumor necrosis factor-alpha.

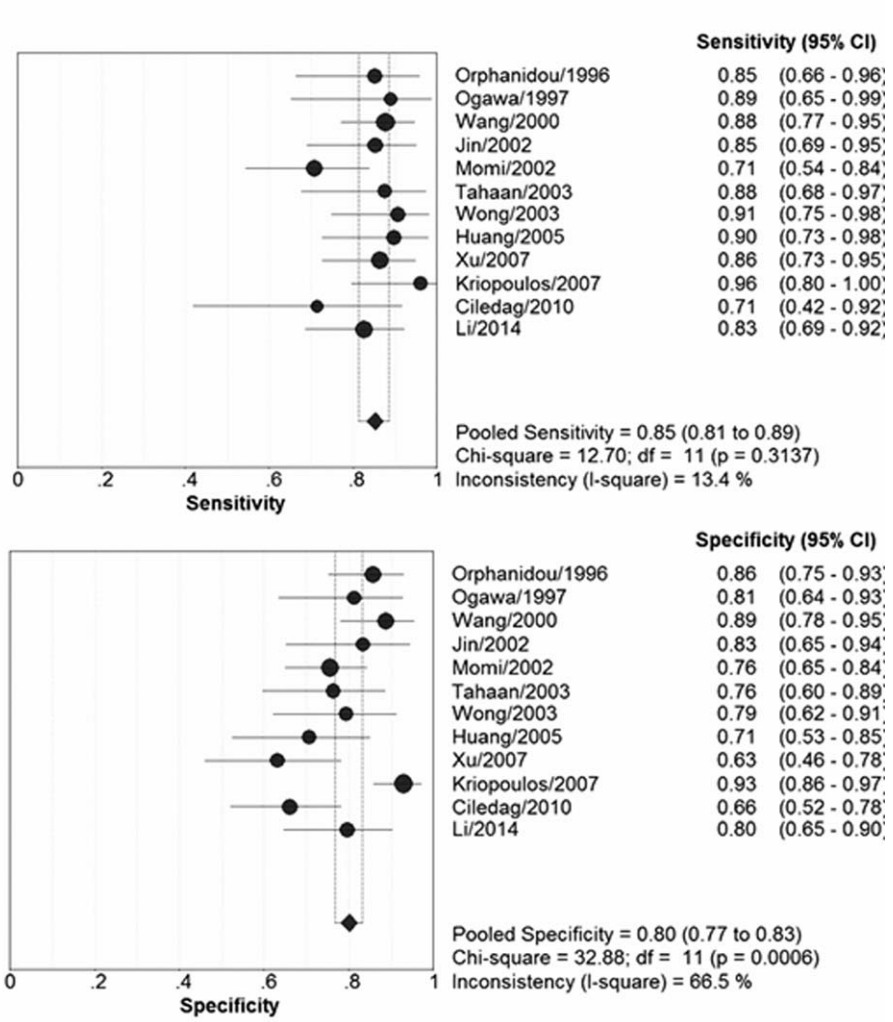

Figure 3. Forest plots of sensitivity and specificity for TNF-α assay for the diagnosis of TPE. The point estimates of sensitivity and specificity from each study are shown as solid circles. Error bars indicate 95% CI. CI = confidence interval, TNF-α = tumor necrosis factor-alpha, TPE = tuberculous pleural effusion.

articles.[9,10,19–23] One study was excluded because the same authors published the research on the same patient; thus, only the best quality study was chosen.[24–30] Consequently, the remaining 12 studies were eligible for the meta-analysis,[24–28,31–37] with a total number of 1022 patients. The flowchart of study selection is shown in Fig. 1.

3.2. Quality of the literatures and study characteristics

In our meta-analysis, the average sample size of the included studies was 85 (range 50–127). Diagnosis of TPE in 7 studies was made based upon histological or bacteriological confirmation, which are considered "gold standard."[28,31–34,36,37] Whereas in the other remaining 5 studies, TPE patients were diagnosed based upon "gold standard" or on their clinical course which included clinical presentation, pleural fluid analysis, radiology, and the responsiveness to anti-tuberculous therapy.[24–27,35] All the included studies mentioned the TNF-α assay method. One study used the RIA assay as the test method,[23] whereas the remaining 11 studies used ELISA assay. Among the 12 included studies, 2 studies reported blinded interpretation of TNF-α assay independent of the reference standard.[35,36] All the studies except 4[24–27] were designed as prospective studies. The clinical characteristics and other information are outlined in Table 1. By the QUADAS-2 tool, it was found that the quality of studies for our research was generally good. The results are presented in Fig. 2A and B.

3.3. Diagnostic accuracy

The forest plots of sensitivity and specificity of TNF-α test for the diagnosis of TP are shown in Fig. 3. The sensitivity varied between 0.71 and 0.96 (pooled 0.85, 95% CI, 0.81–0.89), whereas specificity ranged from 0.63 to 0.93 (pooled 0.80, 95% CI, 0.77–0.83). The PLR was 4.12 (95% CI, 3.07–5.53), the NLR was 0.20 (95% CI, 0.15–0.27), and the DOR was 21.93 (95% CI, 12.85–37.43). The I^2 values of sensitivity, specificity, PLR, NLR, and DOR were 13.4%, 66.5%, 67.1%, 33.4%, and 52.7% respectively. So the overall sensitivity and NLR were pooled by the mixed-effects model ($I^2 < 50\%$), and the others were pooled by the random-effects model to perform the analysis because the heterogeneity across studies showed significant difference ($P < 0.05$, $I^2 > 50\%$).

We also performed subgroup analysis. In the 5 studies performed in area with high TB incidence,[24–28] the pooled

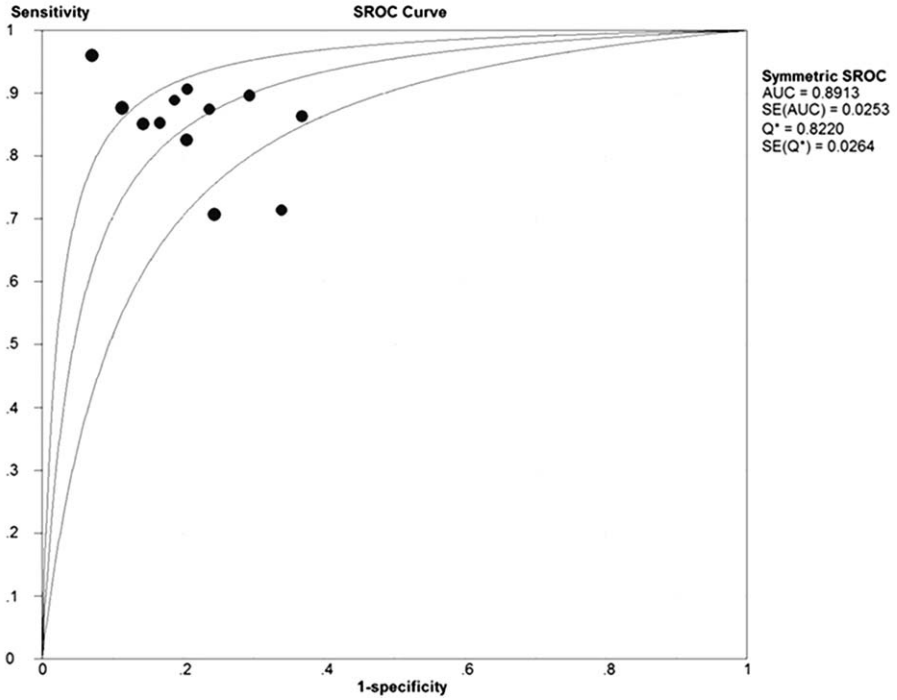

Figure 4. Summary receiver operating characteristic curve (SROC) of TNF-α assay for the diagnosis of TPE. The size of each solid circle represents the sample size of each study. The regression SROC curve indicates the overall diagnostic accuracy. SROC = Summary receiver operating characteristic curve, TPE = tuberculous pleural effusion.

sensitivity was 0.86 (95% 0.80–0.90) and specificity was 0.78 (95% 0.72–0.84). The remaining 7 studies conducted in area with low TB incidence, the pooled sensitivity and specificity was 0.84 (95% 0.78–0.89) and 0.81 (95% 0.77–0.85) respectively. Subgroup analysis difference was not statistically significant compared with pooled results from all included studies ($P = 0.978$).

To summarize the global diagnostic performance of the test, the summary receiver operating characteristic (SROC) curve was generated and the Q-value, the point represents the maximum polymerization spot of sensitivity and specificity in the SROC curve, was also calculated.[38] As is shown in Fig. 4, in our study, the area under the curve (AUC) was 0.89 and the Q-value was 0.82, suggesting a relatively high diagnostic accuracy.

3.4. Meta-regression analysis

To explore the possible reasons for the heterogeneity, a meta-regression analysis based on sample size (≥100 or <100), setting (area with high TB incidence or area with low TB incidence) and diagnosis standard (by gold standard or clinical course) was performed. In our study, none of the above covariates included in the meta-regression was found to be the significant source of heterogeneity ($P < 0.05$) (Table 2).

3.5. Publication bias

The Deeks' test was performed to test the publication bias and it was insignificant ($P = 0.71$). The funnel plot for publication bias (Fig. 5) is also basically symmetry. The results suggested a very low likelihood of publication bias.

4. Discussion

With the high prevalence of tuberculosis and the complexities in diagnosing pleural tuberculosis, it is crucial to develop new methods that are rapid, efficient, and noninvasive. Detection of

Table 2

Meta-regression of potential heterogeneity within the included studies.

Covariates	Number of studies	Co-effecient	RDOR (95 CI)	*P*
Sample size				
≥ 100	3	0.867	2.38 (0.20–28.1)	0.4339
< 100	9			
Setting				
Area with high TB incidence	5	−0.026	0.97 (0.12–8.20)	0.9777
Area with low TB incidence	7			
Diagnosis standard				
Gold standard	7	−0.484	0.62 (0.08–4.72)	0.5985
Gold standard or clinical course	5			

CI = confidence interval, RDOR = relative diagnostic odds ratio.

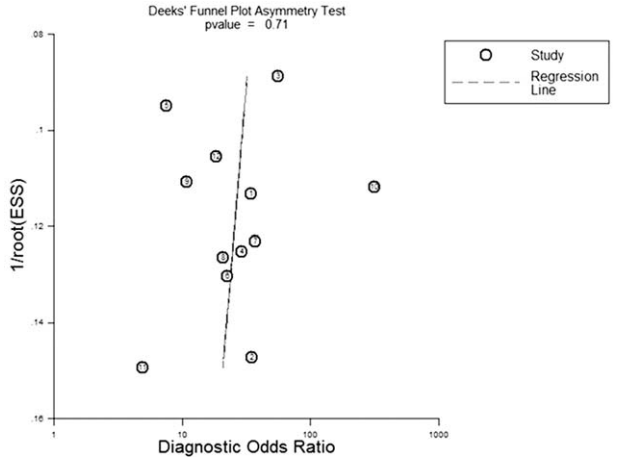

Figure 5. Deeks's funnel graph of publication bias of included studies. The statistically insignificant value ($P=0.70$) for the slope coefficient suggested symmetry in the data and a low likelihood of publication bias.

TNF-α level in pleural fluid has been widely studied throughout the world. Some researchers proposed that the TNF-α assay was a useful noninvasive tool to aid the diagnosis of pleural tuberculosis, whereas others hold the opposite opinion.

The present meta-analysis investigated the overall accuracy of pleural TNF-α test in the TPE with a sensitivity of 0.85 (95%CI, 0.81–0.89) and a specificity of 0.80 (95% CI, 0.77–0.83) and, which means nearly 15% of non-TPE patients would be missed and almost 20% of patients without tuberculosis would be inaccurately treated. So the positive results may not confirm TPE entirely and negative tests do not indicate the absence of TPE. To present a global summary of the test performance, the SROC curve was applied. The present meta-analysis based on the SROC curve has shown the maximum joint sensitivity and specificity (Q value) was 0.82, and the AUC was 0.89, indicating that the level of the overall accuracy was relatively high.

DOR, the ratio of the odds of positive test results in the diseased relative to the odds of positive test results in the nondiseased, is another indicator of test accuracy. DOR combines the data from sensitivity and specificity into a single number, reflecting the correlation between the diagnostic method results and the likelihood of the disease. A higher DOR value indicates a better discriminatory ability of the diagnostic method.

The mean DOR value was 21.93 (95% CI, 12.93–37.43) in the present study, indicating that the TNF-α test plays a role for the diagnosis of TPE. Meanwhile, both PLR and NLR are also presented as measures of diagnostic accuracy in our study because likelihood ratios are considered to be more clinically expressive.[28] A greater PLR or a lower NLR means a better diagnostic value of the diagnostic test. The pooled PLR was 4.12 and NLR was 0.20 in our study, indicating that compared to patients without TPE, TPE patients have an ~4-fold higher chance of being TNF-α assay positive. However, a patient could have a 20% chance of having TPE if he gets a negative TNF-α assay result.

Exploration of heterogeneity is an important part of the meta-analysis. In our study, the I^2 test for the pooled specificity, PLR, and DOR suggested that the heterogeneity among the studies was significant. Because of the different cut-offs between the included studies, the threshold effect is one of the most important causes of heterogeneity; therefore, we used the Spearman correlation coefficient to analyze the threshold effect. The results found that there is no correlation between the sensitivity and specificity ($P < 0.05$), suggesting that the threshold effect is not the source of heterogeneity. Meta-regression was performed to find the potential reason for heterogeneity. Variables like sample size (≥ 100 or < 100), setting (area with high TB incidence or area with low TB incidence), and diagnosis standard (by gold standard or clinical course) were included in the meta-regression analysis but none of them were observed to substantially affect the diagnostic accuracy of TNF-α for TPE.

The present meta-analysis suggests that the TNF-α assay play a vital role for TPE but it is far from perfection. Combination with other markers may be a reliable way to improve the diagnostic accuracy. Momi et al[33] found that combined sensitivity and specificity of TNF-α plus VEGF is better than testing TNF-α alone, with a higher sensitivity of 88.9%. Wong et al[35] reported that the combination of TNF-α with IFN-γ gained a high-diagnostic performance. The combination of TNF-α and ADA has been found to improve the diagnostic value of TPE with a high specificity of 96.3%.[27]

Our results suggest that the accuracy of TNF- α test was relatively high, which was in accordance with numerous previous studies. However, it is in disagreement with those of Soderblom et al[8] and Chomej et al[10] who found that TNF-α is not a good marker to separate tuberculous from malignant or parapneumonic pleural fluid. This discrepancy may be due to the inhomogeneity of the patients included in their nontuberculous group.[21,22]

It should be emphasized that this meta-analysis still has some limitations although comprehensive search strategy and data extraction were carried out. First, studies published in languages other than English or Chinese were excluded, and unpublished studies or abstracts from conferences were also filtered due to insufficient data, which may lead to publication bias, although the present meta-analysis shows no publication bias. Second, only 12 studies with 1022 cases were included. The pooled results generated from the limited samples may limit the interpretation of the meta-analysis. Third, the misclassification bias may occur since not all the tuberculous pleurisy patients in the studies were diagnosed by bacteriological or histological assessments or on the gold standard combination of both. In fact, 5 studies included in the meta-analysis used a mixture of bacteriological, histological, or clinical assessments.[24–27,35] The issue regarding accuracy of diagnosis can cause nonrandom misclassification, contributing to biased results.

5. Conclusion

In conclusion, our study demonstrated that the TNF-α assay play a vital role in the diagnosis of TPE, whereas other test results or clinical findings should be interpreted together with the test to improve the diagnostic accuracy.

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References

[1] Vorster J, Brian W, Diacon H, et al. Tuberculous pleural effusions: advances and controversies. J Thorac Dis 2015;7:981–91.

[2] Dixon G, Fonseka D, Maskell N. Pleural controversies: image guided biopsy vs. thoracoscopy for undiagnosed pleural effusions? J Thorac Dis 2015;7:1041–51.
[3] Wang X, Lin Y. Tumor necrosis factor and cancer, buddies or foes? Acta Pharmacol Sin 2008;29:1275–88.
[4] Kleine TO, Zwerenz P, Zofel P, et al. New and old diagnostic markers of meningitis in cerebrospinal fluid. Brain Res Bull 2003;61:287–97.
[5] Surbatovic M, Padkovic S. Tumor nercosis factor-α early in severe acute pancreatitis:is there predictive value regarding severity and outcome ? J Clin Gastroenterol 2013;47:637–43.
[6] Tebruegge M, Dutta B, Ritz N, et al. Mycobateria-specific cytokine responses detect tuberculosis infection distinguish latent from active tuberculosis. Am J Respir Crit Care Med 2015;192:485–99.
[7] Maeda J, Ueki N, Ohkawa T, et al. Local production and localization of transforming growth factor-beta in tuberculous pleurisy. Clin Exp Immunol 1993;92:32–8.
[8] Soderblom T, Nyberg P, Teppo AM, et al. Pleural fluid interferon-γ and tumour necrosis factor-α in tuberculous and rheumatoid pleurisy. Eur Respir J 1996;9:1652–5.
[9] Xirouchaki N, Tzanakis N, Bouros D, et al. Diagnostic value of interleukin-1alpha, interleukin-6, and tumor necrosis factor in pleural effusions. Chest 2002;121:815–20.
[10] Chomej P, Bauer K, Bitterlich N, et al. Differential diagnosis of pleural effusions by fuzzy-logic-based analysis of cytokines. Respir Med 2004;98:308–17.
[11] Whiting PF, rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Inter Med 2011;155:529–36.
[12] Jones CM, Ashrafian H, Skapinakis P, et al. Diagnostic accuracy meta-analysis. a review of the basic principles of interpretation and application. Int J Cardiol 2010;140:138–44.
[13] Liberti A, Altman GD, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:65–94.
[14] Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–316.
[15] Lau J, Ioannidis JP, Balk EM, et al. Diagnosing acute cardiac ischemia in the emergency department: a systematic review of the accuracy and clinical effect of current technologies. Ann Emerg Med 2001;37: 453–60.
[16] Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med 1994;120:667–76.
[17] Vamvakas EC. Meta-analyses of studies of the diagnostic accuracy of laboratory tests: a review of the concepts and methods. Arch Pathol Lab Med 1998;122:675–86.
[18] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.
[19] Söderblom T, Pettersson T, Nyberg P, et al. High pleural fluid hyaluronan concentrations in rheumatoid arthritis. Eur Respir J 1999; 13:519–22.
[20] Yang CS, Lee JS, Lee HM, et al. Differential cytokine levels and immunoreactivities against Mycobacterium tuberculosis antigens between tuberculous and malignant effusions. Respir Med 2008;102:280–6.
[21] Barnes PF, Fong SJ, Brennan PJ, et al. Local production of tumor necrosis factor and IFN-gamma in tuberculous pleuritis. J Immunol 1990;145: 149–54.
[22] Kim YC, Park KO, Bom HS, et al. Combining ADA, protein and IFN-gamma best allows discrimination between tuberculous and malignant pleural effusion. Korean J Intern Med 1997;12:225–31.
[23] Söderblom T, Nyberg P, Teppo AM, et al. Pleural fluid interferon-gamma and tumour necrosis factor-alpha in tuberculous and rheumatoid pleurisy. Eur Respir J 1996;9:1652–5.
[24] Jing ZD, Sun JS, Huang YX, et al. Investigation on the diagnosis of IFN-γ and TNF-α examination in the discrimination between tuberculous hydrothorax and carcinomatous hydrothorax. Jilin Med J 2002;23: 25–7.
[25] Xu JH, Chen LH, Hou QX, et al. Diagnostic value of TNF-α, INF-γ and ADA for the malignant and belign effusions. Med Lab Sci Clin 2007;18:60–1.
[26] Wang JP, Gu SX, Liu DY. Significance of detecting interferon — gamma (IFN) and tumor necrosis factor-α(TNF-α) concentrations in pleural effusion in the diagnose of tuberculosis pleurisy. Tuberc Thor Tumo 2000;4:265–9.
[27] Huang CL. Diagnostic value of ADA and TNF-α for the tuberculosis pleurisy. J Youjiang Med Coll Nationalities 2005;27:639–40.
[28] Li MY, Wang HL, Wang X, et al. Diagnostic accuracy of tumor necrosisfactor-alpha, interferon-gamma, interlukine-10 and adenosine deaminase 2 in differential diagnosis between tuberculous pleural effusion and malignant pleural effusion. J Cardiothorac Surg 2014;9: 118–24.
[29] Sun JS, Chen YX, Zhou DJ. Diagnostic value of TNF-α for the tuberculosis pleurisy. Chin Community Doct 2008;18:130.
[30] Deville' WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: did actic guidelines. BMC Med Res Methodol 2002;2:9.
[31] Orphanidou D, Gaga M, Rasidakis A, et al. Tumour necrosis factor, interleukin-1 and adenosine deaminase in tuberculous pleural effusion. Respir Med 1996;90:95–8.
[32] Ogawa K, Koga H, Hirakata Y, et al. Differential diagnosis of tuberculous pleurisy by measurement of cytokine concentrations in pleural effusion. Tuber Lung Dis 1997;78:29–34.
[33] Momi H, Matsuyama W, Inoue K, et al. Vascular endothelial growth factor and proinflammatory cytokines in pleural effusions. Respir Med 2002;96:817–22.
[34] Tahhan M, Ugurman F, Gozu A, et al. Tumour necrosis factor-alpha in comparison to adenosine deaminase in tuberculous pleuritis. Respiration 2003;70:270–4.
[35] Wong CF, Yew WW, Leung SK, et al. Assay of pleural fluid interleukin-6, tumour necrosis factor-alpha and interferon-gamma in the diagnosis and outcome correlation of tuberculous effusion. Respir Med 2003;97: 1289–95.
[36] Kiropoulos TS, Kostikas K, Oikonomidi S, et al. Acute phase markers for the differentiation of infectious and malignant pleural effusions. Respir Med 2007;101:910–8.
[37] Ciledag A, Kaya A, Erol S, et al. The comparison of pleural fluid TNF-alpha and IL-10 levels with ADA in tuberculous pleural effusion. Curr Med Chem 2010;17:2096–100.
[38] Deeks JJ. Egger M, Smith GD, Altman DG. Systematic reviews of evaluations of diagnostic and screening tests. Systematic Reviews in Health Care: Meta-analysis in Context. London, UK:BMJ Publishing Group; 2001. 24.