Review Article
Diagnosis of tuberculosis pleurisy with adenosine deaminase (ADA): a systematic review and meta-analysis

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Abstract: This systematic review and meta-analysis was performed to determine accuracy and usefulness of adenosine deaminase (ADA) in diagnosis of tuberculosis pleurisy. Medline, Google scholar and Web of Science databases were searched to identify related studies until 2014. Two reviewers independently assessed quality of studies included according to standard Quality Assessment of Diagnosis Accuracy Studies (QUADAS) criteria. The sensitivity, specificity, diagnostic odds ratio and other parameters of ADA in diagnosis of tuberculosis pleurisy were analyzed with Meta-DiSC1.4 software, and pooled using the random effects model. Twelve studies including 865 tuberculosis pleurisy patients and 1379 non-tuberculosis pleurisy subjects were identified from 110 studies for this meta-analysis. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnosis odds ratio (DOR) of ADA in the diagnosis of tuberculosis pleurisy were 45.25 (95% CI 27.63-74.08), 0.86 (95% CI 0.84-0.88), 0.88 (95% CI 0.86-0.90), 6.32 (95% CI 4.83-8.26) and 0.15 (95% 0.11-0.22), respectively. The area under the summary receiver operating characteristic curve (SROC) was 0.9340. Our results demonstrate that the sensitivity and specificity of ADA are high in the diagnosis of tuberculosis pleurisy especially when ADA≥50 (U/L). Thus, ADA is a relatively sensitive and specific marker for tuberculosis pleurisy diagnosis. However, it is cautious to apply these results due to the heterogeneity in study design of these studies. Further studies are required to confirm the optimal cut-off value of ADA.

Keywords: Tuberculosis pleural effusion, ADA, diagnostic test, meta analysis

Introduction

Tuberculosis is one of the most common infectious bacterial diseases and has threatened the human health worldwide [1]. Tuberculosis has high morbidity and mortality around of the world, and caused estimated 1.4 million deaths in 2011 [2]. Tuberculosis can be classified as intrapulmonary, extra-pulmonary and disseminated tuberculosis. Tuberculosis pleurisy (TP) is a common manifestation of extra-pulmonary tuberculosis (EPTB) [3]. The pleural tissue biopsy and pleural fluid examination are two major methods for the diagnosis of tuberculosis pleurisy effusion (TPE). However, mycobacterium culture of the pleural fluid has a relative lower success rate (36%) [4], and thus its role in the diagnosis of TP is still controversial. Due to the non-specific clinical manifestations and nega-

tive laboratory findings, it is difficult to distinguish TPE from malignant pleural effusion (MPE), both of which are the most common types of pleural effusion [5]. Moreover, there are still conflicting findings on the sensitivity and specificity of biopsy and mycobacterium culture of pleural fluid in the diagnosis of TP. Consequently, it is imperative to develop a reliable molecular marker that can be used to rapidly and accurately diagnose TPE and MPE [6].

Adenosine deaminase (ADA), interferon-γ, C-reactive protein (CRP), carcinoembryonic antigen, interleukin-6 (IL-6), lactate dehydrogenase (LDH), tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF) are markers used in the diagnosis of TPE [7]. The ADA activity in TPE is one of the most common biomarkers used for the diagnosis and treat-
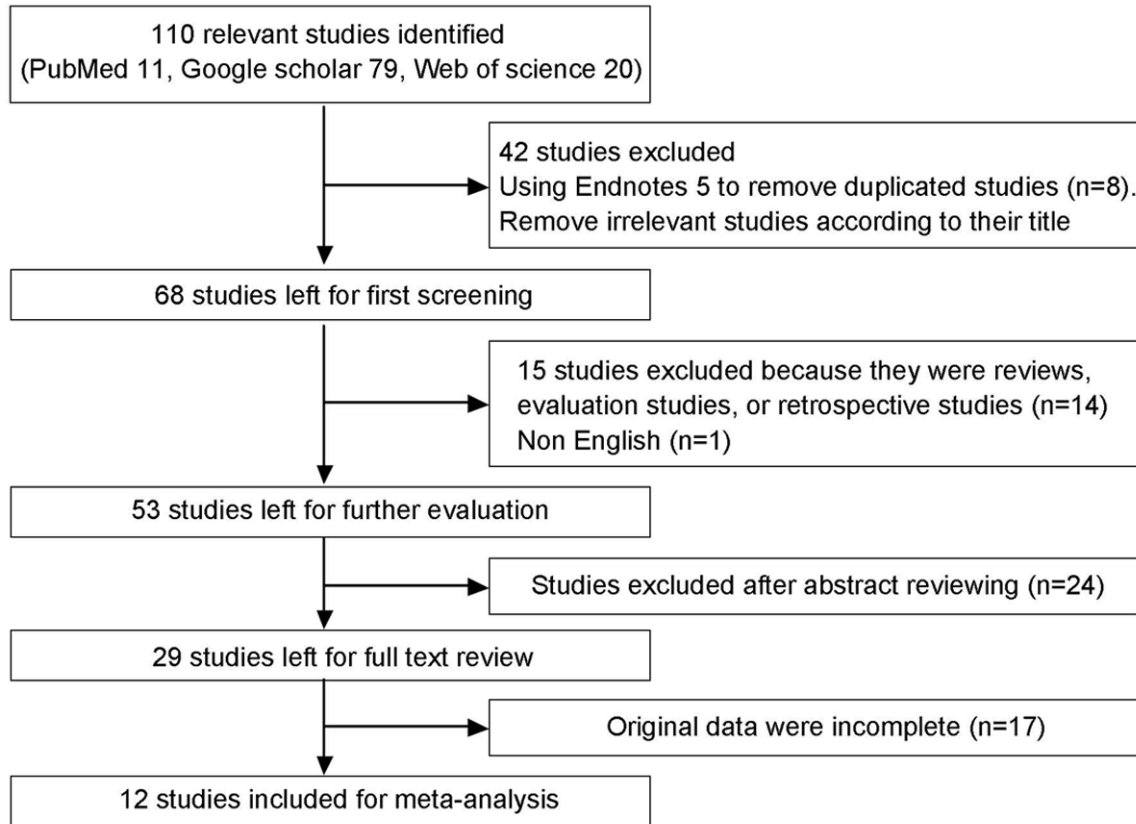
Figure 1. Processes for study selection.

ment decision of tuberculosis, having a high sensitivity [8]. The role of ADA in the diagnosis of TPE has been evaluated, and results showed it is helpful to distinguish TPE from MPE [9]. Numerous studies have been conducted to improve our understanding of the diagnostic value of ADA in TPE. Two meta-analyses have displayed that ADA has a favorable diagnostic value in TP [10, 11].

The diagnostic accuracy of ADA in TPE has been extensively studied. However, the optimal cut-off value of ADA is still to be elucidated. In the present study, we systematically assessed and analyzed the overall efficiency and accuracy of ADA in the diagnosis of TPE through meta-analysis, and distinguished factors related to the heterogeneity of results among studies. This study aimed to perform as systemic review to evaluate the diagnostic value of ADA as compared to the gold standard. The sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR) and the area of SROC were used for the evaluation.

Materials and methods

Search strategy and study selection

We systematically hand-searched three database: Medline, Google scholar and Web of science using the following key words ("tuberculosis pleurisy" or "tuberculosis pleural effusion") and ("adenosine deaminase" or "ADA") from 1990-2014.

Although there was no language restriction in the initial searching of studies, only English articles were obtained for reviewing and final analysis due to limitations in the resources. Conferences, letters to editor, case reports and reviews were not included because of incomplete original data. Studies having involvement of the accuracy of ADA in diagnosing TP were included. These studies had complete information, such as sensitivity, specificity, and numbers of TB and NTB. Then, true positive (TP), true negative (TN), false positive (FP) and false negative (FN) were calculated.

Table 1. Characteristics of included studies for meta-analysis

NO	Author	Country	Year	Method	Blind	Consecutive	QUADAS
1	Denise Duprat Neves	Brazil	2006	Diagnostic test	YES	Yes	13
2	Yoshiko Ogata	Japan	2011	Diagnostic test	NO	Yes	11
3	Lesley J.Burgess	Tygerberg	1995	Diagnostic test	YES	Yes	14
4	Khalid Hassanein	Egypt	2010	Diagnostic test	YES	Yes	11
5	Pınar Birsen Yıldız	Turkey	2011	Diagnostic test	YES	Yes	11
6	Hongxiu Wang	China	2011	Diagnostic test	YES	Yes	12
7	Nariman A. Helmy	Egypt	2012	Diagnostic test	Not clear	Yes	13
8	Alberto Garcia-Zamalloa	Spain	2012	Diagnostic test	NO	Yes	12
9	Mo-Lung Chen	China	2003	Diagnostic test	NO	NO	12
10	Fahmi Yousef Khan	Doha-Qatar	2013	Diagnostic test	YES	Yes	13
11	Yung-Ching Liu	China	2011	Diagnostic test	NO	Yes	12
12	Li-Ta Keng	China	2013	Diagnostic test	YES	Yes	14

Table 2. Characteristics of included studies for meta-analysis

NO	First author	Age	Men %	Assay method	Source	Reference standard
1	Denise Duprat Neves	33.8	73	Giusti method	pleural fluid	Radiological and Histopathological
2	Yoshiko Ogata	69	76.6	auto analyzer	pleural fluid	Histological
3	Lesley J. Burgess	49	58	Giusti method	pleural fluid	Radiological and Microbiology
4	Khalid Hassanein	35	76	Giusti method	serum and BALF	Radiological and laboratory
5	Pınar Birsen Yıldız	45	73.5	Giusti method	pleural fluid	histopathology
6	Hongxiu Wang	44.1	78.2	Giusti method	pleural fluid	histopathology
7	Nariman A. Helmy	29.2	45	auto analyzer	pleural fluid	histopathology
8	Alberto Garcia-Zamalloa	66.2	62.3	automated ultraviolet kinetic assay	pleural fluid	Radiological and Microbiology
9	Mo-Lung Chen	57.7	68	automated ultraviolet kinetic assay	pleural fluid	histopathology or cytopathol ogy
10	Fahmi Yousef Khan	38.9	84.5	automated ultraviolet kinetic assay	pleural fluid	Thoracocentesis and histopathology
11	Yung-Ching Liu	61	75	Giusti method	pleural fluid	histopathology
12	Li-Ta Keng	63.9	74	Giusti method	pleural fluid	Radiological

Note: BALF: bronchoalveolar lavage fluid.

Table 3. Summary of included studies

NO	Author	TB/NTB	ADA(U/L)	TP	FP	TN	FN	Se	Sp
1	Denise Duprat Neves	104/111	39	99	19	92	5	95.2	82.9
2	Yoshiko Ogata	124/311	36	106	42	269	42	85.5	86.5
3	Lesley J. Burgess	143/104	50	130	20	84	13	91	81
4	Khalid Hassanein	20/30	26.2	19	5	25	1	95	83.3
5	Pınar Birsen Yıldız	114/82	55	99	11	71	15	86.6	86.6
6	Hongxiu Wang	78/44	40	73	4	40	5	93.6	90.9
7	Nariman A. Helmy	19/21	30	16	6	15	3	84.2	71.4
8	Alberto Garcia-Zamalloa	73/399	40	65	29	370	8	89	92.7
9	Mo-Lung Chen	63/147	55.8	55	12	135	8	87.3	91.8
10	Fahmi Yousef Khan	72/31	16.65	62	8	23	10	86	74
11	Yung-Ching Liu	24/42	30	17	2	40	7	70.8	95.2
12	Li-Ta Keng	31/57	15.5	26	7	50	5	83.9	87.7

Inclusion and exclusion criteria

Two reviewers independently reviewed and evaluated all the studies. Disagreement was resolved following a discussion between them. Studies were included if they met following criteria: 1) The diagnosis of TP and non-TP was confirmed by histological and pathological

examinations. 2) Information about the samples, sensitivity, specificity (95% confidence intervals [CI]) and number of patients was complete. 3) They were original articles. 4) They were published in English. Exclusion criteria: 1) It was no a case-control study. 2) They were case reports, letters to editor, reviews and Meta-analyses. 3) There were English in language. 4) Information was incomplete. **Figure 1** shows the processes for the inclusion of studies using above criteria.

Data extraction

Two investigators independently extracted following information from the included studies: the name of the first author, the year of publication, the country of origin, the proportion of men and women, the number of patients and controls, gender, age, assay methods, sensitivity and specificity data, cut-off values, study design, and sample detection (**Tables 1** and **2**). All the data were collected from the published studies.

Assessment of quality of included studies

Two reviewers independently assessed the quality of included studies by using the QUADAS (Quality Assessment of Diagnosis Accuracy Studies) (UK and Netherland) criteria [12], which were developed as a validated instrument for diagnostic studies. All criteria were classified as "YES", "NO" or "Not clear" based on available information in the included studies. Furthermore, following information was also obtained: (1) consecutive or random samples of patients; (2) blind design (single or double). Disagreement was resolved by discussion between two investigators or the third-party adjudication.

Data synthesis and statistics analysis

The sensitivity, specificity, and number of TB patients and NTB patients were obtained from the retrieved articles, and the TP, FP, TN and FN were calculated according to the following formula: sensitive = TP/TP+FN, specificity = TN/FP+TN, TB+NTB = TP+FP+TN+FN, reach a 2*2 tables (**Table 3**). The pooled sensitivity (true positive rate, TPR), specificity (true negative rate, TNR or 1-false positive rate, FPR), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR) of ADA in

diagnosing TP were calculated using the Meta-Disc1.4 software (XI Cochrane Colloquium, Barcelona, Spain). These parameters were pooled using the random effect model [13].

Data were analyzed using Meta-Disc 1.4 software. Forest plots were used to determine the pooled sensitivity, specificity, DOR, LR+ and LR- and the corresponding 95% CI. A summary receiver operating characteristic curve (SROC) [14] was delineated and the area of SROC was calculated to evaluate the diagnostic accuracy of ADA. The heterogeneity among these studies was assessed using the chi square test.

The random-effect model was used for meta-analysis. Moreover, analysis of diagnostic threshold effects was quantified by the Spearman correlation coefficient and suggested the absence of heterogeneity caused by threshold effect. The non-threshold effect was evaluated by the Cochran-Q method and the test of inconsistency index (I^2). A low *P* value (<0.005) and a high I^2 (>50%) suggested the presence of heterogeneity caused by the non-threshold effect. Stratified analyses were used to evaluate study design, golden standard and test-related factors responsible for heterogeneity caused by non-threshold effects [15].

Results

Detailed information of the included literature and quality assessment

Figure 1 displays the processes in the selection of eligible studies. A total of 110 studies were identified from the Medline, Google scholar and Web of Science database, 42 studies were excluded due to repeated publication, and 15 studies were excluded because they were reviews, evaluation studies, retrospective studies or published in other languages. The abstract and full texts of remained studies were screened, and 51 studies were excluded due to incomplete original information. Thus, 12 potentially eligible studies were included for meta-analysis. Included studies had information about the sensitivity, specificity, number of TP and non-TP patients, which were extracted for the calculation of TP, FP, TN and FN. Of 12 studies, there were 865 TP patients and 1379 non-TP patients. The quality of included studies was evaluated using the QUADAS criteria [12] and they were graded from 1 to 14 as shown in **Table 1**.
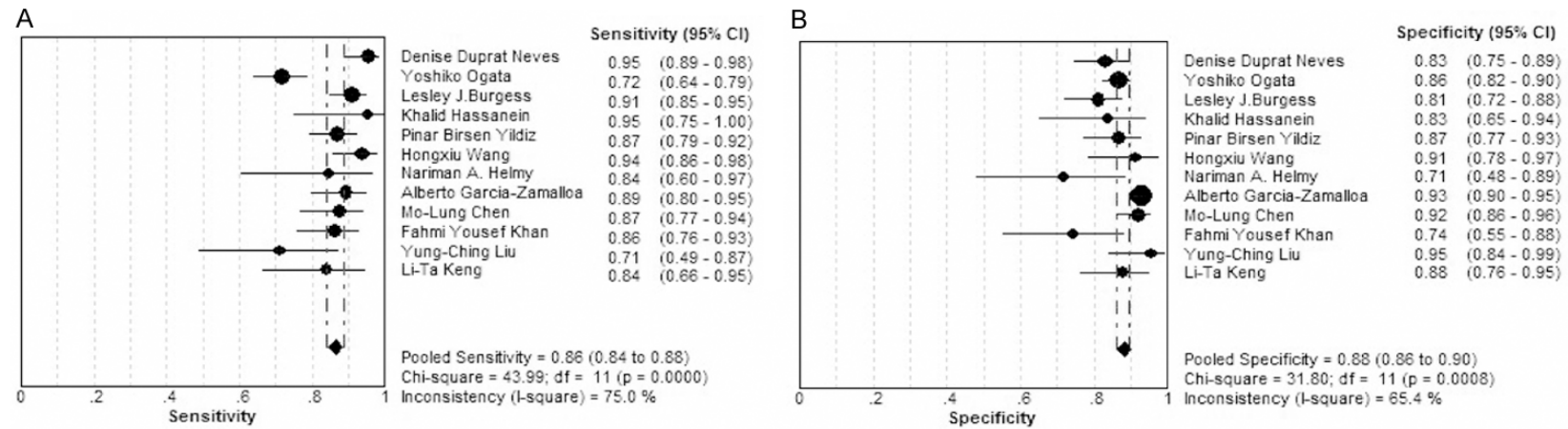
Figure 2. Forest plot for estimation of sensitivity and specificity of ADA in the diagnosis of tuberculosis pleurisy. Point estimates from all studies are displayed as solid circles and show sensitivity and specificity of each study. Error bars: 95% CI. Pooled estimates for ADA are as follows: A. Sensitivity, 0.86 (95% CI 0.84-0.88). B. Specificity, 0.88 (95% CI 0.86-0.90).
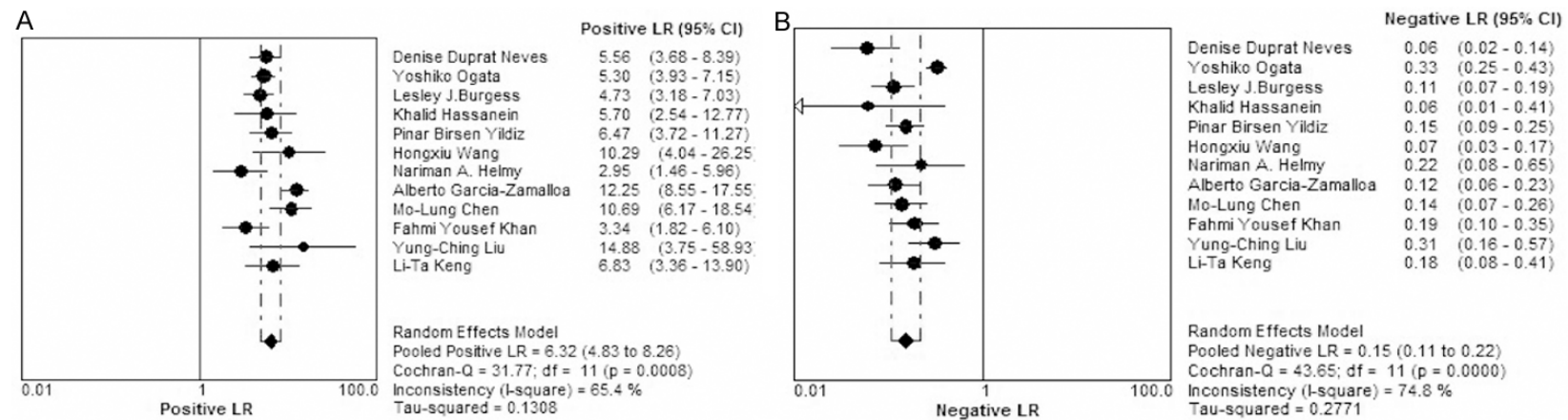

Figure 3. Forest plot for estimation of positive likelihood ratio and negative likelihood ratio of ADA in the diagnosis of tuberculosis pleurisy. Pooled estimates for ADA are as follows: A. Positive likelihood ratio (PLR), 6.32 (95% CI 4.83-8.26). B. Negative likelihood ratio (NLR), 0.15 (95% CI 0.11-0.22).
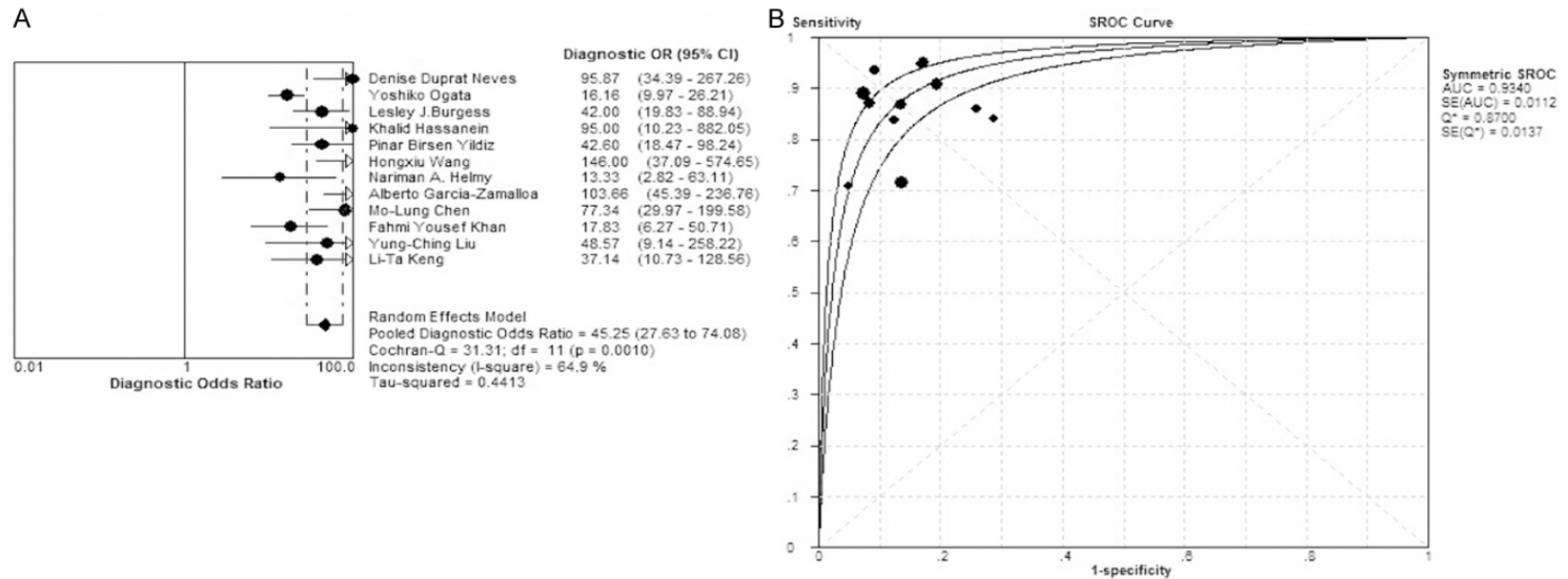
Figure 4. Forest plot for the diagnosis odds ratio (DOR) and Summary receiver operating characteristic curves (SROC). A. DOR: 45.25 (95% CI 27.63-74.08). B. AUC: 0.9340.
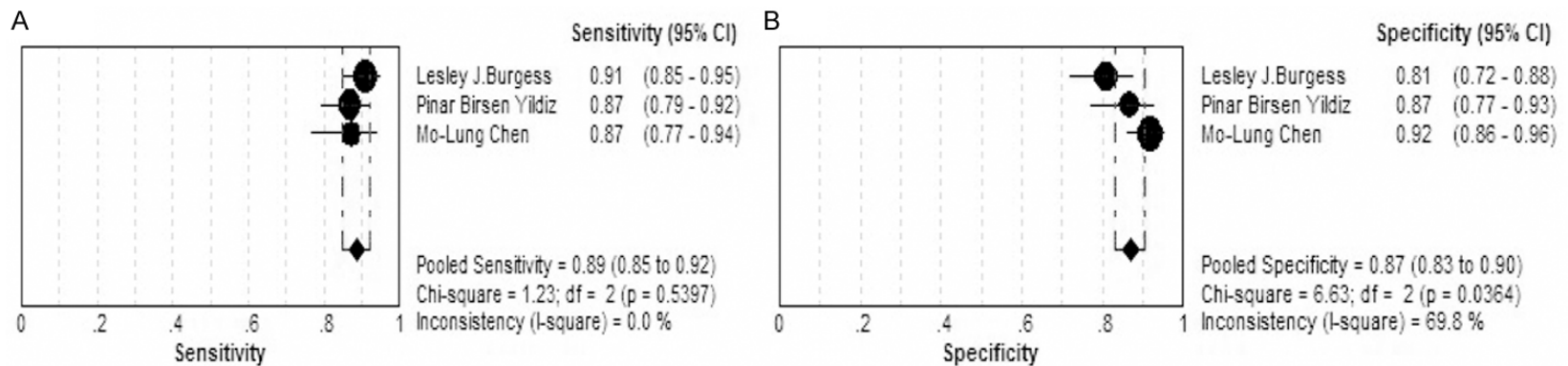

Figure 5. Forest plots for subgroup analysis of sensitivity and specificity. Subgroup analysis reveals studies (ADA≥50 U/L) have a good homogeneity. A. The pooled sensitivity of subgroup (ADA≥50 U/L) is 0.89 (95% CI 0.85-0.92). B. The pooled specificity of subgroup (ADA≥50 U/L) is 0.87 (95% CI 0.83-0.90).
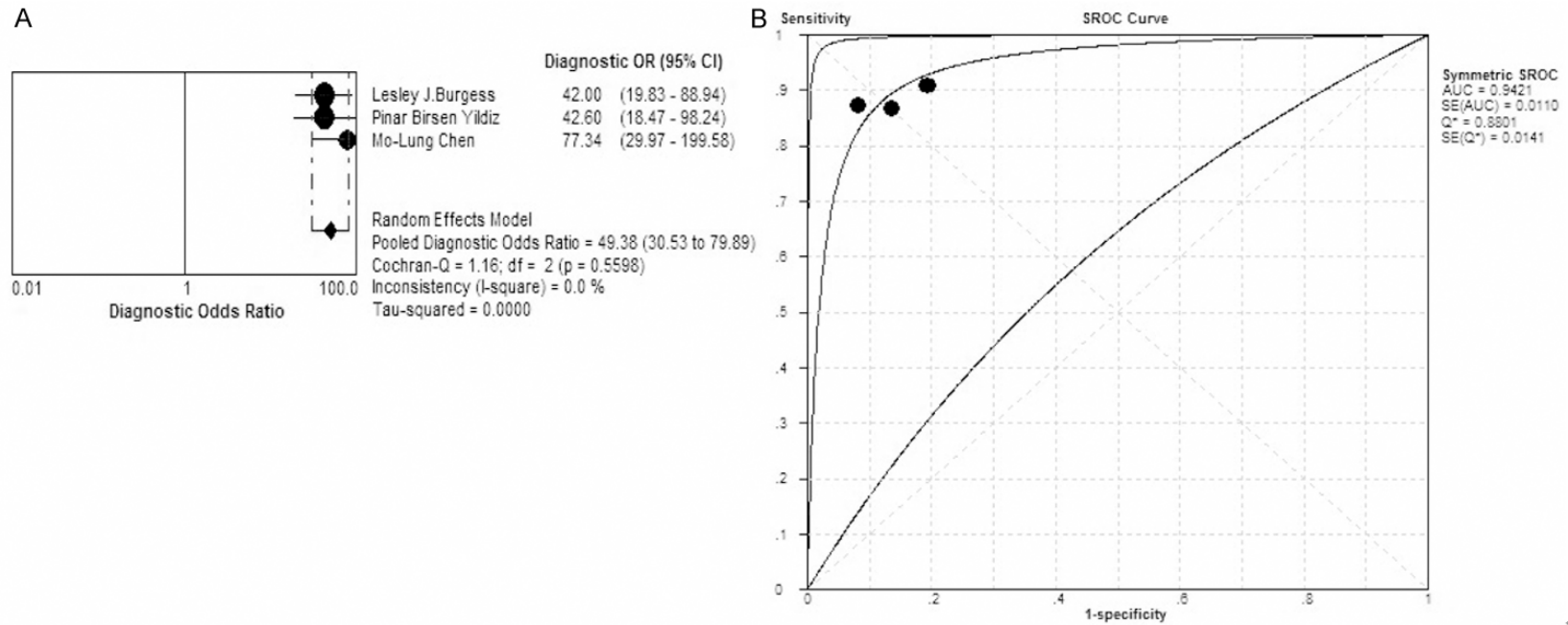
Figure 6. Forest plot for the diagnosis odds ratio (DOR) and Summary receiver operating characteristic curves (SROC) in a subgroup (ADA≥50 U/L). A. DOR: 49.38 (95% CI 30.53-79.89). B. AUC: 0.9421. SROC of ADA shows the diagnostic performance in a subgroup (ADA≥50 U/L).

Determination of diagnostic accuracy

The sensitivity, specificity, LR+, LR- and DOR of ADA in the diagnosis of TP are presented in the forest plot (**Figures 2**-**4**). The overall diagnostic sensitivity (SEN) and specificity (SPE) were 0.86 (95% CI 0.84-0.88) and 0.88 (95% CI 0.86-0.90), respectively. The LR+, LR- and DOR were 6.32 (95% CI 4.83-8.26), 0.15 (95% 0.11-0.22) and 45.25 (95% CI 27.63-74.08), respectively. Almost all the studies showed favorable sensitivity and specificity. Chi square test showed the chi square value of the sensitivity, specificity, PLR, NLR and DOR was 43.99 (P = 0.0000), 31.80 (P = 0.0008), 31.77 (P = 0.0008), 43.65 (P = 0.0000) and 31.31 (P = 0.0010) respectively, suggesting a substantially high heterogeneity for sensitivity, specificity, PLR, NLR and DOR among included studies. The SROC plot can be used to evaluate the effects of different thresholds on the sensitivity and specificity in a study. SROC curve can display the cutoff value between sensitivity and specificity. Our results showed that the AUC was 0.934, suggesting a high accuracy of ADA in the diagnosis of TP.

Heterogeneity and threshold effect

In the diagnosis test, included studies using different diagnostic cut-off values may cause heterogeneity. Therefore, it is important to explore the heterogeneity before data pooling. When there is a threshold effect, the sensitivity and specificity may correlate with each other negatively (sensitivity and 1-specificity correlate with each other positively) and the SROC is shoulder-shaped. The threshold effect was evaluated with the SROC, sensitivity and specificity, and results showed that SROC was not shoulder–shaped (**Figure 4**) and Spearman correlation coefficient was 0.175 (P = 0.587>0.05). Above findings proved that there was no threshold effect among included studies.

Non-threshold effect

In the diagnosis meta-analysis, the heterogeneity among included studies is due to the threshold effect and the non-threshold effect. The non-threshold effect contains the population (the severity of disease and sex); experiment test (such as different technology, operator, reagent and instrument); reference standard, etc. Therefore, the Cochran-Q of DOR is usually used to detect if there is heterogeneity due to non-threshold effect in diagnosis methods.

The heterogeneity due to non-threshold effect was evaluated with sensitivity, specificity, and DOR. Results showed the chi square value of sensitivity, specificity and DOR was 43.99 (P-0.0000), 31.8 (P = 0.0008), and 31.31 (P = 0.001). It indicates the heterogeneity due to non-threshold effect.

Meta-regression and subgroup analysis

Because of the non-threshold effect due to heterogeneity among included studies, the random effect model was used to assess the overall accuracy of ADA in the diagnosis TP. To investigate the reasons for heterogeneity, meta-regression was performed. According to materials provided by the literature, blind method (blind design: 0, not blind design: 1, not clear: 2), test method (Giusti method: 0, automated ultraviolet kinetic assay: 1), source of samples (pleural fluid: 0, other sources: 1), gold standard (pathological diagnosis is 0, others are 1) and consecutiveness (YES: 0, NO: 1)were set for ADA assay. Nine factors were included in meta-analysis according to *P* value from big to small to remove above factors gradually (QUADAS, consecutive, age, source, blind, assay, men and standard). Results showed that the source of heterogeneity in included studies was correlated with ADA. Due to the heterogeneity in the included studies, a subgroup analysis was performed. On the basis of results from meta-regression analysis, 12 studies were divided into two subgroups according to the ADA level. When the ADA was higher than 50 U/L (n = 3), analysis of diagnosis threshold showed the spearman correlation coefficient of sensitivity and 1-specificity was 0.5 (P = 0.667>0.05), indicating no threshold effect. The non-threshold effect was also evaluated. Results showed the absence of non-threshold effect (**Figures 5** and **6**). Therefore, the homogeneity is favorable in subgroups (ADA≥50 U/L).

Discussion

TP is an ordinary extra-pulmonary formation of tuberculosis all over the world and also the most common manifestation of tuberculosis [16]. Mycobacterium affects approximately 30% of the world's populations and causes

about 1.7 million deaths every year. Although, there are several methods used to diagnose the tuberculosis, such as tuberculin skin test, interferon-γ release assay and imaging method, but they are non-mandatory in clinical practice. In addition, there is still difficulty in the diagnosis of TP. Thus, it is imperative to develop a new method used to conveniently and effectively diagnose TP [17]. At present, the methods used to diagnose TP mainly include pleural biopsy, X-ray and ultrasonography. In addition, other assistant examinations may be done if necessary, such as diagnostic pleural puncture, routine thoracic fluid inspection, biochemical examination and bacterial culture.

Moreover, it is important and useful to identify some biochemical markers for the diagnosis of TP. There are some target biomarkers (such as interferon-γ, C-reactive protein (CRP), LDH, ADA, carcinoembryonic antigen, IL-6, TNF-α and VEGF) used in the diagnosis of TPE. ADA is a classical and highly sensitive biomarker for the diagnosis of TP, and can be used to distinguish TPE from non-TPE. In recent years, numerous studies [18] have shown that ADA provides a favorable diagnostic value in TP [17, 18]. In the present study, we searched three databases and a total of 110 studies were identified. Finally, 12 studies were included for Meta-analysis of the diagnostic value of ADA in TP.

In this systematic review, the included 12 studies demonstrated that ADA plays an important role in the diagnosis of TP and the quality of these 12 articles was high. However, there was heterogeneity among these studies. Thus, Moses-Shapiro-Littenber model was used for statistical analysis. Results showed that non-threshold effect caused the heterogeneity among these included studies. Subgroup analysis revealed that the cut-off value of ADA was a source of non-threshold effect. Homogeneity was relatively favorable when ADA was ≥50 U/L. The value of ADA is quite significant in diagnosing tuberculosis pleurisy especially when ADA≥50 U/L. In conclusion, ADA can serve as a biomarker for the diagnosis of TP, especially when ADA is higher than 50 U/L.

The present meta-analysis had several limitations. First, studies were excluded using following criteria: insufficient original data, non-English language, incomplete patient number and unlisted test method, and so on, which may cause potential selection bias and affect the evaluation of diagnostic accuracy. Second, significant heterogeneity was observed in the included studies. The heterogeneity may influence the systemic evaluation. Third, there might be misclassification bias, and the qualities of included studies had inconformity. In addition, only 12 studies met the inclusion criteria and used for meta-analysis. It also limits the expansion of our findings.

In conclusion, the present meta-analysis demonstrates that ADA is a promising marker for the diagnosis of TP (especially when ADA is ≥50 U/L) with high sensitivity and specificity. This may be useful in clinical findings and traditional measurements including microbiological examination and pleural biopsy.

However, due to the limitations of our study, more studies with large sample size are required to confirm our findings.

Disclosure of conflict of interest

None.

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