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Diagnostic accuracy of adenosine deaminase for tuberculous pericarditis: a meta-analysis

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Abstract. – OBJECTIVE: Many studies suggest that adenosine deaminase is a marker for tuberculous pericarditis, while controversy exists as to its diagnostic utility. This study aims to summarize the overall diagnostic performance of adenosine deaminase for tuberculous pericarditis through a meta-analysis.

MATERIALS AND METHODS: Literatures published before May 2015 were searched in PubMed and EMBASE. The data were retrieved and the sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), diagnostic odds ratio (DOR) of adenosine deaminase for diagnosing tuberculous pericarditis were pooled, and the summary receiver operating characteristic (SROC) curves were used to examine the overall performance of adenosine deaminase.

RESULTS: In total, 11 studies with 938 subjects were included in the meta-analysis. The summary estimates of adenosine deaminase for diagnosing tuberculous pericarditis were listed as follows: sensitivity of 0.90 (95% CI: 0.86-0.93), specificity of 0.86 (95% CI: 0.83-0.89), PLR of 5.90 (95% CI: 4.46-7.82), NLR of 0.15 (95% CI: 0.09-0.26), and DOR of 42.55 (95% CI: 21.51-84.18). The area under the SROC curve was 0.92, and the Q value was 0.85. No publication bias was identified.

CONCLUSIONS: Adenosine deaminase is a valuable marker with both high sensitivity and specificity in the diagnosis of tuberculous pericarditis. Nevertheless, the results of adenosine deaminase assays should be interpreted in combination with other test results and clinical characteristics of patients.

Key Words:
Tuberculous pericarditis, Adenosine deaminase, Diagnosis, Meta-analysis.

Introduction

Tuberculous pericarditis is a form of extrapulmonary tuberculosis, and it is associated with both high morbidity and mortality even if anti-tuberculosis treatment is administered[1]. The incidence of tuberculous pericarditis is increasing because of the human immunodeficiency virus (HIV) epidemic, especially in the area of sub-Saharan Africa, and such trend is likely to appear in other parts of the world where the spread of HIV is leading to a resurgence of tuberculosis[2]. The mortality of tuberculous pericarditis is as high as 26% at 6 months but is even higher as 40% among patients with the acquired immunodeficiency syndrome[3]. Despite the high burden and mortality of tuberculous pericarditis, its diagnosis remains a clinical challenge, limited to the difficulty to establish tuberculous pericarditis diagnosis using current available clinical, radiological, cytological, microbiologic, and even histopathological examinations[4]. It is imperative to find a reliable and affordable marker to facilitate the diagnostic accuracy.

Adenosine deaminase (ADA) is an important enzyme that catalyzes the deamination of adenosine and deoxyadenosine into their respective inosine nucleosides, high ADA activity is indirectly related to the subsets of T cell lymphocytes which involved in the inflammatory response induced by tuberculosis[5]. Many studies[6,7] have confirmed the diagnostic potential of ADA for tuberculous serous effusions, such as pleural effusion, peritoneal effusion. ADA activity in pericardial fluid also plays a role in the diagnosis of tuberculous pericarditis, and many studies have investigated the diagnostic performance of ADA for tuberculous pericarditis, but with inconsistent results[8-10]. To make a better conclusion about the diagnostic performance of ADA, the present meta-analysis aims to summarize the overall diagnostic accuracy of ADA in pericardial effusion for tuberculous pericarditis.

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Materials and Methods

Search Strategy

Literature search was performed in PubMed and EMBASE for original articles regarding the diagnostic usefulness of ADA for tuberculous pericarditis until May 2015. The following search terms were used: "Adenosine deaminase *or* ADA" and "Tuberculous pericarditis *or* Tuberculous pericardial effusion" and "Sensitivity *or* Specificity *or* Accuracy". Articles were also identified using the related-articles function in PubMed. References within these articles were also searched manually to identify potential studies.

Selection of Publications

We screened the title and abstract of searched publications. Relevant publications were retrieved for further full-text evaluation. Publications were included in our meta-analysis if they: (1) used adenosine deaminase in pericardial effusion to diagnose tuberculous pericarditis; (2) reported complete data to calculate true positive (TP), false positive (FP), false negative (FN), and true negative (TN) of adenosine deaminase for diagnosing tuberculous pericarditis, and (3) constituted original research published in English. Conference abstracts, reviews, editorials, and case reports were excluded.

Data Extraction and Quality Assessment

Two different reviewers judged the eligibility of publications and extracted data from included publications independently. All discrepancies in the interpretation were resolved by consensus. The following characteristics were retrieved from each selected articles: name of first author, year of publication, country, number of cases and controls, diagnostic standard, ADA assay method, cut-off values, TP, FP, FN, TN, and study design.

Two independent reviewers evaluate the methodological quality of included articles using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist[11]. It is a validated tool to evaluate the presence of bias in diagnostic studies. Differences between reviewers were resolved by discussion.

Data Analysis

Standard methods recommended for systematic review and meta-analysis of diagnostic studies were used for present study[12]. We analyzed the test accuracy of each study by calculating the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), with their corresponding 95% CIs. Summary receiver operating characteristic (SROC) curves and area under the curve (AUC) were also calculated.

Heterogeneity among included studies was evaluated by using the χ^2 test and Fisher's exact tests. The pooled sensitivity, specificity and other related indexes across studies were calculated using a random-effects model or a fixed-effects model, respectively, based on whether there was significant heterogeneity. Meta-regression analysis was performed to identify potential covariates which may cause the heterogeneity. Publication bias was tested using Deeks' funnel plots[13]. Two statistical software programs were used in this meta-analysis: STATA 12.0 (Stata Corp., College Station, TX, USA), and Meta-DiSc 1.4 (XI, Cochrane Colloquium, Barcelona, Spain). All statistical tests were two-sided, and $p < 0.05$ was considered to be statistically significant.

Results

After independent review, 11 studies with 938 subjects on the use of pericardial ADA for diagnosing tuberculous pericarditis were included in this meta-analysis[14-24]. Figure 1 outlines the process of selecting eligible studies, two studies were excluded because they contained the same patients[8,25].

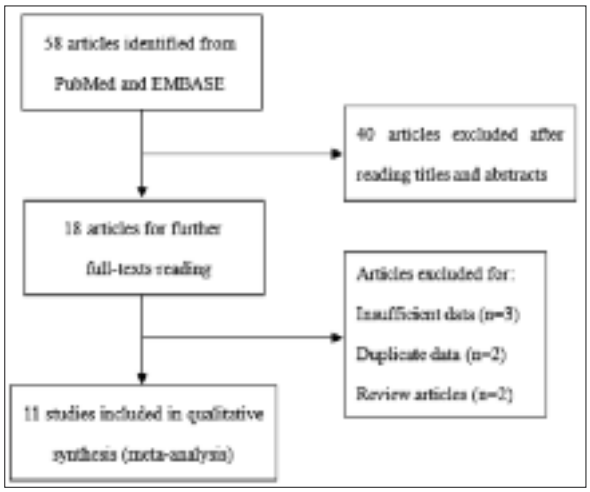

Figure 1. Studies selection process for the meta-analysis.

Quality Reporting of Included Studies

The 11 publications included 403 tuberculous pericarditis cases and 535 controls, and were published from 1995 to 2014. The mean included subjects were 85 (38-212). The major diagnostic criteria were bacteriology and histopathology, which were considered as the gold standard for tuberculous pericarditis diagnosis. Except for four studies were performed in high tuberculosis incidence countries (South Africa and Brazil)[18,20,22,24], the other studies were performed in low incidence areas. For ADA assay method, most studies used classical Giusti's method, the cut-off values ranged from 32.5 U/L to 72 U/L. Of the 11 included publications, eight had QUADAS scores ≥9, suggesting the reliability of our statistical results. The main clinical summaries of included studies, along with the QUADAS scores, were outlined in Table I.

Diagnostic Accuracy

Heterogeneity examination suggested that the χ^2 values of five diagnostic indexes were listed as follows: sensitivity, 28.98 (p = 0.0013); specificity, 14.61 (p = 0.1468); PLR, 15.98 (p = 0.1002); NLR, 23.79 (p = 0.0082); and DOR, 17.13 (p = 0.0714). This suggests substantial heterogeneity among the studies. Thus, the random effects model approach was selected to pool data.

The forests plot of the sensitivity and specificity for ADA assays in diagnosing tuberculous pericarditis were shown in Figures 2 and 3. The pooled sensitivity was 0.90 (95% CI: 0.86-0.93), specificity was 0.86 (95% CI: 0.83-0.89). The PLR was 5.90 (95% CI: 4.46-7.82), the NLR was 0.15 (95% CI: 0.09-0.26) and the DOR was 42.55 (95% CI: 21.51-84.18) (Figure 4). The Figure 5 showed the SROC curve which analyses of studies reporting different cutoff values of ADA in tuberculous pericarditis patients. The AUC was 0.92, suggesting the overall accuracy of ADA was high. The Q value was 0.85.

Meta-regression and Publication Bias

Significant heterogeneity was identified among included studies. Thus, a meta-regression was performed to investigate the potential covariates. The following covariates were reported by most included studies and so were analyzed as possible sources of heterogeneity: area setting (high incidence *vs.* high incidence), blinding (yes vs. no or not reported), ADA cut-off value (< 40 U/L *vs.* ≥ 40 U/L), design (prospective vs. retrospective), QUADAS score (< 9 *vs.* ≥ 9), sam-

Table I. Clinical summary of included studies.

Author	Year	Country	TP	Control	Standard	ADA assay method	Cut off value	TP	FP	FN	TN	QUADAS
Komsuoglu et al	1995	Turkey	20	88	B+HP+CD	Giusti's method	70 U/L	20	8	0	80	7
Koh et al	1997	Korea	21	30	B+HP+CD	Giusti's method	40 U/L	18	4	3	26	8
Dogan et al	1999	Turkey	24	61	B+HP	Modified Karger	50 IU/L	24	10	0	51	9
Aggeli et al	2000	Greece	7	34	B+HP	Giusti's method	72 U/L	7	2	0	32	9
Burgess LJ	2002	South Africa	64	46	B+HP	Giusti's method	35 U/L	57	12	7	34	9
Lee et al	2002	Korea	12	55	B+HP	Giusti's method	40 IU/L	10	12	2	43	10
Cubero et al	2006	Spain	18	65	B+HP	Giusti's method	60 IU/L	18	6	0	59	8
Reuter et al	2006	South Africa	151	61	B+HP	Giusti's method	40 U/L	131	7	20	54	11
Tuon et al	2007	Brazil	9	39	B+HP	Giusti's method	40 U/L	6	4	3	35	11
Emadi Koochak et al	2013	Iran	7	31	B+HP	NA	32.5 U/L	4	6	3	25	10
Pandie et al	2014	South Africa	70	25	B+HP	Giusti's method	35 U/L	67	4	3	21	11

ADA: Adenosine deaminase; TP: Tuberculous pericarditis; B: Bacteriology; HP: Histopathology; CD: Clinical Diagnosis; NA: Not available; TP, true positive; FP, false positive; FN, false negative; TN, true negative; QUADAS, quality assessment for studies of diagnostic accuracy.

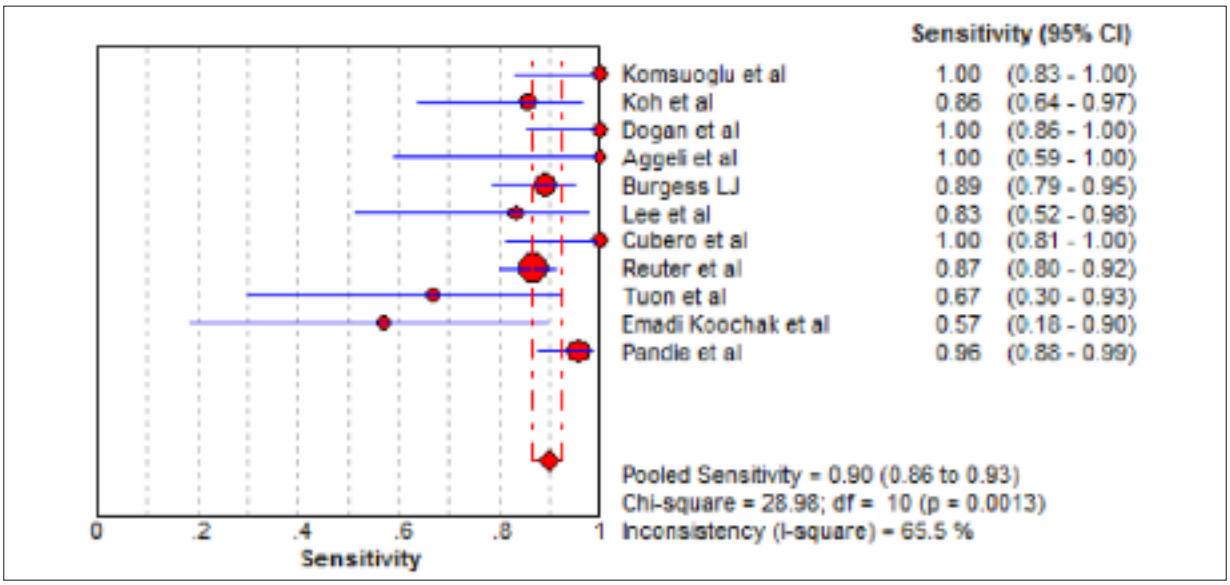

Figure 2. Forest plot of the summary sensitivity of adenosine deaminase for the diagnosis of tuberculous pericarditis. The sensitivity/specificity of individual study is represented by a circle, through which runs a horizontal line (95% CI). The diamond at the bottom represents the pooled sensitivity from the studies.

pling method (consecutive vs. nonconsecutive/not reported), and sample size (< 100 subjects *vs.* ≥ 100 subjects). In this study, none of the above covariates were found to be significant sources of heterogeneity (all $p > 0.05$). The outcomes of the regression are shown in Table II.

The publication bias was assessed by Deeks' funnel plot, the shape of the funnel plot did not reveal any evidence of obvious asymmetry (Figure 6). The slope coefficient was associated with a p value of 0.50, indicating that there was low likelihood of such bias.

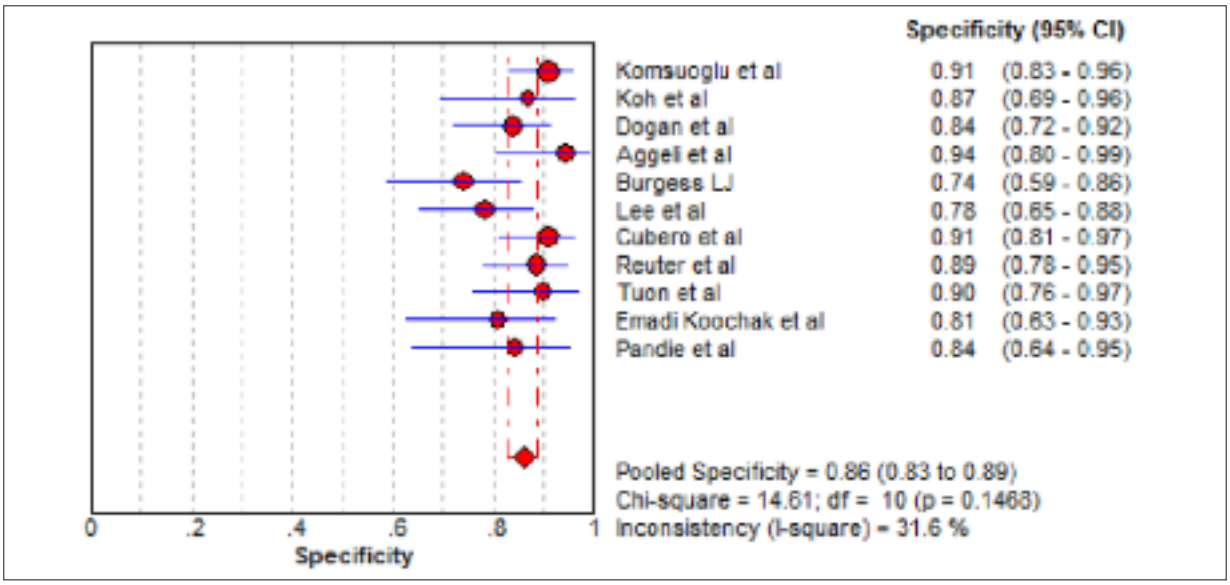

Figure 3. Forest plot of the summary specificity of adenosine deaminase for the diagnosis of tuberculous pericarditis. The sensitivity/specificity of individual study is represented by a circle, through which runs a horizontal line (95% CI). The diamond at the bottom represents the pooled specificity from the studies.

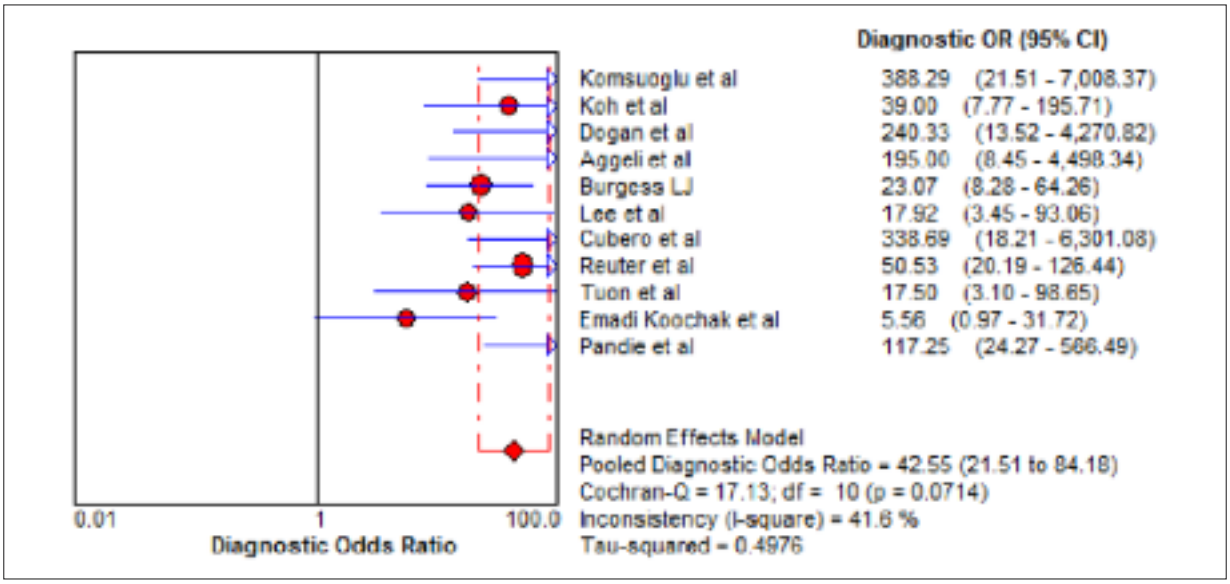

Figure 4. Forest plot of the summary diagnostic odds ratio of adenosine deaminase for the diagnosis of tuberculous pericarditis. The sensitivity/specificity of individual study is represented by a circle, through which runs a horizontal line (95% CI). The diamond at the bottom represents the pooled diagnostic odds ratio from the studies.

Discussion

ADA is an important enzyme required for the conversion of adenosine to inosine, increased ADA level in pericardial and other body fluids of tuberculosis patients may be the result of T cells activation in response to the stimulus of mycobacterial antigens, thus, providing diagnostic information for tuberculosis[26,27]. In fact, Tuon et al had conducted a systematic review to analyze the diagnostic role ADA for tuberculous pericarditis[28]. According his inclusion criteria, only five publications were included even with a study containing only three tuberculous pericarditis patients, while very small studies may be vulnerable to selection bias, and in the past years, more studies concerning pericardial ADA and tuberculous pericarditis were published, so we set more strict inclusion criterion and conduct this updated meta-analysis.

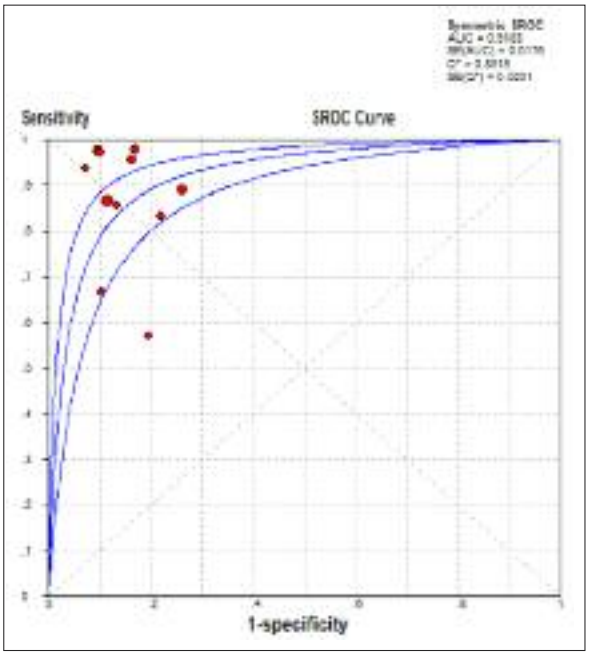

Figure 5. Summary receiver operating characteristic (SROC) curve of adenosine deaminase for the diagnosis of tuberculous pericarditis. AUC = area under the curve.

The AUC of ADA in the diagnosis of tuberculous pericarditis was 0.92, and a summary estimate of 0.90 for sensitivity and 0.86 for specificity, suggesting a relatively low rate of missed diagnosis (10%), and misdiagnosis (14%). The Q value was the maximum joint sensitivity and specificity of ADA for tuberculous pericarditis, and it was 0.85. DOR is a measure of the effectiveness of a diagnostic test, and it is defined as the ratio of the odds of the test being positive if the subject has tuberculous pericarditis relative to the odds of the test being positive if the subject does not have tuberculous pericarditis. with higher values indicating better discriminatory test performance. In this study, the DOR was 42.55, indicating that ADA levels measurement should

Table II. Weighted meta-regression to assess the effects of covariates on diagnostic accuracy of adenosine deaminase.

Covariate	Number of studies	Coefficient	RDOR (95% CI)	*p*-value
Area setting				
High incidence	4	0.887	2.43 (0.03-171.45)	0.4646
Low incidence	7			
Blinding				
Yes	2	-2.673	0.07 (0.00-41.47)	0.2141
No	9			
Cut-off value				
≥ 40 U/L	8	2.241	9.41 (0.17-519.38)	0.13841
< 40 U/L	3			
Design				
Prospective	10	1.796	6.03 (0.01-6286.39)	0.3818
Retrospective	1			
QUADAS score				
≥ 9	8	-0.988	0.37 (0.01-20.09)	0.398
< 9	3			
Sampling method				
Consecutive	6	0.966	2.63 (0.02-344.15)	0.4837
Other	5			
Sample size				
≥ 100 subjects	3	-1.332	0.26 (0.01-12.44)	0.2753
< 100	8			

RDOR, relative diagnostic odds ratio; QUADAS, quality assessment for studies of diagnostic accuracy.

be helpful in the diagnosis of tuberculous pericarditis. PLR/NLR summarizes information about a diagnostic test by combining sensitivity and specificity, which can be easier to be interpreted during clinical practice than SROC and DOR. The pooled PLR value of 5.90 suggests that patients with tuberculous pericarditis have an approximately six-fold higher chance of giving a positive ADA test result than do patients without tuberculous pericarditis. While the pooled NLR was 0.15, indicating that even a negative ADA test result is 15% likely to be a false negative, which meant ADA measurement couldn't rule out tuberculous pericarditis by the negative results. The lack of publication bias demonstrated the reliability of our results.

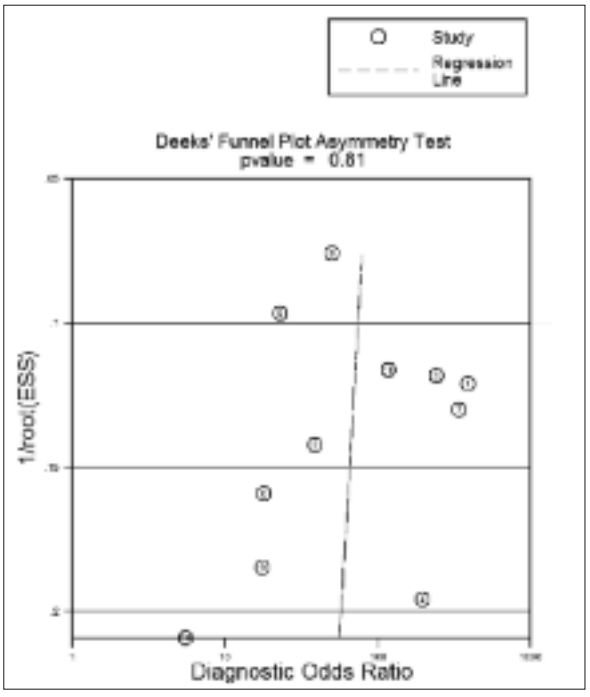

Figure 6. Funnel plots for assessing the risk of publication bias.

Current diagnostic tests for tuberculous pericarditis are difficult and time-consuming. Mycobacterial cultures might take a long time and its sensitivity is not satisfied, in addition, its result depends on the quality of samples cultured and methods utilized, and acid-fast stained smears of pericardial effusion are disappointingly insensitive[4]. Although pericardial biopsy is valuable for rapid diagnosis of tuberculous pericarditis, such invasive procedures may not be available in all levels hospitals and may increase mortality. Thus, the importance of ADA detection is not only provides a high diagnostic accuracy, but also guides the inclusion of patients who might benefit from further invasive examinations.

As mentioned above, pericardial biopsy is useful in the definite diagnosis of tuberculous pericarditis, while such procedure is so invasive, and co-infection with HIV impacts on the histopathological features of tuberculous pericarditis, and leads to a decrease in the sensitivity of pericardial biopsy[28]. While pericardial ADA levels were not affected by HIV infection, suggesting the reliability of ADA measurement results[20]. Additionally, ADA is a quick and affordable diagnostic marker for everyone who was suspected tuberculous pericarditis. What's should be pay attention to is that none of markers including ADA is specific for tuberculous pericarditis, the combination of ADA and other marker may improve the diagnostic accuracy. For example, quantitative PCR (Xpert MTBRIF) combined with ADA increased the sensitivity to 0.984 and specificity to 1. Thus, the results of ADA assays should be interpreted in parallel with clinical findings and the results of other tests.

There are several limitations that should be addressed when interpreting the results of our mate-analysis. First, we set strict inclusion criteria, exclusion of conference abstracts, reviews, editorials, case reports may bias our results. Our omission of unpublished studies, studies published in other languages and studies published in journals indexed other databases also make contribution to such bias. Second, we identified significant heterogeneity among the included studies; although we performed a meta-regression to determine possible covariates, we did not find meaningful covariates. Thus, the heterogeneity could not be fully explained by meta-regression analysis. Third, we noticed that in three of our included studies[17,22,23], there contained less than 10 tuberculous pericarditis patients, which may exist selection bias to some extent. Further studies should pay attention to this problem.

Conclusions

Based on the evidence compiled in this meta-analysis, pericardial ADA measurement is likely to be a useful diagnostic tool for tuberculous pericarditis, the results of ADA assays should be interpreted in parallel with clinical findings of patients and the results of other tests.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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