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Interferon-Gamma Release Assays for the Diagnosis of Tuberculosis: A Systematic Review and Meta-analysis

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Abstract

Background and Objective We conducted a systematic review and meta-analysis to compare the accuracy of the interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST) for the diagnosis of *Mycobacterium tuberculosis* infection.

Methods We systematically searched PubMed, Embase, Cochrane library, and Web of Science databases for relevant published studies in recent decades and calculated pooled estimated sensitivities, specificities, DOR, and SROC curve of the QFT-IT, T-SPOT and TST. Random-effects models were used to assess estimates from studies with significant heterogeneity. Moreover, area under the curve was used to evaluate the accuracy of the tests.

Results Overall, 9 studies for QFT-IT, 12 studies for T-SPOT, and 16 studies for TST involving 3586 participants were included in this analysis. We found that sensitivities of the QFT-IT, T-SPOT, and TST were respectively 0.842 (95 % CI 0.811–0.870), 0.840 (95 % CI 0.814–0.864), and 0.665 (CI 0.635–0.693); specificities were respectively 0.745 (95 % CI 0.715–0.775), 0.658 (95 % CI 0.621–0.693), and 0.633 (CI 0.605–0.661); positive likelihood ratios were respectively 3.652 (95 % CI 2.180–6.117), 2.196 (95 % CI 1.727–2.794), and 1.825 (95 % CI 1.351–2.464); negative likelihood ratios were respectively 0.212 (95 % CI 0.109–0.414), 0.246 (95 % CI 0.161–0.377), and 0.556 (95 % CI 0.385–0.804); the SROC curves were 19.205, 10.397, and 3.810.

Conclusions The two IGRAs showed better performance than TST for the diagnosis of the tuberculosis. However, neither of them showed stability in the diagnosis of TB.

Keywords Interferon-gamma release assays · Tuberculin skin test · Tuberculosis · Specificity · Diagnosis

Abbreviations

TB   Tuberculosis
TST   Tuberculin skin test
BCG   Bacille Calmette–Guérin
IGRAs   Interferon (IFN)-γ release assays
QFT-IT   Quantiferon-TB gold in-tube test

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Introduction

Tuberculosis (TB) remains a worldwide infectious disease attracting extensive attention, whose morbidity rate under persistent elevation displayed inevitable hazards. In 2013, approximately 9.0 million people developed into TB with 1.5 million deaths, 360,000 of whom were HIV positive.

The proportion of cured TB patients every year is almost constant with subtle declinations, for instance, only estimated 37 million people were cured between 2000 and 2013 ascribed to advanced and effective methods of diagnosis in conjunction with treatments (WHO) [1]. Meanwhile, tuberculosis's early diagnosis remains an intricate problem. Nowadays, tuberculin skin test (TST) is one of the most widely applied methods in major countries considering its lower cost and convenience. However, this recommended diagnostic approach has several deficiencies, such as its low specificity, cross-reactions with bacille Calmette-Guérin (BCG) vaccination, and infection of nontuberculous mycobacteria (NTM) [2]. Ample evidences have demonstrated that Interferon (IFN)-γ release assays (IGRAs) seems to be an alternative for the diagnosis of the TB. IGRAs applies proteins that are more unique and specific for *Mycobacterium tuberculosis* than the purified protein derivative (PPD) which is encoded by genes located in the region of difference 1 (RD1) among the whole *M. tuberculosis* genome. These genes are not found in the BCG substrains or the most environmental mycobacteria (apart from *Mycobacterium kansasii*, *Mycobacterium szulgai*, *Mycobacterium marinum*, and *Mycobacterium flavescens*) [3]. Several studies have depicted the relative accuracy of IGRAs, but the majority of them were just verified in one aspect, respectively, such as children's tuberculosis [4], active tuberculosis [5], and latent tuberculosis [6], which had restricted a comprehensive application of IGRAs.

Therefore, aiming to access the exact diagnostic value of IGRAs, we performed this meta-analysis to investigate the accuracy of IGRAs and determine whether IGRAs has the probability to replace the conventional diagnostic approaches.

Methods

Search Strategy

A systematic search was performed in the PubMed, Embase, Cochrane Library, and Web of Science databases in recent decades up to May 2015. The following terms were used to search for relevant investigations: "Tuberculosis/diagnosis" and "T-SPOT" or "QFT-IT" and "specificity".

Inclusion and Exclusion Criteria

Researches retrieved from the databases were first scanned through titles with abstracts, and then full-text studies were further reviewed for eligibility. The studies will be included if TB patients have been diagnosed etiologically or sufficient information such as false or true positives and negatives have been provided to construct the analysis.

The studies will be excluded by the following reasons: case reports, editorials, or animal studies; systematic review and meta-analysis; sensitivity and specificity were not reported or could not be calculated; full text were not available or published in English. Two investigators participated in the search of available references individually and they reached the consensus on each eligible study.

Data Extraction

The following data were collected: first author, publishing year, numbers of cases and controls, country of origin, individuals' characteristics, age, percent of male, percent of BCG vaccinated, percent of HIV-positive, TST reagent, cutoff for TST, percent with TST, T-SPOT, QFT-IT results, and percent of indeterminacy.

Statistical Analysis

To decrease heterogeneity, data extraction was separated by T-SPOT, QFT-IT, and TST. Indeterminate results were rejected from these studies. We used Statistical analysis I^2 and P value to describe the heterogeneity, and use correlation coefficient to determine its threshold effect. Pooled sensitivity and specificity of each assay and their 95 % confidence interval (CI) were calculated using random effects [7]. The meta-analysis was performed using Meta-DiSc and Review Manager version 5.3.
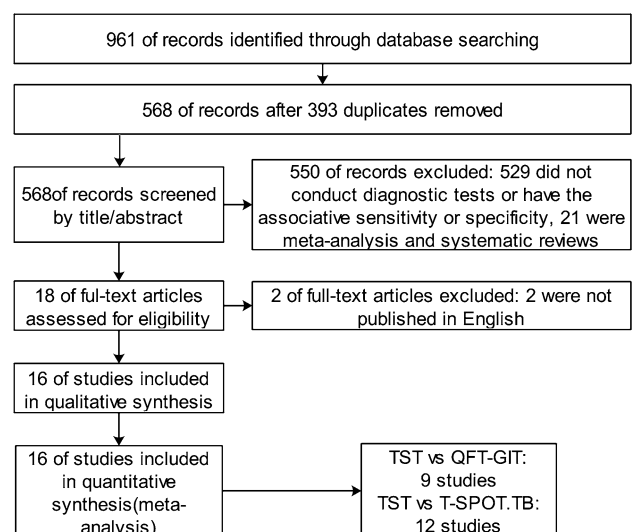

Fig. 1 Flow chart of the literature search and selection strategy

Table 1 Studies in which TST was compared with QFT-GIT (N = 9)

Study	Chung and Han [9]	Lee et al. [11]	Kabeer et al. [10]	Detjen et al. [2]	Goletti et al. [13]	Jung et al. [14]	Syed et al. [12]	Kang et al. [15]	Lee et al. [16]
Case n	54	100	177	28	216	37	177	67	87
Control n	43	43	100	45	197	74	100	77	131
Country	South Korea	Korean	India	United Kingdom	6 Different European centers	South Korea	India	South Korea	South Korea
Individual Characteristics	Tuberculous pleural effusion	Active tuberculosis Smear-negative	Active tuberculosis	Childhood tuberculosis A low incidence of tuberculosis	Active tuberculosis	Smear-negative pulmonary tuberculosis Immunocompromised patients	Active tuberculosis	Active tuberculosis	
Age case	43 (median)	22 (median)	29 (median)				37 (median)		48.0 (median)
Age control	69 (median)	21 (median)	37 (median)				29 (median)		
Age all				38 months (median)	40 (median)	64 (median)		55 (median)	
% Male	72.2	98.6	70.0	49.3	63.4	72.3		54.0	
% Bcg-vaccinated		71.3		5.5	46.0	29.9		36.0	80.7
% HIV-positive	0	0	0	0	1.7		0		0
TST reagent	0.1 mL (2 TU)	0.1 mL (2 TU)	2 TU RT23	10 U of PPD	5 U or 2 U (RT23) or 5 U of PPD	2-TU RT23	2-TU RT23	2-TU RT23	2TU PPD RT23
Cutoff for TST (mm)	≥10	≥10	≥10	≥15	≥10	≥10	≥10	≥10	≥10
% with TST results	100	99.3	98.6	100	100	90.0	76.9	100	100
% with QFT-GIT results	85.6	100	99.3	90.6	45.8	64.7	99.3	99.3	100
% Indeterminate	14.4	3.5	1.4	6.8	2.6	1.3		3.5	0

BCG bacille Calmette-Guérin; TST tuberculin skin test; QFT-IT quantiferon-TB gold in-tube test

Table 2 Studies in which TST was compared with QFT-GIT (N = 12)

Study	Detjen et al. [2]	Goletti et al. [13]	Jung et al. [14]	Kang et al. [15]	Lee et al. [16]	Ball et al. [17]	Dilektasli et al. [3]	Fei et al. [18]	Feng et al. [19]	Simsek et al. [20]	Yu et al. [21]	Zhong et al. [22]
Case n	28	216	37	67	87	18	34	83	75	47	46	13
Control n	45	197	74	77	131	90	57	52	107	89	74	10
Country	United Kingdom	6 European centers	South Korea	South Korea	South Korea	France	Ataturk	China	China	Ataturk	China	China
Individual	Childhood tuberculosis	Active tuberculosis	Smear-negative tuberculosis	Active tuberculosis	Tuberculosis	Uveitis tuberculosis		Laryngeal tuberculosis	Active tuberculosis	Active and latent tuberculosis	Active tuberculosis	Breast tuberculosis
Characteristics	A low incidence of tuberculosis		Immuno-compromised patients			Consecutive non-immuno-compromised					HIV-infected	
Age case					48.0 (median)			47.1 (mean)	41 (median)		40.2 (mean)	35.4 (mean)
Age control								48.3 (mean)	51 (median)		40.7 (mean)	30.1 (mean)
Age all	38 months (median)	40 (median)	64 (median)	55 (median)		49.4 (mean)	36.7 (mean)		52 (median)		40.5 (mean)	
% Male	49.3	63.4	72.3	54.0		80.0		63.0	47.8		91.7	0
% BCG-vaccinated	5.5	46.0	29.9	36.0	80.7	85.2	93.4			91.9		
% HIV-positive	0	1.7			0				0		100	0
TST reagent	10 U of PPD	5 U of PPD	2-TU RT23	2-TU RT23	2TU PPD RT23	0.1 mL	5 TU of PPD	5 TU of PPD	5TU of PPD	5TU of PPD-S	5TU of PPD-S	5 TU of PPD
Cutoff for TST (mm)	≥15	≥10	≥10	≥10	≥10	≥10	≥15	≥5	≥10	≥15	≥5	≥5
% with TST results	100	100	90.0	100	100	100	100	100	70.9	69.1	96.7	100
% with T-SPOT results	90.6	45.8	64.7	97.9	100	100	96.7	100	80.5	69.1	100	100
% Indeterminate	6.8	2.6	1.3	3.0	0	0	3.4	0	7.5		0	0

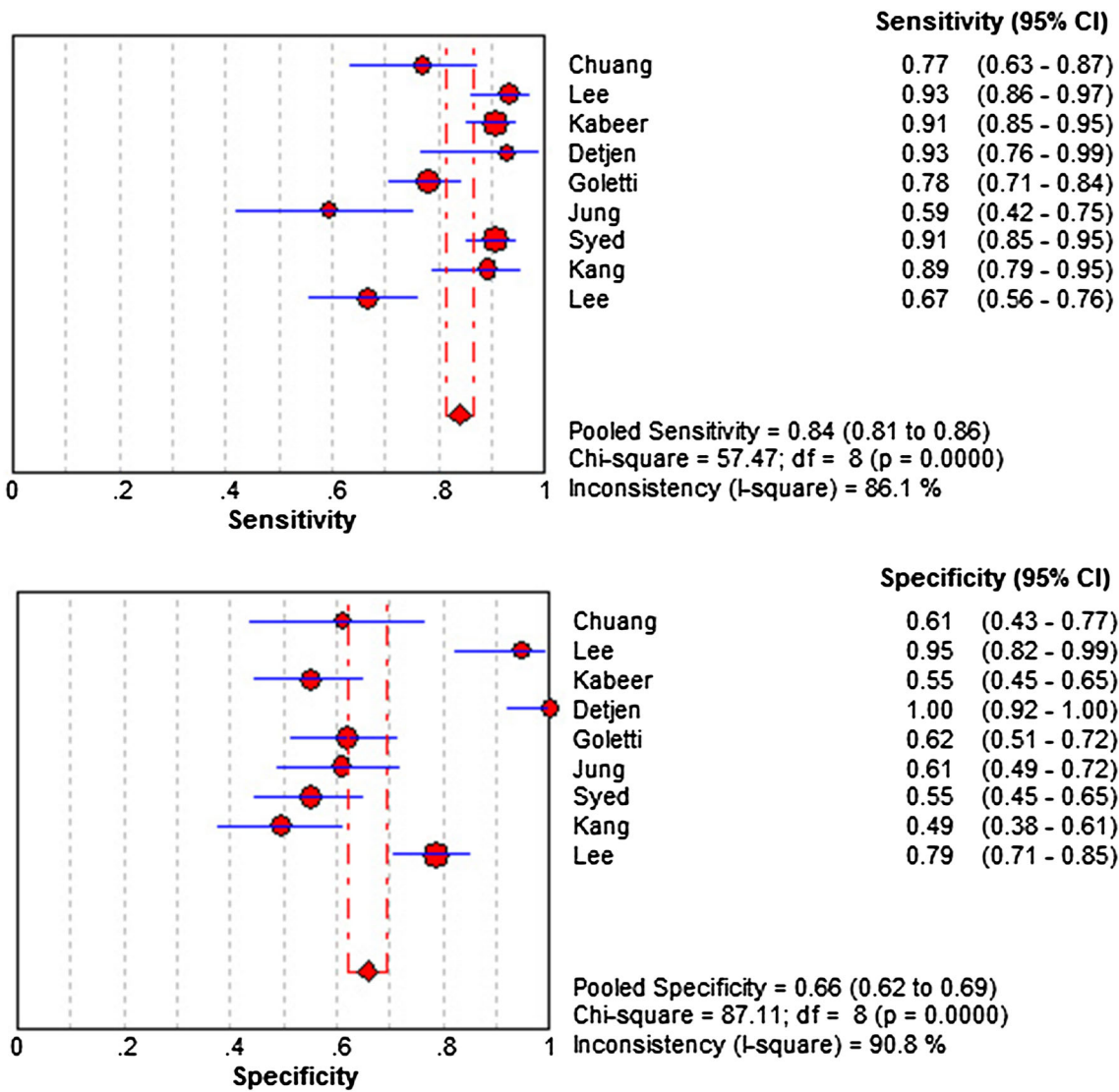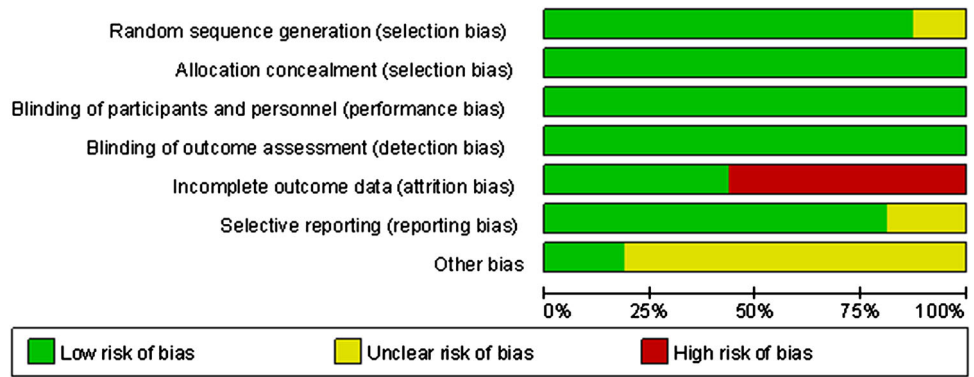**Fig. 2** Risk of bias graph included in the meta-analysis

Fig. 3 Sensitivity and specificity of the QFT-IT

Quality Assessment

The risk of bias table, which consists of seven domains covering (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias, was used to access the inclusive studies' risk of bias considering a total

Fig. 4 DOR and SROC curve of the QFT-IT
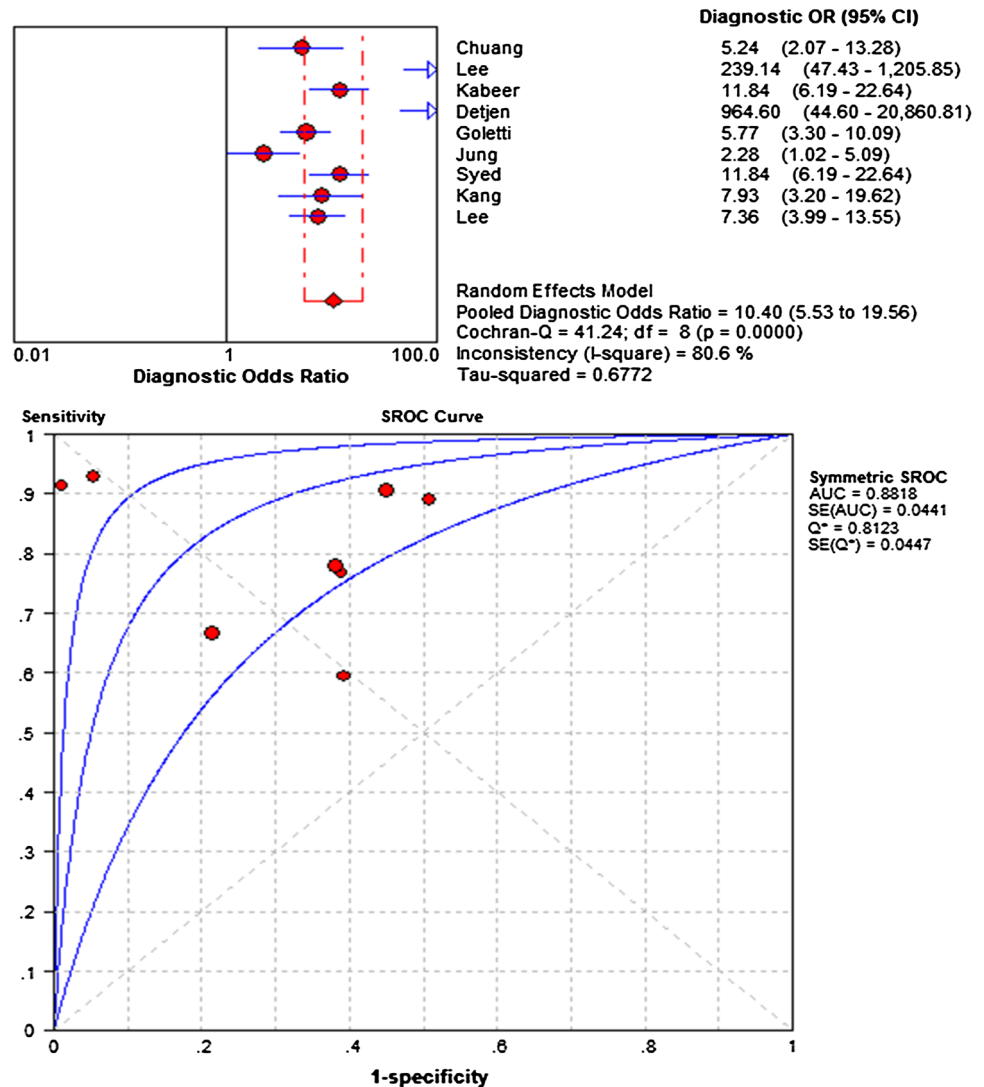
of five aspects, including the selection bias, the performance bias, the detection bias, the attrition bias, and the reporting bias. The risk of bias was finally judged as "low," "high," or "unclear" according to the answers of the signaling questions. The "unclear" category was used only when insufficient data were reported [8].

Results

Characteristics of the Studies

The search and selection process is described in Fig. 1. A total of 961 studies were found through retrieval, except for 393 duplications. In the remaining 568 studies, 529 did not conduct diagnostic tests or have the associative sensitivity or specificity, and 21 were meta-analysis and systematic reviews. Consequently, after further excluding 2 studies not

published in English, a total of 16 studies were available as full texts for the final analysis [2, 3, 9–22]. Furthermore, among the 16 studies, 4 made comparison between QFT-IT and TST including 1855 participants, 7 compared T-SPOT and TST including 1731 participants, and the other 5 studies distinguished TST and T-SPOT from QFT-IT. All of these studies were representative in which a total of 3586 participants took part in the present analysis (Tables 1, 2). The risk of bias is shown in Fig. 2, with the incomplete outcome data locating in the high risk of bias and other bias under relatively low risk.

Sensitivity and Specificity of Interferon-γ Release Assays

We identified 9 studies correlated with QFT-IT, and the pooled sensitivity and specificity in diagnosis were 0.840 (95 % CI 0.814–0.864) and 0.658 (95 % CI 0.621–0.693),
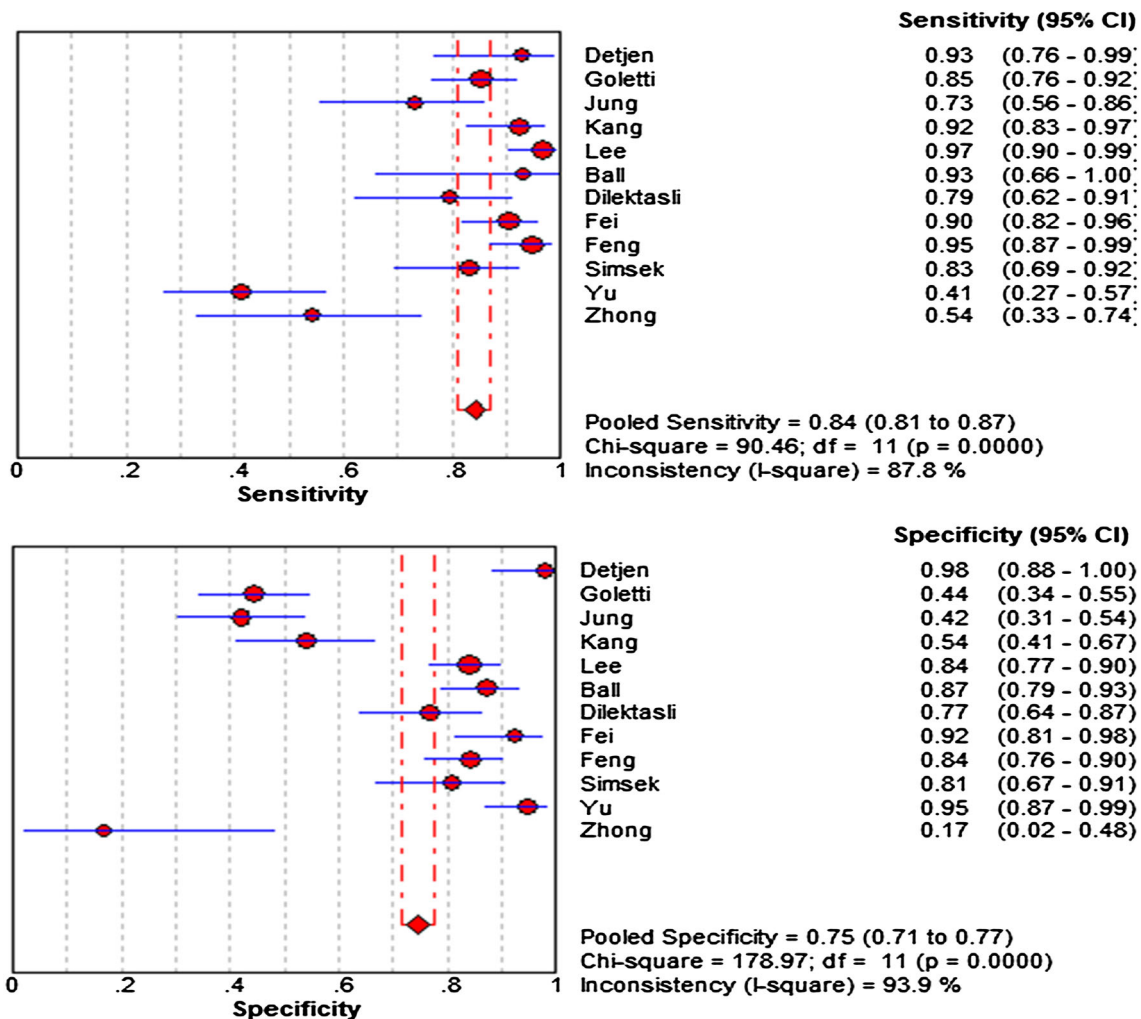
Fig. 5 Sensitivity and specificity of the T-SPOT

respectively (Fig. 3). The positive likelihood ratio, negative likelihood ratio, and pooled DOR of QFT-IT for the diagnosis of TB were 3.652 (95 % CI 2.180–6.117), 0.212 (95 % CI 0.109–0.414), and 10.397 (95 % CI 5.527–19.560) (Fig. 4), respectively. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and pooled DOR of the T-SPOT were 0.842 (95 % CI 0.811–0.870), 0.745 (95 % CI 0.715–0.775), (Fig. 5), 2.196 (95 % CI 1.727–2.794), 0.246 (95 % CI 0.161–0.377), and 19.205 (95 % CI 7.049–52.326) (Fig. 6).

## Sensitivity and Specificity of the Tuberculin Skin Test

Sixteen studies were identified to describe the tuberculin skin test. The meta-analytic estimate for sensitivity and specificity were 0.665 (CI 0.635–0.693) and 0.633 (CI 0.605–0.661) (Fig. 7). In addition, the positive likelihood ratio, negative likelihood ratio, and pooled DOR of the TST were 1.825 (95 % CI 1.351–2.464), 0.556 (95 % CI 0.385–0.804), and 3.810 (95 % CI 1.837–7.902) in Fig. 8.

SROC Curve of Interferon-γ Release Assays and the Tuberculin Skin Test

Area under the curve (AUC) was adopted to measure the accuracy of the tests. SROC curve of Interferon-γ release assays and the tuberculin skin test are shown in Figs. 6, 7, and 8. The AUC of the QFT and T-SPOT were 0.8818 and 0.9006, which were significantly higher than 0.7301 which was the AUC of the TST. From the SROC curve, we came to the assumption that all of the three methods might have a threshold effect. The analysis of diagnostic threshold of the QFT, T-SPOT and TST are conveyed in Figs. 6, 7, and 8. Their spearman correlation coefficients were, respectively,

Fig. 6 DOR and SROC curve of the T-SPOT
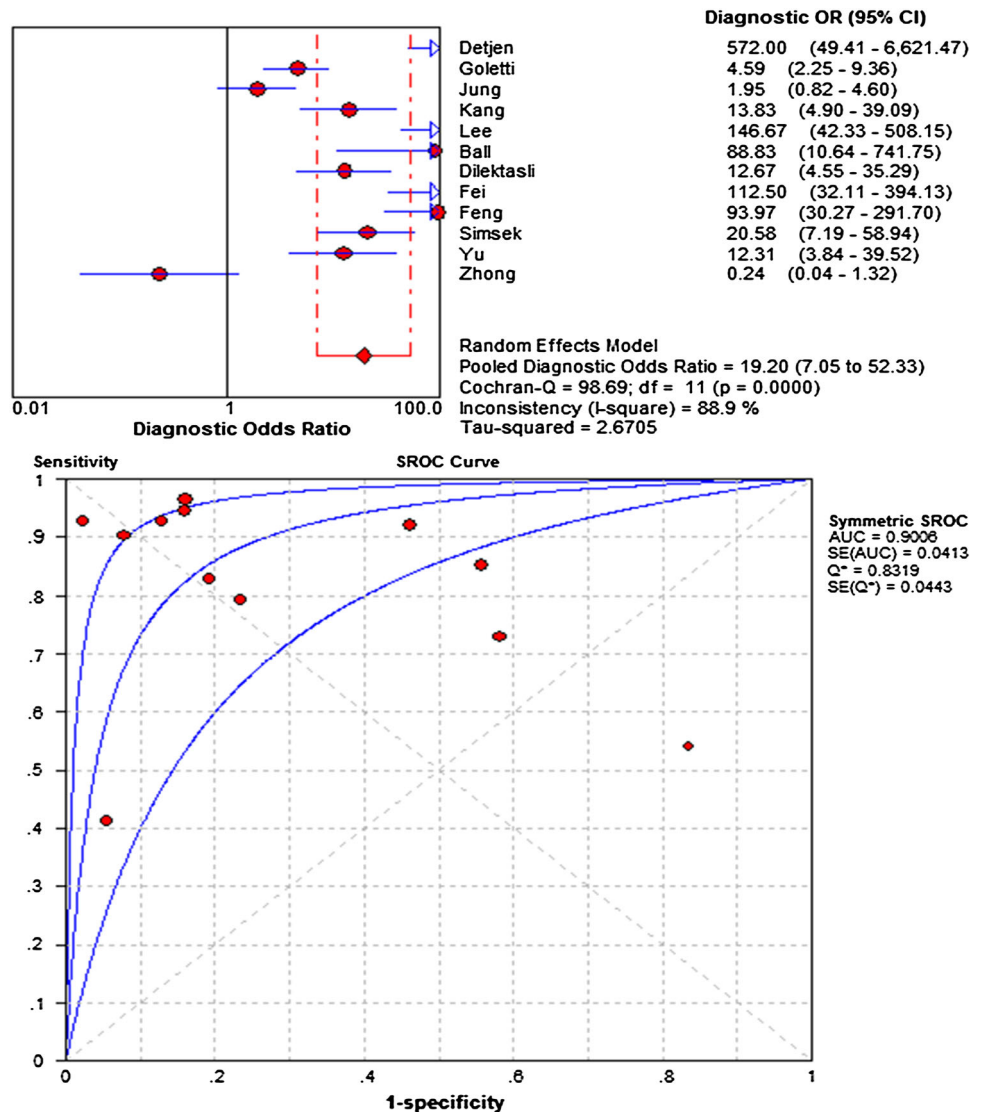
-0.375, -0.227, and -0.063, which proved the hypothesis that all the three methods had a threshold effect.

Discussion

This meta-analysis aimed to inquire the accuracy of IGRAs, which was witnessed as an accurate diagnostic method for latent and active TB, considering its unique preponderance. The summary results, as derived from 16 studies, indicated that both the sensitivity and the specificity of the IGRAs were significantly higher than those of the conventional TST. Moreover, the DOR of the TST was signally lower than the IGRAs, which meant the IGRAs had distinctly higher diagnostic value than TST. Besides, the reported TST sensitivity fluctuated between 0.258 and 1.000, with its specificity ranging from 0.336 to 0.919,

while the sensitivity of the T-SPOT ranged from 0. 557 to 0.929, with its specificity were from 0.493 to 1.000. Hence, these results accounted for the better accuracy of IGRAs, although the outcomes were a little bit unsteady.

Through sub-analysis, we found that young adults, latent tuberculosis, TB patients with immunodeficiency, and TB patients with concurrent HIV infection may explain their stability [23–26] of data.

Because of the discontinuation of BCG mass vaccination in countries with a low incidence of TB, there has been an increase in NTM infection [27, 28], from which TST fails to distinguish NTM infection. However, IGRAs has a propensity for discriminating cross-reactivity induced by nontuberculous mycobacteria from bacille Calmette–Guérin vaccination, which demonstrates its superior capability of reducing over-diagnosis of TB and guiding clinical management.
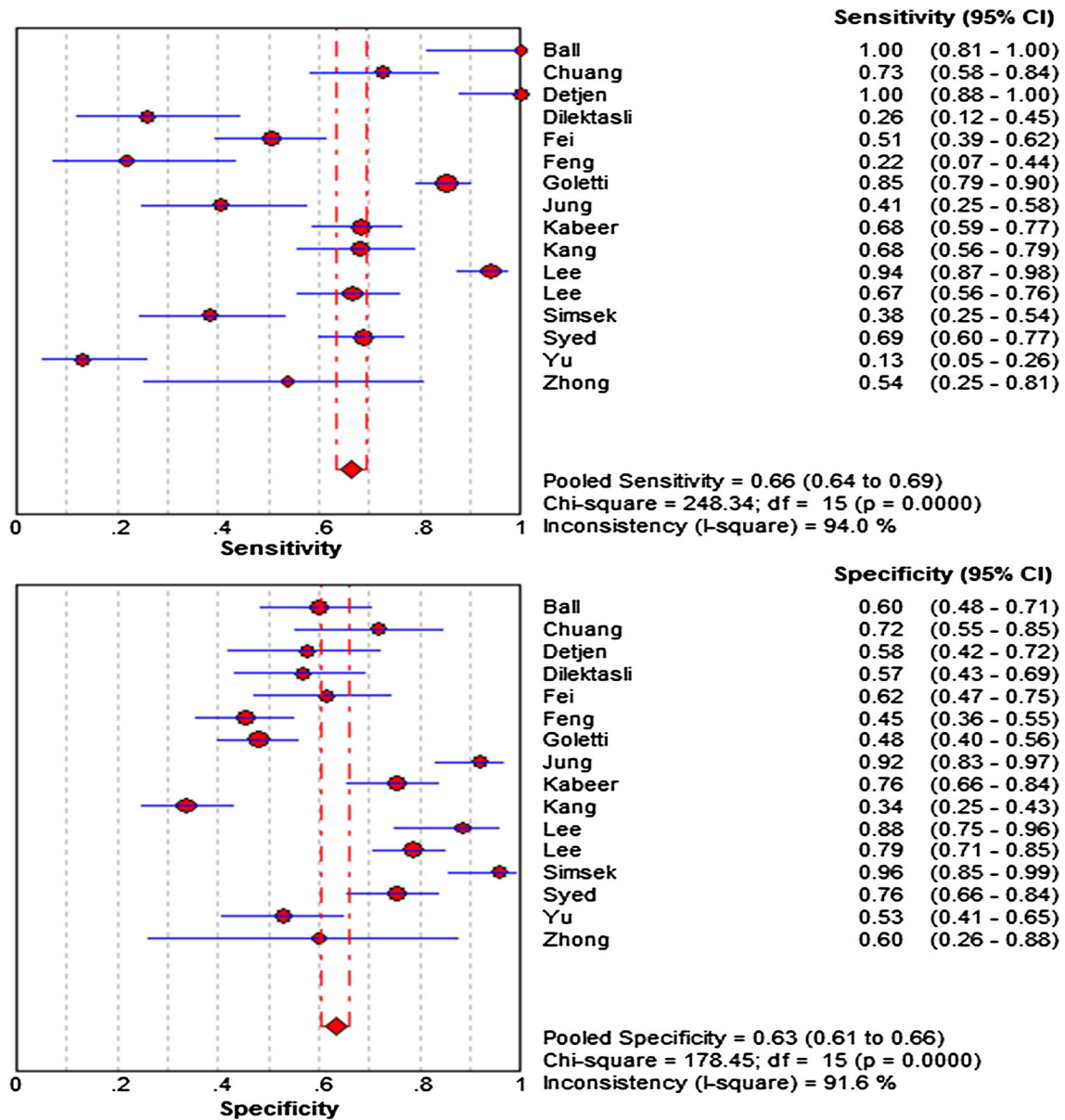
Fig. 7 Sensitivity and specificity of the TST

As a fact that about one-third people in the world have been infected by *M. tuberculosis* in which estimated 2 billion people under latent tuberculosis infection (LTBI) have a 10 % lifetime risk of developing active TB [29], there is an urgent need to develop the golden standard of early LTBI's diagnosis to solve the problems separating the LTBI from the ATB. Although increasing studies has demonstrated that the IGRAs promoted diagnosing LTBI because of its better specificity [20], there is no doubt that the false-positive rate is still high, which may lead to abundant unnecessary treatments resulting in drug resistance. So more researches are needed to be conducted to evaluate the value of the diagnosis of IGRAs.

The risk of tuberculosis (TB) in patients with an immunocompromised medical condition is greater than that in the general population [30]. Several studies conducted in South Korean populations have manifested that IGRAs had a predominant diagnostic sensitivity in active TB patients who were immunosuppressed [31–33]. The sensitivity of the T-SPOT was 0.720 (95 % CI 0.542–0.862), which was far higher than the TST (0.423), while the specificity of the T-SPOT was 0.423 and the specificity of the TST was 0.918. T-SPOT's low specificity could make it insufficient to rule out TB disease, and the TST's low sensitivity made it fail to rule in TB disease. So when referring to the immunocompromised TB patients,

Fig. 8 DOR and SROC curve of the TST
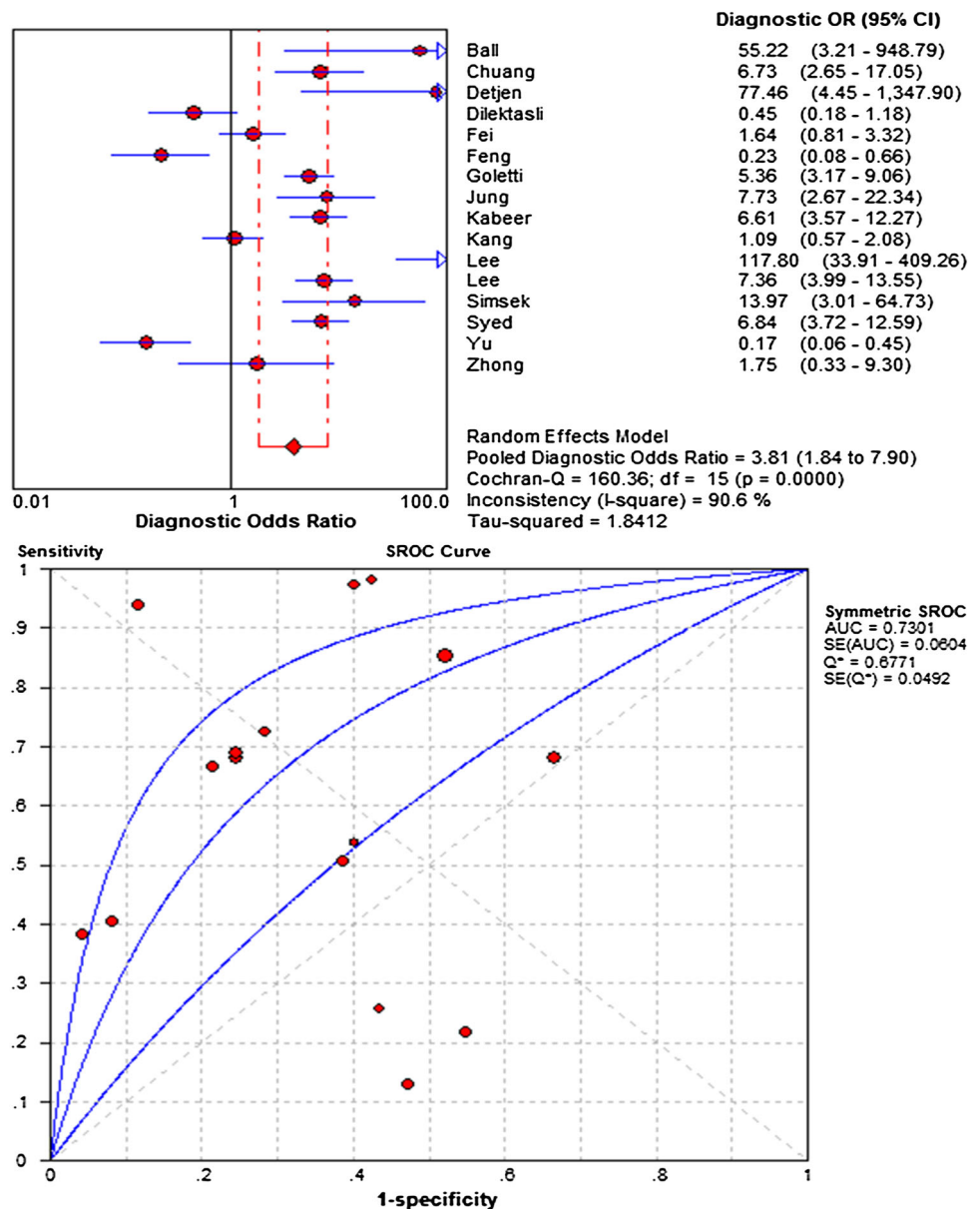
IGRAs might replace T-SPOT or TST for a definite diagnosis.

Besides, it is difficult to detect tuberculosis infections in HIV-infected patients, since the decreased number of CD4+ and CD8+ cells in their immune system brings about immune escape [34]. In this study, the sensitivity of the T-SPOT was 0.413 (95 % CI 0.354–0.488), which might be inaccurate due to different microenvironments in patients with other latent diseases or diverse received treatments. This was also far lower than the pooled sensitivity of 72 % in low/middle-income countries in a meta-analysis [35]. Another limitation of IGRA testing among HIV-infected patients was the rate of indeterminate results. Previous reports from the UK described indeterminate T-SPOT results in 2–7.4 % of HIV-infected patients [36–38]. However, in this study, it had not been found. As to TST, it failed to be a diagnostic method for the TB patients infected by HIV taken its sensitivity of 12.9 % into consideration.

In conclusion, IGRAs showed a superior capability than the TST to be a diagnostic approach for the tuberculosis because of its far higher sensitivity and specificity contributing to tell the TB patients apart. Also, its higher DOR and accuracy made it a valid alternative to the TST. However, neither the IGRAs nor the TST revealed ideal stability, which led to their restricted use. Furthermore, both of their costs and trauma should be considered. So we finally concluded that without a better precise

diagnosis, the IGRAs could be a priority option to detect TB patients.

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