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REVIEW

Latent tuberculosis infection in transplant candidates: a systematic review and meta-analysis on TST and IGRA

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Abstract

Introduction The diagnostic accuracy of interferon-gamma release assays (IGRAs) and the tuberculin skin test (TST) for latent tuberculosis infection (LTBI) in transplant candidates is uncertain.

Methods Pubmed, Embase and Cochrane library were searched to identify relevant studies. Quality of included studies was assessed with RevMan5 software (via GUADAS2 checklist). Accuracy measures of IGRAs and TST assays (sensitivity, specificity and others) were pooled with random effects model. Data were analyzed by STATA and Meta-DiSc.

Results Twenty-eight studies were selected for full review, and 16 were included in the final analysis. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) for TST were 46% [95% confidence interval (CI) 38–54%], 86% (95% CI 75–93%), 46.3% (95% CI 40–52), 88.7% (95% CI 87–89), 3.3 (95% CI 1.6–6.4), 0.63 (95% CI 0.52–0.77) and 5 (95% CI 2–12), respectively. For QFT-G, the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 58% (95% CI 41–73%), 89% (95% CI 77–95%), 72.7% (95% CI 68–76), 80.6% (95% CI 78–82), 5.3 (95% CI 2.0–14.0), 0.47 (95% CI 0.30–0.75) and 11 (95% CI 3–46), respectively. Likewise, for T-SPOT.TB, the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 55% (95% CI 40–70%), 92% (95% CI 87–95%), 60.4% (95% CI 47–72), 90.2% (95% CI 86–92), 6.7 (95% CI 4.0–11.1), 0.52 (95% CI 0.31–0.85) and 16 (95% CI 7–37), respectively.

Conclusions IGRAs were more sensitive and specific than the TST with regard to the diagnosis of LTBI in the transplant candidates. They have added value and can be complementary to TST.

Keywords Latent tuberculosis infection (LTBI) · Interferon-gamma release assays (IGRAs) · Tuberculin skin test (TST) · Transplantation

Introduction

Tuberculosis (TB) is the leading cause of death from infectious diseases worldwide. Approximately one-third of the global population is latently infected by *M. tuberculosis* (LTBI) [1]; 5–15% will develop active TB during their lifetime [2]. The risk of disease is significantly higher in some population groups (i.e., transplant patients) [2–5]. The estimated TB incidence rate of this population group is 20–70 times higher than that of the general population, with a mortality rate of up to 30% [5, 6]. TB disease usually occurs for the reactivation of a LTBI [5], whose probability depends on the degree of their immunologic impairment [7, 8]. TB occurrence can be avoided with an accurate and timely LTBI diagnosis and therapy, but this approach can be hampered by limitations in the diagnostic accuracy of available

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diagnostic tests for LTBI [9–11]. World Health Organization (WHO) recommends interferon-gamma release assays (IGRAs) or tuberculin skin test (TST) to diagnose LTBI [2]. Utility of the TST is limited by poor specificity in BCG-vaccinated people and in those living in high-TB incidence countries [12]. Recently, Interferon-Gamma Release Assays (IGRAs), which measure the interferon-gamma released by sensitized T cells after in vitro stimulation with *M. tuberculosis* antigens, were developed to improve the specificity shortcomings of TST [12]. Several studies, including systematic reviews and meta-analyses, evaluated the usefulness of IGRAs and TST in immunocompromised adults (e.g., persons infected with HIV, patients with end-stage kidney disease and receiving hemodialysis, etc.) [13–15]. However, IGRA and TST diagnostic accuracy is poorly known in transplant candidates. Therefore, we carried out a systematic review and meta-analysis to assess the accuracy of TST and IGRAs for the diagnosis of LTBI in this population group.

Methods

Search strategy

A systematic search was carried out in PubMed, Embase, and Cochrane library from January 2000 to May 2018 for studies in which TST and/or IGRA (T-SPOT.TB, QFT-GIT, or both) were performed in transplant candidates. The search strategy was based on a combination of key terms, such as "tuberculin skin test", "TST", "interferon-γ assay", "quantiferon", "IGRA", "ELISPOT", "T-Spot", "transplant", "tuberculosis", ''latent tuberculosis infection'', ''LTBI'' and "TB". Lists of references of selected articles and relevant review articles were hand-searched to identify further studies. Only studies written in English were selected.

Study selection

Two reviewers (MJN and AP) independently performed the review of titles and abstracts and chose those fitting selection criteria for full-text evaluation. Discrepancies were discussed with a third reviewer (MM). Inclusion criteria were the following: test accuracy referred to LTBI, and TST and IGRAs (QFT-GIT and T-SPOT.TB) used with standard cut-offs for positive test results for TST; according to the national guidelines, a test was considered positive if there was ≥ 5 mm or ≥ 10 mm of induration at 48–72; for QFT-GIT (Cellestis, Australia), a result of ≥ 0.35 IU/mL of IFN-g in the TB antigen tube minus the negative control tube was considered a positive result; and for T-SPOT.TB, interpretation of test results was according to the criteria defined by the manufacturer used in the studies (Oxford Immunotec, UK). As there is no gold standard to ascertain LTBI, two separate populations were selected to estimate sensitivity (individuals with high risk of TB) and specificity (healthy low-risk individuals) [14, 16, 17]. Participants with any previous TB contact or with history of TB or with previous radiologic evidence or with abnormal chest radiograph consistent with TB or residing in a country with a high TB burden were assigned as high risk for LTBI [16, 18].

The following articles were excluded: studies focused on active TB; use of assays other than QFT-GIT or T-SPOT.TB, case reports, reviews and editorials.

Data extraction and quality assessment

The following variables were extracted: first author; year of publication; study duration, type of study, country/ies where the study was conducted; number of transplant candidates; age; gender; Bacillus Calmette–Guérin (BCG) vaccination status; HIV/AIDS status; previous active TB; history of previous contact with a TB case, type of transplantation the candidates are going to receive, TST and IGRAs cut-off values; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) of TST and IGRAs and comorbidities. Data were independently collected by two authors (MJN, SZ).

Study quality and risk of bias were assessed with Review Manager 5 (RevMan) version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) based on quality assessment of diagnostic accuracy studies-2 (QUADAS-2) [19]. This tool consists of four domains: patient selection, index test, reference standard, and flow and timing.

Data synthesis and analysis

The sensitivity was defined as the number of true positives divided by the sum of true positives and false negatives. The specificity was defined as the number of true negatives divided by the sum of true negatives and false positives. As there is no gold standard to ascertain LTBI, studies on sensitivity included individuals recruited in high-TB incidence countries and settings where the population has a highest risk of being infected, and there is suspicion or evidence of LTBI or prior TB [18]. The PPV is defined as the number of true-positive test results divided by the sum of true- and false-positive results. This value reflects a test's ability to correctly predict that an LTBI score-positive individual is at the risk of developing active TB in later life. The NPV was defined as the number of true-negative test results divided by the sum of true- and false-negative results. The NPV measures the degree to which a test does not score a person infected with *M. tuberculosis* as score negative, i.e. the certainty that a score-negative person does not have LTBI [18]. The PLR is calculated as sensitivity/(1 − specificity),

whereas the NLR is calculated as (1 − sensitivity)/specificity. A clinically useful test shows a PLR > 5.0 and a NLR < 0.2. DOR is calculated as PLR/NLR [20].

Pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR with 95% confidence intervals were calculated for each test. The Cochrane Q test and I^2 statistic values were used to assess heterogeneity for the pooled estimates [21]. To explore sources of studies' heterogeneity, sensitivity analyses were carried out with meta-regression and subgroup analysis. Publication bias was assessed with the Deeks regression model [22]. The summary receiver operating characteristic (SROC) curve was constructed based on a bivariate regression approach. All statistical analyses were performed with STATA (version 14 IC; Stata Corporation, College Station, TX, USA) and Meta-DiSc 1.4 for Windows (Cochrane Colloquium, Barcelona, Spain).

Results

A total of 381 articles were screened for analysis but only 16 studies met the inclusion criteria [8, 23–37]. Figure 1 shows the selection process. Characteristics of the included studies are described in Table 1. They were conducted in nine different countries: Korea was the most frequently represented country (3 out of 16, 18.8%). The majority of studies (15 out of 16, 93.8%) were carried out prospectively for an average length of 15 months; all of them evaluated only suspected adults. The sample size ranged from 48 to 735 individuals enrolled per study.

Quality assessment

Based on QUADAS-2 tool (Fig. 2), included studies had a low risk of bias.

Test accuracy

Nine published studies evaluated the IGRAs and/or TST sensitivity and specificity in a total of 2023 subjects (Table 2). The pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR for TST were 46% [95% confidence interval (CI) 38–54%], 86% (95% CI 75–93%), 46.3% (95% CI 40–52), 88.7% (95% CI 87–89), 3.3 (95% CI 1.6–6.4), 0.63 (95% CI 0.52–0.77) and 5 (95% CI 2–12), respectively. For QFT-G, the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 58% (95% CI 41–73%), 89% (95% CI 77–95%), 72.7% (95% CI 68–76), 80.6% (95% CI 78–82), 5.3 (95% CI 2.0–14.0), 0.47 (95% CI 0.30–0.75) and 11 (95% CI 3–46), respectively. Likewise, For T-SPOT.TB, the pooled sensitivity, specificity, PPV, NPV, PLR, NLR, and DOR were 55% (95% CI 40–70%), 92% (95% CI 87–95%), 60.4% (95% CI 47–72), 90.2% (95% CI 86–92), 6.7 (95% CI 4.0–11.1), 0.52 (95% CI 0.31–0.85) and 16 (95% CI 7–37), respectively.

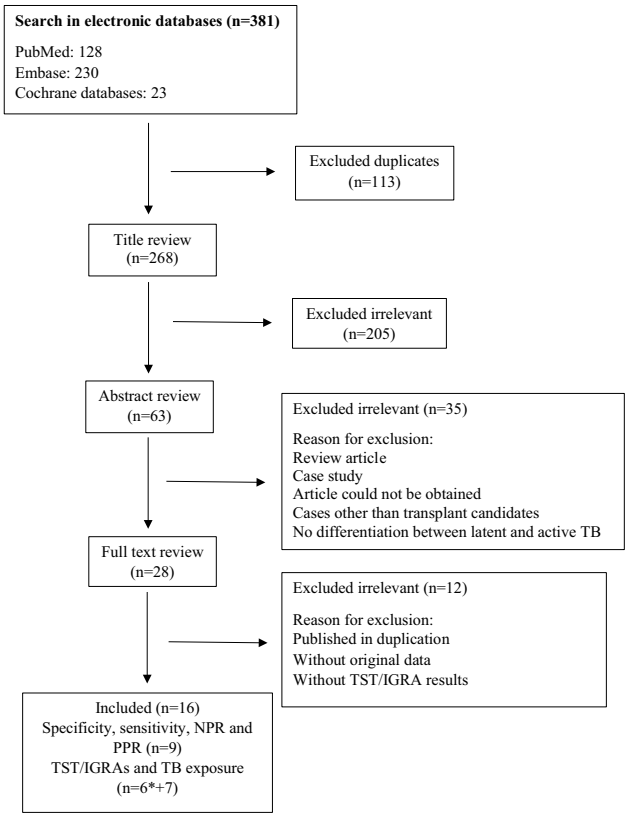


Fig. 1 Flowchart of study selection for inclusion in the systematic review and meta-analysis. Asterisk indicates these studies were also used for specificity and sensitivity

As shown in Figs. 3 and 4, in-between study heterogeneity was found. Sample size resulted as a significant source of heterogeneity in TST studies. Additionally, the Deeks regression model did not show potential publication bias. The pooled sensitivity and specificity of IGRAs were higher in comparison with those recorded for TST. SROC shows summary of test performance, visual assessment of threshold effect, and heterogeneity of data in ROC space between sensitivity and specificity. The area under the curve (AUC) of TST and IGRAs was found to be 0.52 and 0.80, respectively (Figs. 5, 6).

Association of IGRAs and the TST with *M. tuberculosis* exposure and BCG vaccination

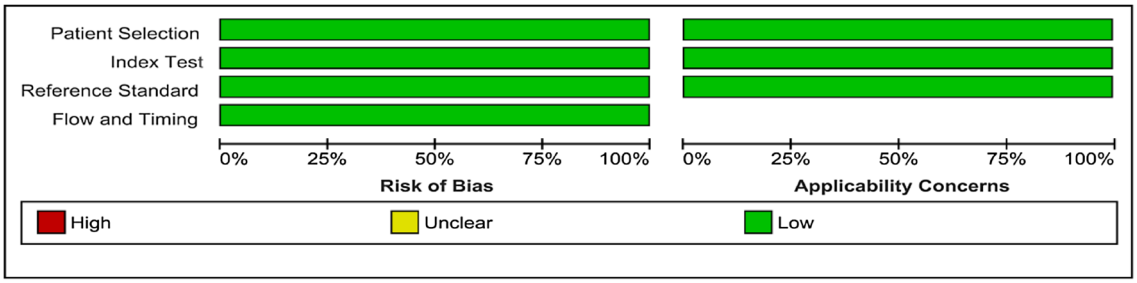
13 studies assessed the influence of BCG vaccination and/or *M. tuberculosis* exposure on tests positivity [8, 27, 30–40]. Only in 2 (15.4%), IGRAs/TST positivity was associated with *M. tuberculosis* exposure. Furthermore, there was generally a poor agreement between IGRA and TST results (Table 3).

Table 1 Characteristics of included studies

First author	Country	TB rate[a]	Publication year	Duration of study	Type of study	Type of transplant candidates	Number of transplant candidates	Age (mean)	Male %	BCG vaccination %	Diagnostic assays
Manuel	Canada	5.5	2007	2006–2007	Prospective	Liver	153	54	79	82	QFT-GIT and TST
Kim	Korea	70	2010	2008–2009	Prospective	Kidney	209	42	56	78	IGRAs only
Ahmadinejad	Iran	14	2012	2008–2011	Prospective	Liver/kidney	164	40	54	92	QFT-GIT and TST
Mansour	Egypt	13	2012	2010–2011	Prospective	Liver	97	56	75	NR	QFT-GIT and TST
Theodorpoulos	USA	3.1	2011	2008–2009	Prospective	Liver/Kidney	735	58	60	NR	IGRAs only
Lindemann	Germany	7.5	2009	2004–2007	Prospective	Liver	48	54	56	30	IGRAs only
Casas	Spain	10	2011	2008–2010	Prospective	Liver	95	56	76	31	QFT-GIT and TST
Kim	Korea	70	2013	2009–2012	Prospective	Kidney	102	44	62	NR	IGRAs only
Jafri	USA	3.1	2011	2004–2008	Retrospective	Liver	420	52	61	NR	QFT-GIT and TST
Edathodou	Saudi Arabia	10	2017	2008–2013	Prospective	Kidney	241	45	59	NR	QFT-GIT and TST
Mardani	Iran	14	2014	2011–2012	Prospective	Lung/heart	55	37	85	100	QFT-GIT and TST
Moon	Korea	70	2012	2009–2011	Prospective	Hematopoietic stem cell	244	47	56	82	QFT-GIT and TST
Qin	China	63	2013	2011–2013	Prospective	Hematopoietic stem cell	295	37	61	NR	T-SPOT.TB and TST
Richeldi	Italy	6.9	2009	2006–2007	Prospective	Liver	120	53	70	3	T-SPOT.TB, QFT-GIT and TST
Sester	Germany	7.5	2014	2008–2011	Prospective	Solid organ	145	56	58	NR	T-SPOT.TB, QFT-GIT and TST
Sherkat	Iran	14	2014	2010–2011	Prospective	Kidney	44	44	34	27	T-SPOT.TB and TST

NR Not reported

[a]Rates are per 100,000 population (Global tuberculosis report 2018)



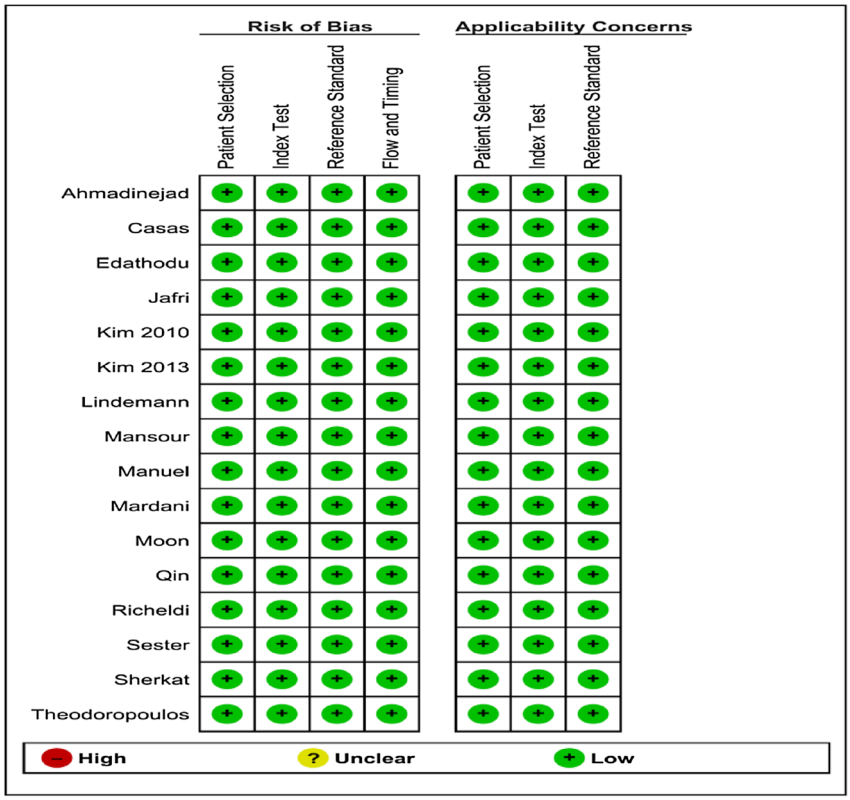


Fig. 2 Summary of QUADAS-2 assessments of included studies. Patient selection: describes methods of patient selection; index text: describes the index test and how it was conducted and interpreted; reference standard: describes the reference standard (gold standard test) and how it was conducted and interpreted; flow and timing: describes any patients who did not receive the index tests or reference standard or who were excluded from the 2×2 table, and describes the interval and any interventions between index tests and the reference standard [19]

Discussion

Pre-transplant LTBI screening is recommended with either TST or IGRAs [36, 41–44]. Screening for LTBI allows the administration of preventive therapy to persons at highest risk of active TB [45, 46]. However, to date, the diagnostic accuracy of these assays in transplant candidates has not been entirely investigated.

The key finding of this systematic review is that the pooled sensitivity and specificity of IGRAs was higher than that of TST. Thus, the inclusion of IGRA in screening algorithms could lead to fewer missed cases of LTBI and, therefore, a lower risk of developing active TB. The lower specificity of TST means more false-positive results, resulting in more unnecessary treatments, and, thus, potentially more side effects and costs [47, 48].

TST is non-invasive, inexpensive, and widely available, but its limitations are well recognized [45]. False-positive results in individuals with prior BCG vaccination or infected with nontuberculous mycobacteria can occur [49, 50]. False-negative results can also occur in immunocompromised people [14].

Table 2 Sensitivity and specificity for latent tuberculosis infection (LTBI) diagnosis in transplant candidates tested by IGRAs and/or TST assays

Study (first author, publication year)	Country	Subjects assigned as high risk for tuberculosis infection	Subjects assigned as low risk for tuberculosis infection	Assays test	Rounded sensitivity of IGRA(s)/TST % (95% CI)	Rounded specificity of IGRA(s)/TST % (95% CI)
Manuel, 2007	Canada	69	84	QFT-GIT/TST	35.0 (24.0–48.0)/42.0 (30.0–55.0)	88.0 (79.0–94.0)/90.0 (82.0–96.0)
Kim, 2010	Korea	39	170	T-SPOT.TB/TST	63.0 (45.0–79.0)/54.0 (37.0–70.0)	90.0 (85.0–94.0)/89.0 (84.0–94.0)
Ahmadineja, 2012	Iran	11	153	QFT-GIT/TST	36.0 (11.0–69.0)/27.0 (6.0–61.0)	81.0 (74.0–87.0)/85.0 (78.0–90.0)
Mansour, 2012	Egypt	10	87	QFT-GIT/TST	60.0 (26.0–88.0)/20.0 (3.0–56.0)	78.1 (68.0–86.0)/80.0 (71.0–88.0)
Theodorpoulos, 2011	USA	330	405	QFT-GIT	65.0 (60.0–71.0)	93.0 (90.0–95.0)
Lindemann, 2009	Germany	12	36	T-SPOT.TB	33.0 (10.0–65.0)	100.0 (90.0–100.0)
Casas, 2011	Spain	60	35	QFT-GIT/TST	45.0 (32.0–58.0)/45.0 (32.0–58.0)	57.0 (39.3–74.0)/51.0 (34.0–69.0)
Kim, 2013	Korea	6	96	QFT-GIT	83.0 (36.0–100.0)	99.0 (94.0–100.0)
Jafri, 2011	USA	6	414	QFT-GIT/TST	100.0 (54.0–100.0)/100.0 (54.0–100.0)	95.0 (93.0–97.0)/95.0 (88.0–98.0)

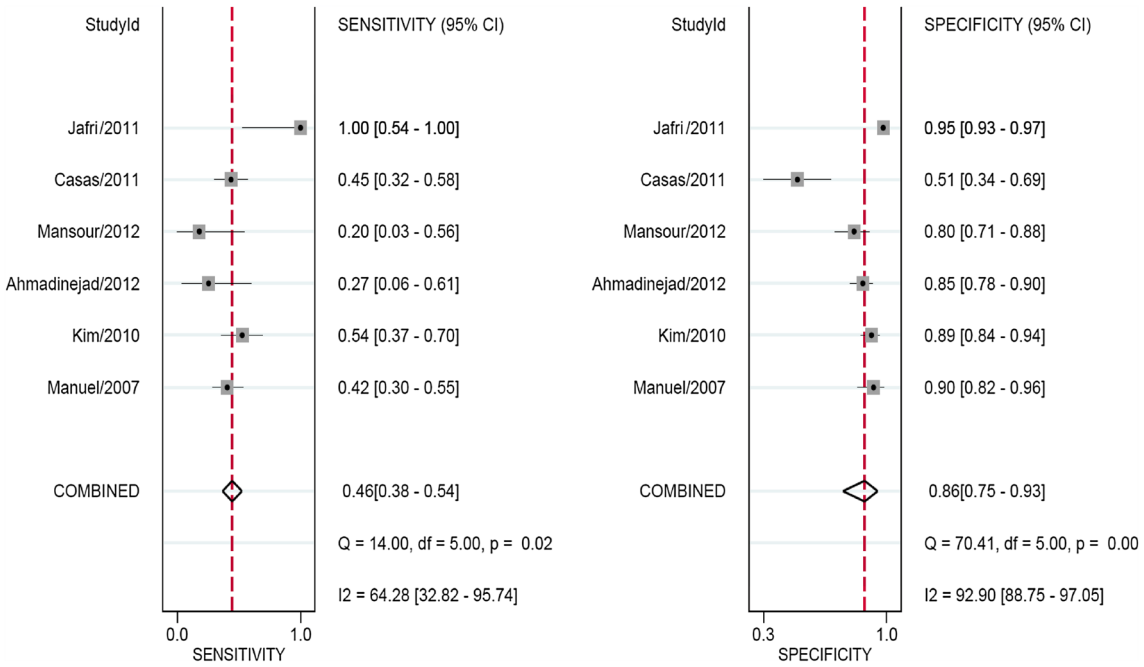


Fig. 3 Paired forest plots of pooled sensitivity and specificity of TST for the diagnosis of LTBI in transplant candidates

Furthermore, IGRA interpretation is less variable than for TST [51]. However, IGRAs are more expensive and require specialized equipment, which are not always available [48]. The main limitation in the evaluation of the IGRAs is the lack of a gold standard for the diagnosis of LTBI [50]. Thus, the majority of the studies correlated IGRAs' results with those of the TST.

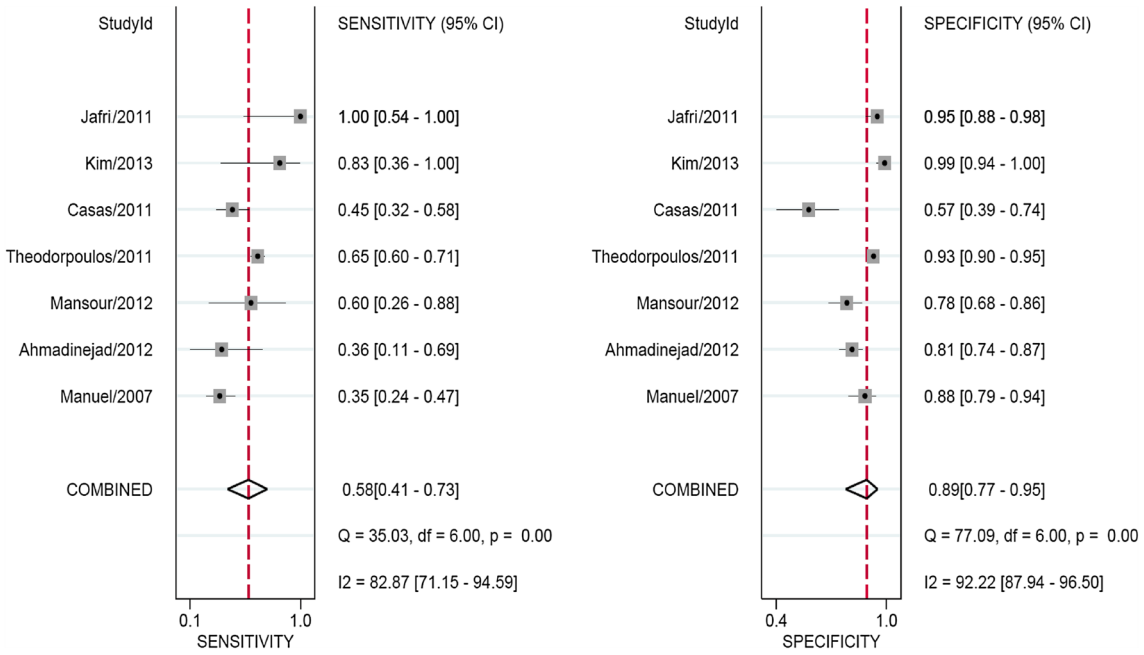


Fig. 4 Paired forest plots of pooled sensitivity and specificity of QFT-G for the diagnosis of LTBI in transplant candidates

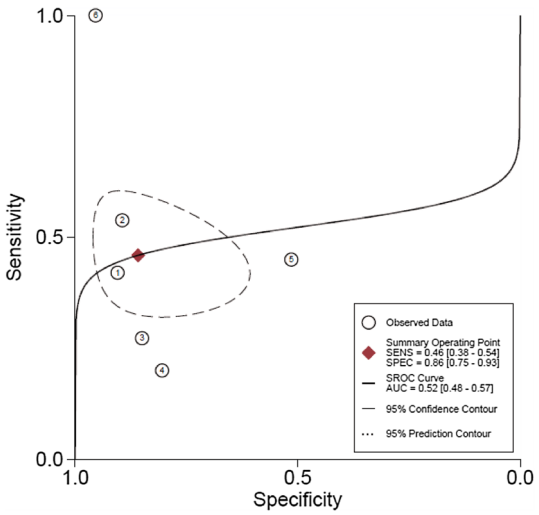


Fig. 5 Summary receiver operating characteristic (SROC) plot for TST test. The SROC plot shows summary of test performance, visual assessment of threshold effect, and heterogeneity of data in ROC space between sensitivity and specificity; each circle in the SROC plot represents a single study, summary operating sensitivity specificity, and SROC curve with both confidence and prediction regions. The dashed line that is around the pooled point estimate shows 95% confidence region. The area under the curve (AUC), acts as an overall measure for test performance. Particularly, when AUC would be between 0.8 and 1, the accuracy is relatively high. As a matter of fact, AUC was 0.52 in this report which represented a relatively moderate level of accuracy. If SROC curve was in the upper left corner it would show the best combination of sensitivity and specificity for the diagnostic test

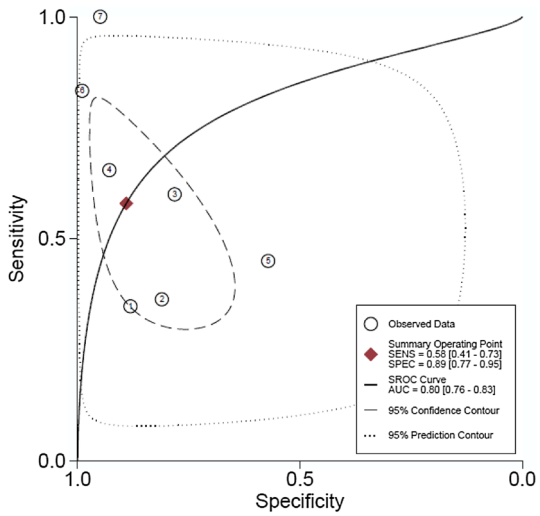


Fig. 6 Summary receiver operating characteristic (SROC) plot for QFT-G test

WHO guidelines for LTBI screening in at-risk populations recommend using IGRAs or TST [2]. However, our results suggest that IGRAs could be used as a supplementary test to the TST for screening of transplant candidates for LTBI.

Some study limitations could hinder the reliability of our findings. The lack of a gold standard method for LTBI diagnosis and the overall study heterogeneity are the major limitations. We systematically explored the issue of heterogeneity: sensitivity analysis confirmed that our findings

Table 3 Studies in which statistical agreement between IGRAs and TST were calculated

Study (first author, publication year)	Country	Incidence of TB	Mean age	Male %	No. of TST positive/total tested	No. of IGRA positive/total tested	Statistical agreement between IGRAs and TST k
Moon, 2012	Korea	Intermediate	47	56	39/244	40/244	0.08 (95% CI 0.06–0.24)
Sherkat, 2014	Iran	High	44	34	8/44	6/44	0.49 (95% CI 0.14–0.83)
Sester, 2014	Italy	Low	56.5	58	13/145	40/197	0.39 (95% CI 0.27–0.53)
Qin, 2013	China	High	37	61	61/295	44/295	0.27 (95% CI 0.17–0.40)
Kim, 2013	Korea	Intermediate	44	62	12/97	19/97	0.27 (95% CI 0.03–0.50)
Richeldi, 2009	Italy	Low	53	70	20/120	28/120	0.09 (95% CI 0.04–0.1)
Edathodou, 2016	Saudi Arabia	High	14–60	59	30/241	57/241	0.08 (95% CI 0.03–0.1)
Mardani, 2014	Iran	High	37	85	3/36	11/36	0.06 (95% CI 0.02–0.1)

were consistent. The potential influence of immunosuppressive treatment on IGRAs and TST results could not be evaluated based on the limited information retrieved from the selected articles.

Furthermore, studies evaluated were performed in geographical areas with different TB prevalence, as well as different BCG vaccination rates. Limitations associated with potential publication bias should be considered.

In conclusion, IGRAs are more sensitive and specific than the TST with regard to the diagnosis of LTBI in the transplant candidates.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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