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MAJOR ARTICLE

Screening for Latent Tuberculosis Infection in Solid Organ Transplant Recipients to Predict Active Disease: A Systematic Review and Meta-Analysis of Diagnostic Studies

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Background. This is a systematic review and meta-analysis of diagnostic test accuracy studies to assess the predictive value of both tuberculin skin test (TST) and interferon-gamma release assays (IGRA) for active tuberculosis (TB) among solid organ transplantation (SOT) recipients.

Methods. Medline, Embase, and the CENTRAL databases were searched from 1946 until June 30, 2022. Two independent assessors extracted data from studies. Sensitivity analyses were performed to investigate the effect of studies with high or low risk of bias. Methodological quality of each publication was assessed using QUADAS-2.

Results. A total of 43 studies (36 403 patients) with patients who were screened for latent TB infection (LTBI) and who underwent SOT were included: 18 were comparative and 25 noncomparative (19 TST, 6 QuantiFERON-TB Gold In-Tube [QFT-GIT]). For IGRA tests taken together, positive predictive value (PPV) and negative predictive value (NPV) were 1.2% and 99.6%, respectively. For TST, PPV was 2.13% and NPV was 95.5%. Overall, PPV is higher when TB burden is higher, regardless of test type, although still low in absolute terms. Incidence of active TB was similar between studies using LTBI prophylaxis (mean incidence 1.22%; 95% confidence interval [CI], .2179–2.221) and those not using prophylaxis (mean incidence 1.045%; 95% CI, 0.2731–1.817; $P = .7717$). Strengths of this study include the large number of studies available from multiple different countries; limitations include absence of gold standard for diagnosis of latent TB and low incidence of active TB.

Conclusions. We found both TST and IGRA had a low PPV and high NPV for the development of active TB posttransplant. Further studies are needed to better understand how to prevent active TB in the SOT population.

Keywords. IGRA; LTBI; SOT; TST.

Patients undergoing solid organ transplantation (SOT) are at a significantly increased risk for developing active tuberculosis (TB), with an incidence ranging from 4 to 30 times that of the general population in intermediate and high TB-burden countries [1]. Posttransplant TB mortality is high, estimated to range between 9% [2] and 30% [3]. Most cases of TB are due to reactivation of latent TB infections (LTBIs), which occurs most frequently within the first year of transplantation. Nevertheless, it has been reported that only one quarter of active TB cases after transplant occurred among patients with a positive tuberculin skin test (TST) before transplantation [4].

There are currently 2 main screening methods for LTBI, namely, tuberculin skin testing (TST) and interferon-gamma release assays (IGRA). The IGRA has several advantages over TST, including not requiring a return visit for reading as well as not being impacted by prior receipt of the Bacillus Calmette-Guérin (BCG) vaccine. Both tests are dependent on the underlying immune function of the host and can have false-negative results due to anergy in patients with end-stage organ disease who are the exact patient population who are SOT candidates. Current American Society of Transplantation guidelines recommend screening for LTBI in all transplant candidates, either by TST or IGRA. If positive, it is recommended to consider therapy for LTBI (ie, prophylaxis) after ruling out active TB [1]. The incidence of TST- or IGRA-positive patients who go on to develop active TB posttransplant is unknown. We therefore conducted this systematic review and meta-analysis of diagnostic test accuracy studies to assess the accuracy of both TST and IGRA in predicting

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posttransplantation active TB among SOT recipients. The primary objective of our study was to estimate the predictive accuracy of IGRA and TST for predicting active TB after transplantation, assessing the positive and negative predictive values of both tests. Our secondary aim was to compare the predictive values of IGRA versus TST.

METHODS

This systematic review and meta-analysis was conducted according to PRISMA for Diagnostic Test Accuracy guidance.

Search Strategy

A comprehensive search for relevant studies was conducted in Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) until June 2022. Search terms for each database are detailed in Supplementary Appendix 1. Citations in retrieved articles, clinical practice guidelines, and review articles were also reviewed, and a gray literature search was done to address the possibility of publication bias.

Inclusion Criteria and Outcomes

Studies eligible for inclusion were studies of any design, including randomized controlled trials, prospective or retrospective cohort studies, and case-control studies. Case series including less than 10 participants and case reports were excluded. The index tests included were TST and the 2 IGRA tests—QuantiFERON gold (QIAGEN) and T-SPOT.TB test (Oxford Immunotec). The target condition identified by these tests is LTBI, according to the cutoffs defined for each test in individual studies. As for reference standard, no gold standard exists. Only studies providing complete information on their binary classification (ie, a 2×2 table(s) of data on true-positive, false-positive, true-negative, and false-negative results could be extracted) were included in the analysis. Studies were included if they included adult patients who were tested for LTBI and who underwent at least 1 solid organ transplant (lung, heart, kidney, liver, pancreas, small bowel). Studies that included other types of immunocompromised host (eg, recipients of stem cell transplants or patients with human immunodeficiency virus infection) data for SOT recipients only was extracted.

To assess the predictive values of the tests, the outcome of interest was newly diagnosed active TB appearing after transplantation, as defined in individual studies. Therefore, only patients who underwent transplant and had follow-up data available were included.

Data Extraction

Two reviewers independently reviewed the search results and retrieved publications that met the inclusion criteria. Two additional independent reviewers extracted data regarding test results as a 2×2 table according to 1 axis—test's results (TST/IGRA positive or negative)—and the other axis—active TB (yes/no). In addition, data were collected including study characteristics, patients baseline characteristics, TB exposure data (personal history or exposure, radiographic findings, residency, immigration, etc), and TB prophylaxis details (the term "prophylaxis" in this manuscript refers to any prophylactic regimen administered for LTBI). Outcomes, including test results and active TB cases, were also collected.

The reviewers also independently assessed the methodological quality of each publication using QUADAS-2 [5]. In cases of discrepancy, a third reviewer was included in the discussion to solve any disagreement. Corresponding authors of included studies were approached via email for additional data, whenever necessary.

Meta-Analysis and Statistical Methods

For each study, we estimated the chance of developing active TB after transplantation, after a positive index test (equaling the positive predictive value [PPV]), or after a negative index test (equaling 1 minus the negative predictive value [NPV]). The PPV of an index test was defined as the number of index test positive patients before transplantation who also developed active TB after transplantation, divided by all index test positive patients before transplantation. The chance of developing active TB after a negative index test was defined as the number of index test negative patients before transplantation who also developed active TB after transplantation, divided by all index test negative patients before transplantation. Because predictive values depend on the incidence of active TB in the relevant patient group, we also estimated the incidence of TB in each included study.

We summarized the estimates of predictive values in a bivariate binomial random effects meta-analysis, as described previously [6] using PROC NLMIXED in SAS 9.4. The different tests were analyzed in subgroups, and potential sources of heterogeneity were added as covariates to the meta-regression analyses to investigate whether they were associated with differences in predictive values. These potential sources of heterogeneity included TB burden in the country in which the study was conducted (high vs low burden based on the World Health Organization list [7], transplantation status [transplanted individuals vs candidates]). Incidence was summarized with a univariate binomial random effects meta-analysis, also using NLMIXED and SAS 9.4. Whenever possible, we also analyzed differences in predictive values between tests including only studies in the meta-analyses that directly compared 2 or more index tests.

Sensitivity analyses were performed to investigate the effect of studies with high or low risk of bias and studies excluding indeterminate results of IGRA tests. Because many studies reported no or very low numbers of active TB cases, it was not possible to estimate predictive sensitivity for all studies. For those studies that reported more than zero cases of active TB, we estimated both sensitivity and specificity. Sensitivity was

defined as the proportion of positive test results before transplantation among those who developed active TB after transplantation. Specificity was defined as the proportion of negative test results before transplantation among those who did not develop active TB after transplantation. We summarized the estimates of sensitivity and specificity in a bivariate binomial random effects meta-analysis [8], using PROC NLMIXED in SAS 9.4.

RESULTS

The trial flow chart is presented in Figure 1. Overall, 43 studies (36 403 patients) were included (9–49): 18 were comparative (17 compared TST to either IGRA test, 1 compared QuantiFERON-TB Gold In-Tube [QFT-GIT] with T-SPOT.TB) [9], and 25 were noncomparative (19 TST, 6 QFT-GIT). One study was a randomized controlled trial [10], 15 were prospective, and 27 were retrospective cohort studies. Most studies included various solid organ transplant recipients, although 8 followed candidates for transplant. Eight studies were conducted in high TB-burden countries [11–18]. Overall, 344 patients had active TB and were tested for LTBI. Detailed data regarding included studies are described in Table 1.

Predictive Value of Screening Tests in Predicting Active Tuberculosis

To address the question of what is the chance of active TB posttransplantation with either a positive or a negative test result (regardless of specific test type), what is the chance of active TB posttransplantation, we compiled 34 studies for TST, 21 for QFT, and 5 studies for T-SPOT, all including one 2 × 2 table per study. Positive predictive value and NPV of any screening test against incidence during the follow-up time of the individual study are provided in Figure 2*A* and *B*, respectively. For IGRA tests taken together, PPV and NPV were 1.2% and 99.6%, respectively. For QFT and T-SPOT separately, PPV was 0.86% and 1.59% and NPV was 99.6% and 97.6%, respectively. For TST, PPV was 2.13% and NPV was 95.5%. The incidence of active TB was calculated and was demonstrated to be higher in studies using TST compared with IGRA studies (TST - 1.65%, 95% confidence interval [CI] = 0.96%–2.8%; QFT - 0.5, 95% CI = 0.21–1.18; T-SPOT - 0.88, 95% CI = 9.54–1.43).

Results according to TST cutoff used (5 or 10 mm) are provided in Table 2. As expected, PPV was 2 times higher using the 10-mm cutoff (2.4%) compared to the 5-mm cutoff (1.2%). The NPV was 97.3% using the 10-mm cutoff and 99.4% using the 10-mm cutoff.

Predictive Value of Tuberculin Skin Test Versus Interferon-Gamma Release Assays

Data from 13 studies reporting both TST and IGRA tests results were available for this analysis. The comparison is reported in Table 2, presented by TST cutoff. Only 2 of the IGRA studies reported T-SPOT; hence, QFT-GIT and T-SPOT test reports are combined. The NPV of both tests is similarly high and higher for TST when the lower cutoff (5 mm) is used. The PPV is low for both tests, as expected by the low pretest probability.

Investigation of Heterogeneity

Tuberculosis Burden

As expected, low-burden countries had a lower incidence of 0.75% (95% CI, 0.21%–1.29%) compared to 1.95% (95% CI, 0.49%–3.41%) in high-burden settings. This difference was nonstatistically significant ($P = .0641$). Predictive value of screening tests according to type of test and TB-burden settings are presented in Table 3. Tuberculosis burden significantly affected PPV ($P = .0025$) but not NPV ($P = .1482$). Overall, PPV is higher when TB burden is higher, regardless of test type, although still low in absolute terms (Table 3).

Prophylaxis Status (Latent Tuberculosis Infection Prophylaxis Yes/No)

Incidence of active TB was similar between studies using prophylaxis (mean incidence 1.22%; 95% CI, 0.2179–2.221) and those not using prophylaxis for LTBI (mean incidence 1.045; 95% CI, 0.2731–1.817; $P = .7717$).

Predictive values of screening tests according to type of test and prophylaxis administration are presented in Table 4. Prophylaxis did not significantly affect either (PPV, $P = .3439$; NPV, $P = .6457$).

Transplant Status (Transplanted or Candidate)

In studies evaluating candidates for transplant (n = 8), we found an incidence of 1.280 (0–0.3731); and in those including only transplant recipients, the incidence was significantly higher, at 1.423 (0.6722–2.173) ($P = .0164$). No significant difference in the PPV was demonstrated between candidates and transplant recipients (Table 5).

Sensitivity and Specificity of Each Test

Twenty-nine studies were included in the analysis of sensitivity and specificity of TST, demonstrating low sensitivity (30.9%; 95% CI, 21.8%–41.7%) and relatively high specificity (77.9%; 95% CI, 72.7%–82.5%). Ten studies were included in the analysis of sensitivity and specificity of IGRA-QFT, showing similar results (sensitivity 37.5%, 95% CI = 11.7%–63.1%; specificity 79.9%, 95% CI = 71.5%–86.3%). For T-SPOT assay, only 3 studies were included, demonstrating sensitivity of 82.3% (95% CI, 10.7%–99.5%) and specificity of 73.5% (95% CI, 61.5%–82.8%). (Supplementary Figure 1). QUADAS-2 scoring was performed for all studies as adopted for our review (Supplementary Table 1). Because all studies but 5 were not scored as low risk of bias, we did not perform sensitivity analysis according to quality assessment. See Supplementary Table 2 for detailed scoring.

DISCUSSION

Patients undergoing SOT are at significantly increased risk of developing active TB compared with the general population.

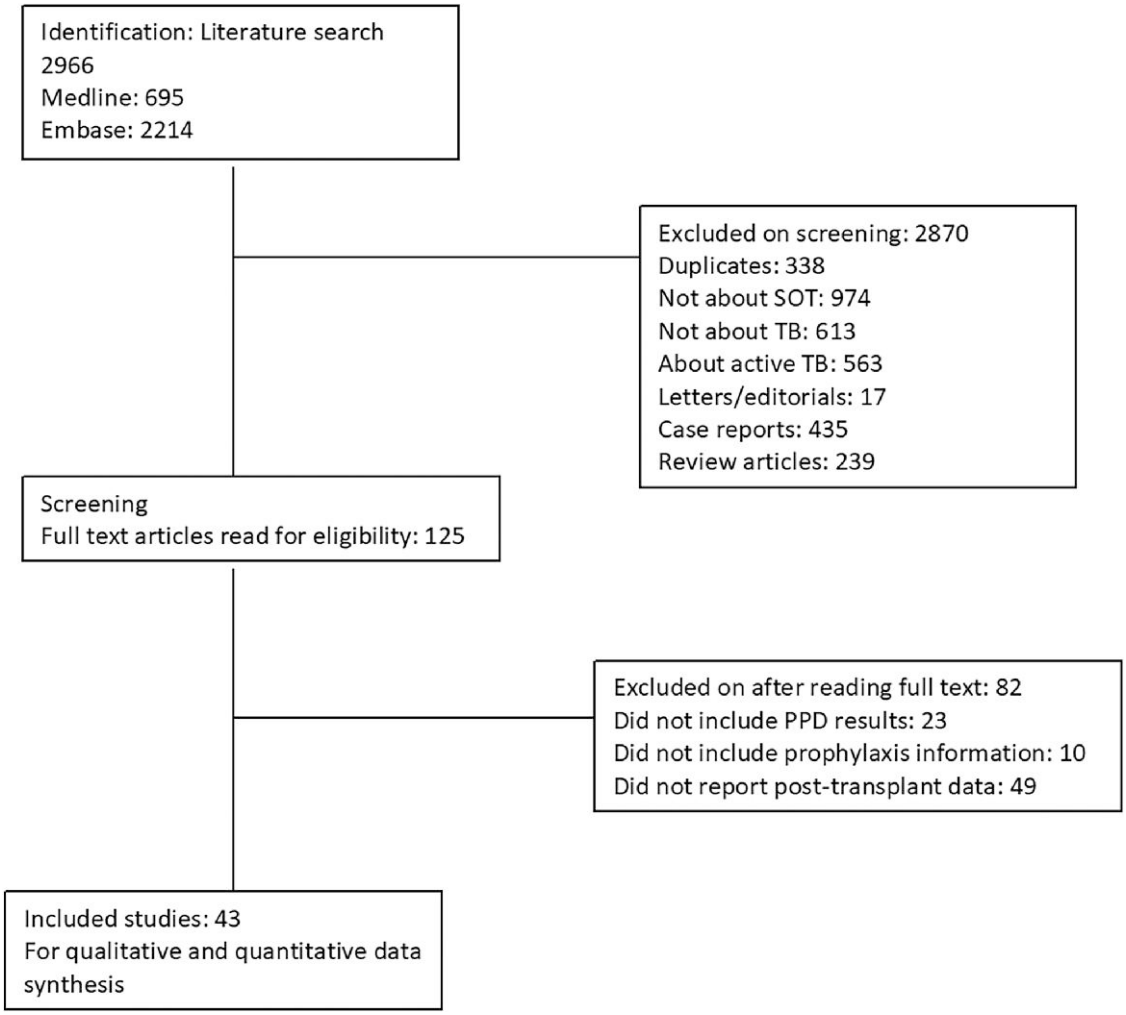

Figure 1. Study flow. PPD, purified protein derivative; SOT, solid organ transplantation; TB, tuberculosis.

Moreover, active TB is associated with poorer outcomes including 15% graft loss and up to 20%–30% mortality [1]. As a result, both the American Society of Transplant and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend pretransplant screening for LTBI [18]. Screening for LTBI using either the TST, T.SPOT, or IGRA has been the cornerstone of LTBI diagnosis for many years. However, our analysis showed that relying solely on these diagnostic tests may not be the optimal strategy for LTBI screening in this population. We found a low PPV (<3%) of any LTBI screening test to predict active TB. The NPV was over 95% for any test. The low PPV was consistent regardless of TB burden (although most studies were conducted in low-burden countries), prophylaxis use for LTBI (administered or not), and transplant status (transplant recipients or candidates for transplant). Low PPV in any TB-burden setting may also be explained by the fact that even in high-burden countries, the incidence of TB may not be equally distributed across the whole population, and potentially transplant recipients' exposure risk to TB does not reflect the entire country's TB burden.

Our study also found no differences in the performance characteristics between TST and QFT-GIT. Both tests demonstrated low sensitivity (30.9% and 37.5%, respectively) and good specificity (77.9% for both tests) in predicting active TB. The T.SPOT demonstrated better sensitivity (82.3%) with similar specificity (73.5%), although a limited number of studies was included for this analysis.

Our findings are in contrast with the conventional wisdom that IGRA is more specific due to a lack of cross-reactivity with patients who received BCG vaccination. It should be noted that TST was primarily used in high prevalence countries. Therefore, the low prevalence in countries using IGRA may have impacted its predictive value. Nevertheless, these countries are not expected to routinely use IGRA, due to cost considerations. We did find that a positive screening test was

Table 1. Characteristics of Included Studies

First Author, Year of Publication	Country or Region	TB Burden[a]	Design	LTBI Test	Participants	N	Universal Prophylaxis[b]	N (%) Received Prophylaxis[c]	Follow Up (Month)	N Active TB
Comparative Studies										
Kim, 2013 [19]	South Korea	Low	Prospective	TST vs QFT-GIT	Kidney transplant recipients	109	No	NS	Mean 24.6 (SD 14.4)	1
Ahmadinejad, 2013 [20]	Iran	Low	Prospective	TST vs QFT-GIT	Solid organ transplant candidates	164	No	100% (26/26)	Mean 18 (range 1–36)	0
					Solid organ transplant recipients	40		100% (4/4)		
Kim, 2013 [21]	South Korea	Low	Prospective	TST vs QFT-GIT	Kidney transplant recipients	126	No	0% (0/56)	Median 12.9 (0.4–22.0) after transplantation	0
Sester, 2014 [22]	Europe	Low	Prospective	TST vs QFT-GIT vs T-SPOT.TB	Solid organ transplant recipients	197	No	NS	Median 21.6 (IQR, 24–36)	0
Sherkat, 2014 [23]	Iran	Low	Prospective	TST vs T-SPOT.TB	Kidney transplant candidates	44	No	100% (10/10)	12 (all patients)	1
Muñoz, 2015 [24]	Spain	Low	Prospective	TST vs QFT-GIT	Liver transplant recipients	50	No	0% (0/26)	Median 47.5 (range 35–53.9) after transplantation	1
Torre-Cisneros, 2015 [10]	Spain	Low	Prospective (RCT)	TST vs IGRA	Liver transplant recipients	64	Yes	100% (64/64)	Median 9.3 (range 1.7–18.0)	0
Kim, 2015 [25]	South Korea	Low	Prospective	TST vs T-SPOT.TB	Kidney transplant recipients	312	No	100% (40/40)	Median 14.5 (IQR, 9.9–19.6)	6
Edathodu, 2017 [26]	Saudi Arabia	Low	Prospective	TST vs QFT-GIT	Kidney transplant candidates	278	No	100% (53/53)	Median 25, mean 27 (range 2–58)	0
					Kidney transplant recipients	173				
Ishikawa, 2017 [9]	Japan	Low	Prospective	QFT-GIT vs T-SPOT.TB	Kidney transplant recipients	92	No	NS	Median 33.1 (IQR, 31.5–35.1) after IGRA testing	0
Fitzpatrick, 2010 [27]	USA	Low	Retrospective	TST vs QFT-GIT	Solid organ transplant candidates	83	No	100% (14/14)	Median 11.6 (range 2.2–25.5)	0
Goto, 2010 [28]	Japan	Low	Retrospective	TST vs QFT-GIT	Kidney transplant recipients	100	No	NS	24 for QFT-GIT positive	2
Jafri, 2011 [29]	USA	Low	Retrospective	TST vs QFT	Liver transplant recipients	420	No	60% (15/25)	Mean 34 for recipients with latent tuberculosis	0
Jeong, 2014 [30]	South Korea	Low	Retrospective	TST vs QFT-GIT	Kidney transplant recipients	129	No	NS	Median 8.4 (IQR, 6.8; range 1.1–29.7)	2
Sidhu, 2014 [31]	Canada	Low	Retrospective	TST vs QFT-GIT	Solid organ transplant candidates	461	No	95% (189/200)	Mean 58.8, median 61.2 (a minimum of 12)	0
					Solid organ transplant recipients	123				
Liu, 2014 [11]	China	High	Retrospective	TST vs IGRA	Liver or kidney transplant recipients	1914	No	0% (0/12)	Median 74.4 (IQR, 31.2–141.6) after transplantation	17 (tested, overall there were 45 active TB cases)
Jambaldorj, 2017 [32]	South Korea	Low	Retrospective	TST vs QFT-GIT	Kidney transplant recipients	446	No	0% (0/18)	Median 30.2	3
Moon, 2017 [33]	South Korea	Low	Retrospective	TST vs QFT-GIT	Liver transplant recipients	277	No	50% (19/38)	Median 32.5 (range 1.5–74.2)	7
Noncomparative Studies										
Ravi Shankar, 2005 [12]	India	High	Prospective	TST	Kidney transplant candidates	108	No	0% (0/46)	Transplant recipients: Mean 23.34 (range 20–30)	4
					Kidney transplant recipients	79				
Bravo, 2005 [34]	Spain	Low	Prospective	TST	Lung transplant recipients	187	Yes	82% (50/61) of those with positive TST; 51% (95/187) of the entire cohort	Mean 18.9 (1.7–78.3)	3
Torre-Cisneros, 2009 [2]	Spain	Low	Prospective	TST	Solid organ transplant recipients	4388	No	43% (147/338)	Median 12 (range 0–24)	6

Table 1. Continued

First Author, Year of Publication	Country or Region	TB Burden[a]	Design	LTBI Test	Participants	N	Universal Prophylaxis[b]	N (%) Received Prophylaxis[c]	Follow Up (Month)	N Active TB
Agarwal, 2010 [13]	India	High	Prospective	TST	Kidney transplant recipients	200	No	0% (0/21)	TST negative: mean 33.4 (SD 21.9); TST positive: mean 24.0 (SD 13.4)	25
Lange, 2012 [35]	Germany	Low	Prospective	QFT-GIT	Solid organ transplant recipients	233	No	NS	Mean 28	1
Poglajen, 2018 [36]	Slovenia	Low	Prospective	QFT-GIT	Heart transplant recipients	140	No	0% (0/26)	12 (all patients)	0
Apaydin, 2000 [37]	Turkey	Low	Retrospective	TST	Kidney transplant recipients	274	No	39% (26/67)	Mean 37.2 (SD 18.5) and 52.4 (SD 34.0) for the groups with and without prophylaxis, respectively	16
Benito, 2002 [38]	Spain	Low	Retrospective	TST	Liver transplant recipients	373	No	18% (16/89)	Median 49 (range 0.5–141)	5
Basiri, 2005 [39]	Iran	Low	Retrospective	TST	Kidney transplant recipients	12 820	No	NS	NS	120
Ribeiro, 2010 [14]	Brazil	High	Retrospective	TST	Kidney transplant candidates Kidney transplant recipients	244 NS	No	63% (26/41)	Median 8.2	0
Agoglia, 2011 [15]	Brazil	High	Retrospective	TST	Liver transplant recipients	191	No	41% (17/41)	Median 63.6	2
Mojahedi, 2011 [40]	Iran	Low	Retrospective	TST	Kidney transplant recipients	508	No	100% (64/64)	Mean 54 (12–168)	9
Theodoropoulos, 2012 [41]	USA	Low	Retrospective	QFT-GIT	Solid organ transplant candidates Solid organ transplant recipients	694 142	No	73% (179/246)	Mean 11.7 after screening; 10.8 after transplantation	3
Jung, 2012 [42]	South Korea	Low	Retrospective	TST	Kidney transplant recipients	1097 729 performed TST	No	0% (0/228)	Mean 53.0 (1.0–127.6)	13
Arreola-Guerra, 2012 [43]	Mexico	Low	Retrospective	TST	Kidney transplant recipients	209	No	97% (58/60)	Mean 49.6 (range 3.6–290)	1
Joo, 2013 [44]	South Korea	Low	Retrospective	TST	Kidney transplant recipients	2799	No	0% (0/185)	Mean 164 (SD 73.2)	7
Higuita, 2014 [45]	Colombia	Low	Retrospective	TST	Kidney transplant recipients	641	No	100% (163/163)	12 (all patients)	11
Meinerz, 2016 [16]	Brazil	High	Retrospective	TST	Kidney transplant recipients	1737 761 performed TST	No	62% (135/217)	Median 63.2 (range 1.2–174.8) after transplantation	32
Guirao-Arrabal, 2016 [46]	Spain	Low	Retrospective	TST	Lung transplant recipients	369 296 performed TST	No	43% (30/70)	Median 18.6 (range 0–221.2)	5 (tested, 6 overall)
Daher Costa, 2017 [17]	Brazil	High	Retrospective	TST	Kidney transplant recipients	1573	No	98% (175/179)	>6 (all patients)	33
Alpaydin, 2018 [47]	Turkey	Low	Retrospective	TST	Liver transplant recipients	403 108 performed TST	No	0% (0/28)	Median 60 (range 6–120) after transplantation	3
Hand, 2018 [48]	USA	Low	Retrospective	QFT-GIT	Liver transplant recipients	148	No	15% (3/20)	Median 30 (IQR, 22–41), 18 (13–26), and 23 (17–30) following screening, for positive, intermediate, and negative QFT-GIT, respectively	3
Rafiei, 2019 [49]	Australia	Low	Retrospective	QFT-GIT	Kidney transplant recipients	660 28 performed QFT-GIT	No	50% (1/2)	3647 person-years	2
Wigg, 2019 [50]	Australia	Low	Retrospective	QFT-GIT	Liver transplant recipients	155	No	100% (8/8)	NS	0
Lauar, 2021 [18]	Brazil	High	Retrospective	TST	Liver transplant recipients	429 213 performed TST	No	34% (12/35)	Mean 38.4 (SD 19.2) after transplantation	0

Abbreviations: IQR, interquartile range; LTBI, latent tuberculosis infection; NS, not significant; QFT-GIT, QuantiFERON-TB Gold In-Tube; RCT, randomized controlled trial; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test.

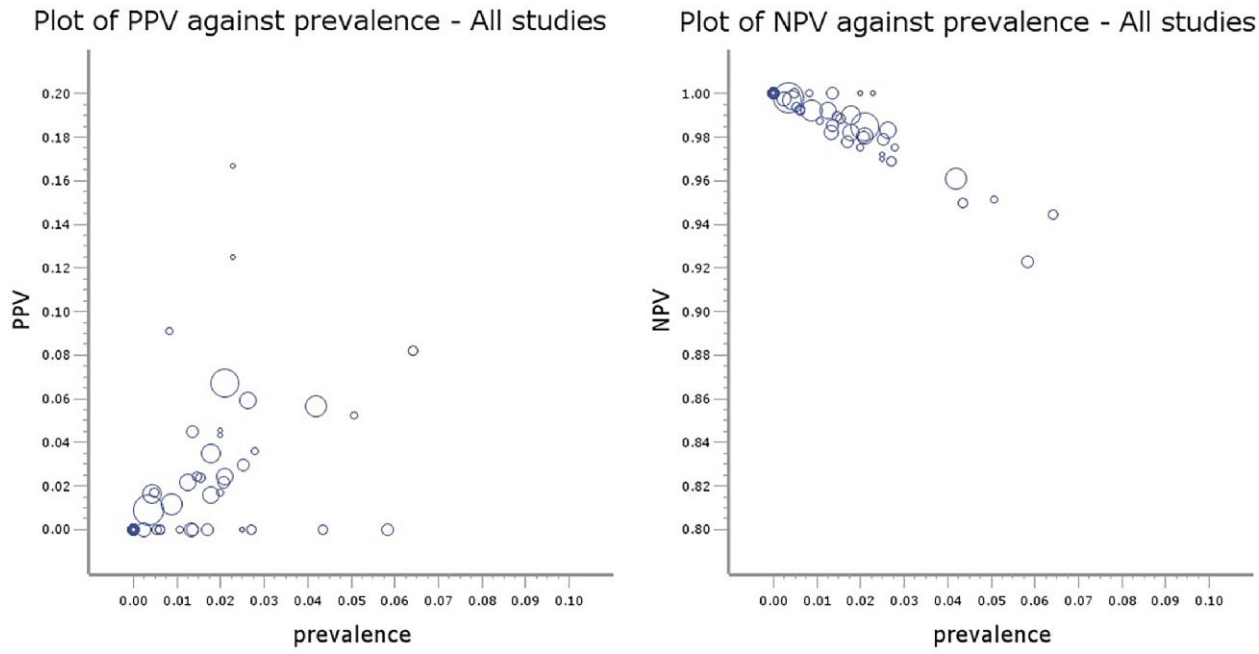

Figure 2. Positive predictive value (PPV) (*A*) and negative predictive value (NPV) (*B*) (y-axis) of any screening test against incidence (x-axis).

Table 2. Direct Comparisons Between TST (Any Cutpoint) and IGRA

First Author	Test	Cutoff	PPV	NPV	Test	Cutoff	PPV	NPV	Delta_PPV	Delta_NPV
Jafri	TST	5	0.00	1.00	IGRA_QFT	0.35	0.09	1.00	−0.09	0.00
Sidhu	TST	5	0.00	1.00	IGRA_QFT	NA	0.00	1.00	0.00	0.00
Torre-Cisneros	TST	5	0.00	1.00	IGRA_QFT	NA	0.00	1.00	0.00	0.00
Munoz	TST	5	0.04	1.00	IGRA_QFT	NA	0.05	1.00	0.00	0.00
Kim	TST	10	0.00	0.99	IGRA_TSPOT	NA	0.04	1.00	−0.04	−0.01
Kim SY	TST	10	0.00	1.00	IGRA_QFT	0.35	0.00	1.00	0.00	0.00
Ahmadinejad	TST	10	0.00	0.99	IGRA_QFT	NA	0.00	0.99	0.00	0.00
Ahmadinejad	TST	10	0.00	0.97	IGRA_QFT	NA	0.00	0.97	0.00	0.00
Sherkat	TST	10	0.13	1.00	IGRA_TSPOT	NA	0.17	1.00	−0.04	0.00
Jambaldorj	TST	10	0.00	0.95	IGRA_QFT	0.35	0.06	0.98	−0.06	−0.03
Moon	TST	10	0.02	0.98	IGRA_QFT	0.35	0.03	0.98	−0.01	0.00
Fitzpatrick	TST	NA	0.00	1.00	IGRA_QFT	NA	0.00	1.00	0.00	0.00
Sester	TST	NA	0.00	1.00	IGRA_QFT	NA	0.00	0.99	0.00	0.01

Abbreviations: IGRA, interferon gamma release assay; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value; QFT, QuantiFERON-TB; TST, tuberculin skin test.

predictive of an increased risk of active TB, but the absolute number of cases (344) was low.

Previous meta-analyses in various populations have similarly demonstrated the limited value of LTBI screening tests for predicting progression to active TB, although with variable results. Auguste et al [51] performed a systematic review and meta-analysis including various populations, aiming to compare the predictive ability of TST versus IGRA for active TB. Only 4 studies were included evaluating immunocompromised patients, showing predictive ability of positive versus negative tests, although the absolute PPV was low. No significant difference was demonstrated between TST and IGRA in this meta-analysis [51]. Diel et al [52] performed a similar meta-analysis including any patient population, and they reported a PPV of 2.7% for IGRA versus 1.5% for TST, with a high NPV for both. The PPV increased when performing an analysis of high-risk population [51]. Rangaka et al [53] included 15 studies evaluating IGRA compared with TST, and they concluded that none of the tests have high accuracy for predicting active tuberculosis. The low PPV in these meta-analysis, similar to our results of PPV <3%, is probably due, at least in part, to the low pretest probability for active TB [54]. The low PPV in

Table 3. Predictive Values of Screening Tests According to TB Burden

a: Predictive Values of Screening Tests According to TB Burden

	Low Burden (Estimate, 95% Confidence Interval); Incidence	Low Burden—Incidence	High Burden (Estimate, 95% Confidence Interval); Incidence	High Burden—Incidence
PPV IGRA	0.0042 (0.0015–0.0116)	0.00586 (0.001429– 0.01030)	0.01721 (0.001322–0.03310)	0.009031 (0.002659–0.01540
PPV TST	0.01151 (0.002840– 0.02018)	0.01369 (0.002674– 0.0247)	0.04616 (0.01448–0.07784)	0.02100 (0.005654– 0.03635
NPV IGRA	0.9973 (0.9950–0.9995)	0.00586 (0.001429– 0.01030)	0.9951 (0.9909–0.9993)	0.009031 (0.002659– 0.01540)
NPV TST	0.9883 (0.9809–0.9956)	0.01369 (0.002674– 0.0247)	0.9791 (0.9659–0.9923)	0.02100 (0.005654 –0.03635)

Abbreviations: IGRA, interferon gamma release assay; NPV, negative predictive value; PPV, positive predictive value; TB, tuberculosis; TST, tuberculin skin test.

Table 4. Predictive Values of Screening Tests According to TB Prophylaxis

	Prophylaxis (Estimate, 95% Confidence Interval)	No Prophylaxis (Estimate, 95% Confidence Interval)
PPV IGRA	0.005667 (–0.00173 to 0.01307	0.009435 (0.001259 to 0.01761)
PPV TST	0.01725 (0.003864 to 0.03064)	0.02850 (0.005281 to 0.05172)
NPV IGRA	0.9974 (0.9944 to 1.0004)	0.9968 (0.9943 to 0.9993)
NPV TST	0.9866 (0.9774 to 0.9958)	0.9834 (0.9719 to 0.9948)

Abbreviations: IGRA, interferon gamma release assay; NPV, negative predictive value; PPV, positive predictive value; TB, tuberculosis; TST, tuberculin skin test.

Table 5. Predictive Values of Screening Tests According to Transplant Status

	Candidates (Estimate, 95% Confidence Interval)	Transplanted (Estimate, 95% Confidence Interval)
PPV IGRA	0.004704 (0.0009 to 0.0245)	0.01021 (0.001077 to 0.01933)
PPV TST	0.01059 (–0.00608 to 0.02725)	0.02281 (0.008762–0.03687)
NPV IGRA	0.9982 (0.9959 to 1.0006)	0.9964 (0.9935 to 0.9993)
NPV TST	0.9920 (0.9819 to 1.0020)	0.9838 (0.9753 to 0.9923)

Abbreviations: IGRA, interferon gamma release assay; NPV, negative predictive value; PPV, positive predictive value; TST, tuberculin skin test.

our meta-analysis implies that a positive test translates to very low risk of active TB (less than 3%). However, the high NPV (~98%) implies that a transplant recipient with a negative test has less than 2% chance for active TB posttransplantation. This may mean that regardless of a positive or negative test, the risk for active TB is very low (<3%).

Our study had some limitations that merit further consideration. First, there are limitations that are common to any studies of LTBI diagnosis. There is no true gold standard for the diagnosis of LTBI; therefore, different studies use different markers to define a case of suspected LTBI, including contact with a case of active TB, prior history of TB, radiographic evidence of prior TB, or some combination thereof. In addition, there is heterogeneity in the cutoff value used for a positive TST. Moreover, most of the studies included in this meta-analysis provided prophylaxis for patients testing positive for LTBI, limiting an assessment of the accuracy of screening tests for predicting the likelihood of active TB posttransplant. The assessment is further limited by lack of data regarding compliance to prophylaxis and results among those not completing the prophylactic course. Of note, even in studies in which patients did not receive prophylaxis, there were still low rates of active TB. This ties into an additional limitation that the outcome of interest, active TB, even in this patient population is rare. Another limitation may be the design of original studies. None of the studies randomized patients to screening versus no screening or one test versus the other. These interventions should be considered for future research, although, as stated above, the outcome of active TB is expected to be scarce. In addition, none of the included studies evaluated the 4-Tube QuantiFERON (QuantiFERON Gold Plus), which has been proposed to lead to less indeterminate results [53]. As opposed to sensitivity and specificity, the predictive value is affected by the prevalence of the examined phenomenon in the population. Accordingly, the PPV/NPV of screening tool for LTBI to predict active TB will probably differ between countries and/or areas. Additional studies from high-burden countries are needed to evaluate the PPV in these countries.

Although the goal is to minimize as many preventable illnesses as possible, currently available screening tests for LTBI

are subject to several limitations that can arise specifically in the pre-SOT population. Completing the prophylaxis course for LTBI may be challenging among SOT recipients, limited by drug-drug interactions and hepatotoxicity. Hence, unnecessary therapy should be avoided.

It has been proposed that abnormal radiographic imaging in SOT candidates from an endemic area may be at higher risk of developing posttransplant active TB, with computed tomography (CT) of the chest being more sensitive than chest x-ray [47]. Introduction of chest CT to the decision-making algorithm regarding antituberculous prophylaxis should be tested.

CONCLUSIONS

In summary, current screening tests for LTBI in candidates for transplant or transplant recipients provide high NPV but low PPV of less than 3% for active TB. These results were demonstrated for both TST and IGRA tests. Other strategies for risk stratification, probably incorporating epidemiological data, chest imaging, as well as screening tests, should be studied to provide decisions on prophylaxis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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