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Review article

Comparison of the QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube interferon-γ release assays: A systematic review and meta-analysis

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ABSTRACT

Purpose: QuantiFERON-TB Gold Plus (QFT-Plus) is a new generation of QuantiFERON assay that differs from QuantiFERON-TB Gold In-Tube test (QFT-GIT). The aim of this study was to compare the performance of the new FDA-approved QFT-Plus interferon (IFN)-γ release assays (IGRAs) with the QFT-GIT version of this assay.
Material and methods: We searched all studies published in English in electronic databases, including PubMed, Scopus, and Web of Science.
Results: The positive proportion of positive results by QFT-Plus was higher than QFT-GIT in cured tuberculosis (TB) cases (82% vs. 73%). The two tests showed a substantial agreement and the majority of the latent tuberculosis infection (LTBI) subjects responded concomitantly to both QFT-Plus and QFT-GIT. However, QFT-Plus showed a stronger association with surrogate measures of TB suspects than QFT-GIT. The QFT-Plus test demonstrated a higher sensitivity than QFT-GIT in the older adults. The sensitivity, specificity, LR+, LR- and DOR overall were 94% (95% CI 89–97), 96% (95% CI 94–98), 24.4 (95% CI 15–39), 0.05 (95% CI 0.03–0.11) and 414 (95% CI 251–685), respectively. The area under summary ROC curve was 0.99 (95% CI 0.97–0.99).
Conclusion: QFT-Plus performs equivalently to the QFT-GIT for detection of patients at risk for LTBI; however, QFT-Plus test had higher sensitivity than the QFT-GIT test, with similar specificity among the older participants. Higher IFN-γ release in TB2 compared to TB1 might be due to recent LTBI.

1. Introduction

Tuberculosis (TB) is still an important global health problem, with approximately 10.4 million new TB cases and 1.7 million TB related deaths per year worldwide [1]. The goal of the World Health Organization is to effectively eliminate TB by 2050. To achieve this goal, accurate diagnosis of latent TB infection (LTBI) is essential, because the large proportion of TB cases are due to LTBI reactivation [2].

While there are a lot of available diagnostic assays to detect active TB, detection of LTBI remains challenging. Current diagnostic testing for LTBI is performed using tuberculin skin test (TST) and interferon (IFN)-γ release assays (IGRAs) [3,4].

The TST is based on an immune reaction in the skin to purified protein derivative from tuberculin. This method has several limitations, including a required repeat test after 48–72 hours, false positive results due to cross-reactivity with Bacillus Calmette-Guérin (BCG) vaccination or infection with other mycobacteria, and false negative results because of immunosuppression [5]. To overcome the TST limitations, IGRAs were developed. Until 2015, there were two commercially available IGRAs - QuantiFERON-TB Gold In-Tube test (QFT-GIT; QIAGEN, Hilden, Germany) and the T-SPOT.TB (T-SPOT; Oxford Immunotec, Abingdon, UK), which are based on the measurement of the IFN-γ concentration after *in vitro* whole-blood/peripheral blood mononuclear cell (PBMC) stimulation with peptides from the RD-1 region of the *Mycobacterium tuberculosis* genome [6,7]. Although these assays provide advantages over the TST and have superior specificity, they are still poor predictors of progression to active TB, and have reduced sensitivity in immunocompromised individuals [8,9].

In 2015, a new generation of QFT-GIT, named QuantiFERON-TB Plus (QFT-Plus), was released by Qiagen, which includes an additional antigen tube (TB2). The TB1 tube contains ESAT-6- and CFP-10-derived peptides (TB-7.7, present in QFT-GIT, has been removed), designed to show cell-mediated immune responses from CD4+ helper T-lymphocytes. The TB2 tube contains new peptides able to elicit IFN-γ

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production by both CD4+ and CD8 + T-lymphocyte responses [10,11]. Theoretically, the inclusion of peptides for stimulation of CD8 + T-cells can improve performance in immunocompromised conditions that affect CD4+ T-cell responses (e.g., human immunodeficiency virus - HIV) and improve discrimination of LTBI from active TB [12–14].

Due to the limited sample size of patients recruited in individual studies, meta-analysis may increase the accuracy of estimates of individual studies; therefore, we conducted a meta-analysis to investigate the performance of new QFT-Plus for TB diagnosis.

2. Materials and methods

2.1. Search strategy

This study was guided by the standard PRISMA protocol (Preferred Reporting Items for Systematic reviews and Meta-analysis) [15]. We searched through all studies published in English and available in electronic databases, including PubMed, Scopus, and Web of Science. All searches were up to date as of September 2018. Our search included the term "Quantiferon TB gold plus AND tuberculosis". Conference abstracts and proceedings, as well as additional references, were added through searching the references cited by the identified studies.

2.2. Study selection and data extraction

The two investigators independently extracted the data from the original studies. These data were cross-checked. If necessary, we tried to contact the author of original reports by e-mail.

As inclusion criteria, we used studies which evaluated the performance of QFT-Plus and simultaneously compared it with QFT-IT assay. The inclusion criterion for selecting the studies was testing of the participants' blood samples by two IGRA methods: QFT-GIT and QFT-Plus (Qiagen, Hilden, Germany), according to the manufacturer's instructions. Test results of the QFT-GIT were interpreted according to the manufacturer's criteria (cut-off level = 0.35 IU/mL). Results were considered positive if the IFN-γ value was ≥0.35 IU/ml after correction for negative control in any of the two tests. A result was considered negative if the IFN-γ value was < 0.35 IU/ml and if the mitogen (positive response control) was ≥0.5 IU/ml.

Since the QFT-Plus has two tubes, a positive result observed in one of the single antigen tubes (TB1 or TB2) was interpreted as a positive result using the criteria above. The QFT-Plus results were interpreted according to the ability of subjects to respond to both TB1 and TB2 ("TB1 and TB2"), only to TB1 ("only TB1") or only to TB2 ("only TB2").

Also, studies must have had sufficient data to calculate the sensitivity, specificity, and positive and negative predictive values with considering QFT-IT as a gold standard. In some cases, we contacted the authors for related information that was not included in the original article.

Two reviewers independently assessed all the titles and abstracts to select the appropriate studies. After primary selection, one author reviewed the full text of all selected citations to determine eligibility for inclusion. The second author repeated this investigation independently. There were no disagreements regarding the excluded studies. Two authors independently extracted data from all the included papers. Differences were resolved by consensus.

2.3. Inclusion criteria

The inclusion criteria for patients with active TB were: laboratory-confirmed active TB and culture isolation of *M. tuberculosis* and/or combination of a characteristic clinical presentation and/or symptoms as well as available radiographs and computed tomography images.

LTBI was diagnosed in asymptomatic patients with both risk factors for TB infection (travel to or origin from a TB endemic country, known TB exposure, etc), and a positive TST (induration ≥ 10 mm) and/or QFT-GIT result, in whom active TB was excluded by history, physical examination and radiographic studies.

The criteria for the healthy volunteers (controls) were: no clear history of exposure to a person with active TB infection and no history of medications for TB.

Cured TB patients were defined as those who had completed a 6-month course of treatment for culture-positive (drug-susceptible) pulmonary TB and who resulted *M. tuberculosis* culture negative upon treatment completion [16].

2.4. Exclusion criteria

We excluded studies which had limited information to calculate true positives, false negatives, true-negatives, and false-positives for further meta-analysis.

2.5. Quality assessment

Two reviewers independently analyzed each study based on a tool known as quality assessment of diagnostic accuracy studies (QUADAS) [17]. Any differences were resolved by discussion or, if an agreement could not be reached, a third author was consulted.

2.6. Data analysis and synthesis

STATA software (version 14, College Station, TX, USA) was used for the meta-analysis. The sensitivity (true positive rate), specificity (true negative rate), positive likelihood ratio and negative (LR+, or LR-) and diagnostic odds ratio (DOR is calculated as the LR + divided by the LR-), with a confidence interval (CI) of 95%, were obtained for each study and subsequently combined.

Following Grimes's criteria [18], we interpreted positive likelihood ratio (PLR) in the range of 2–5, 5–10, and > 10 as representing small, moderate, and large increases of probability when the index test was positive. We also interpreted negative likelihood ratio (NLR) in the range of 0.2–0.5, 0.2–0.1, and < 0.1 as representing small, moderate, and large decreases of probability when the index test was negative.

The I^2 statistic was explored to assess the heterogeneity of the included studies. Random-effects model was used. Additionally, a hierarchical summary receiver operating characteristic (HSROC) type curve of the selected studies was plotted with STATA software.

To assess the potential publication bias, we used the Deeks funnel plot, with $p < 0.05$ indicating the presence of publication bias [19].

3. Results

In total, our search returned 151 articles related to evaluating the QFT-Plus performance (Fig. 1). After removing 68 duplicates, we screened 83 articles of which we excluded 63 articles. We then excluded 8 articles since they did not have the counts in a 2 × 2 table for calculating of the diagnostic accuracy test. Finally, 12 publications were determined to meet the eligibility for inclusion in the present systematic review.

Further details on baseline characteristics of these studies, along with QUADAS score are shown in Table 1.

Among included studies, there were different populations in which QFT-GIT and QFT-Plus IGRAs were compared including active TB patients [16,20–23], HCWs [23–25], immigrants from endemic TB areas undergoing evaluation or follow-up for LTBI [11,23,26], tuberculosis-exposed individuals and TB suspects [16,22,25,27], old residents in long-term care facilities [28] and healthy volunteers [21,22]. There was only one study which compared the accuracy of QFT-Plus in comparison to QFT-GIT in a cohort of subjects with LTBI cured TB [16].

Among the studies included in the meta-analysis, there were a total of 2724 individuals recruited. The median age for included cases was 41 years (35–53 years). The samples were collected from the USA [20,23], Korea [28], Japan [21], Taiwan [29], Germany [11,24,26], Italy [16,27], Netherland and Belgium [25].

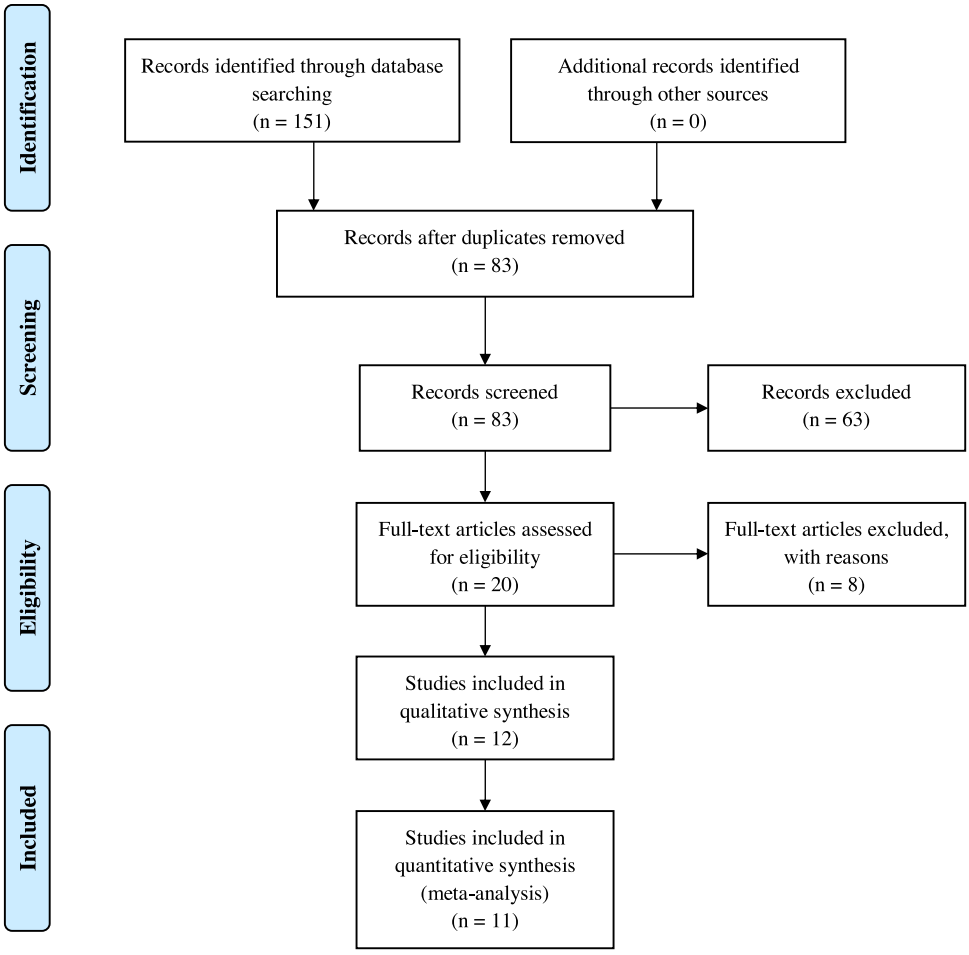

Fig. 1. PRISMA flowchart of study selection. Adapted from Moher et al. [15].

Table 1
Summary of the included studies.

Author	Year	Country	N	QFT-GIT			QFT-Plus			QUADAS SCORE				
				pos	neg	ind	pos	neg	ind		tp	fp	fn	tn
Ryu et al. [28]	2018	Korea	317	92	215	10	88	219	10	6	81	7	11	207
Horne et al. [20]	2018	USA	164	150	9	5	146	11	7	12	144	0	2	9
Chien et al. [29]	2018	Taiwan	229	66	163	–	74	155	–	9	63	11	3	152
Theel et al. [23]	2018	USA	161	34	126	1	33	127	1	10	31	2	3	124
Takasaki et al. [21]	2017	Japan*	106	1	105	–	2	104	–	12	1	0	1	104
			99	97	2	–	98	1	–		97	0	1	1
Pieterman et al. [25]	2017	Netherlands and Belgium	1031	153	859	19	150	861	20	10	131	19	22	835
Petruccioli et al. [16]	2017	Italy**	69	61	8	–	62	8	–	10	61	0	1	7
			33	24	9	–	27	6	–		24	0	3	6
			58	58	0	–	57	1	–		57	1	0	0
Knierer et al. [11]	2017	Germany ***	41	10	31	–	9	32	–	6	8	1	2	30
			41	10	31	–	9	32	–		8	1	2	30
			40	11	29	–	11	29	–		10	1	1	28
			41	11	30	–	11	30	–		11	0	0	30
			41	9	30	2	8	29	4		8	0	0	29
Morales et al. [26]	2016	Germany	134	11	123	–	11	123	–	6	9	2	2	121
Hoffmann et al. [24]	2015-2016	Germany	163**-**	67	94	–	70	93	–	9	64	3	6	90
Barcellini et al. [27]	2014-2015	Italy	119	56	63	–	68	51	–	6	56	12	0	51
Yi et al. [22]	2014-2015	Japan	162	147	10	5	–	–	–	12	–	–	–	–

Abbreviations: pos - positive; neg – negative; ind – indeterminate; tp - true positive; fp - false positive; fn - false negative; tn - true negative.

* 106 control and 99 patients with active tuberculosis.

** 69 patients with active tuberculosis, 33 cured tuberculosis cases and 58 cases with latent tuberculosis.

*** Serial testing of students with a migration (visit 1,2,3,4, and overall).

**** QFTG-IT showed invalid results in two cases.

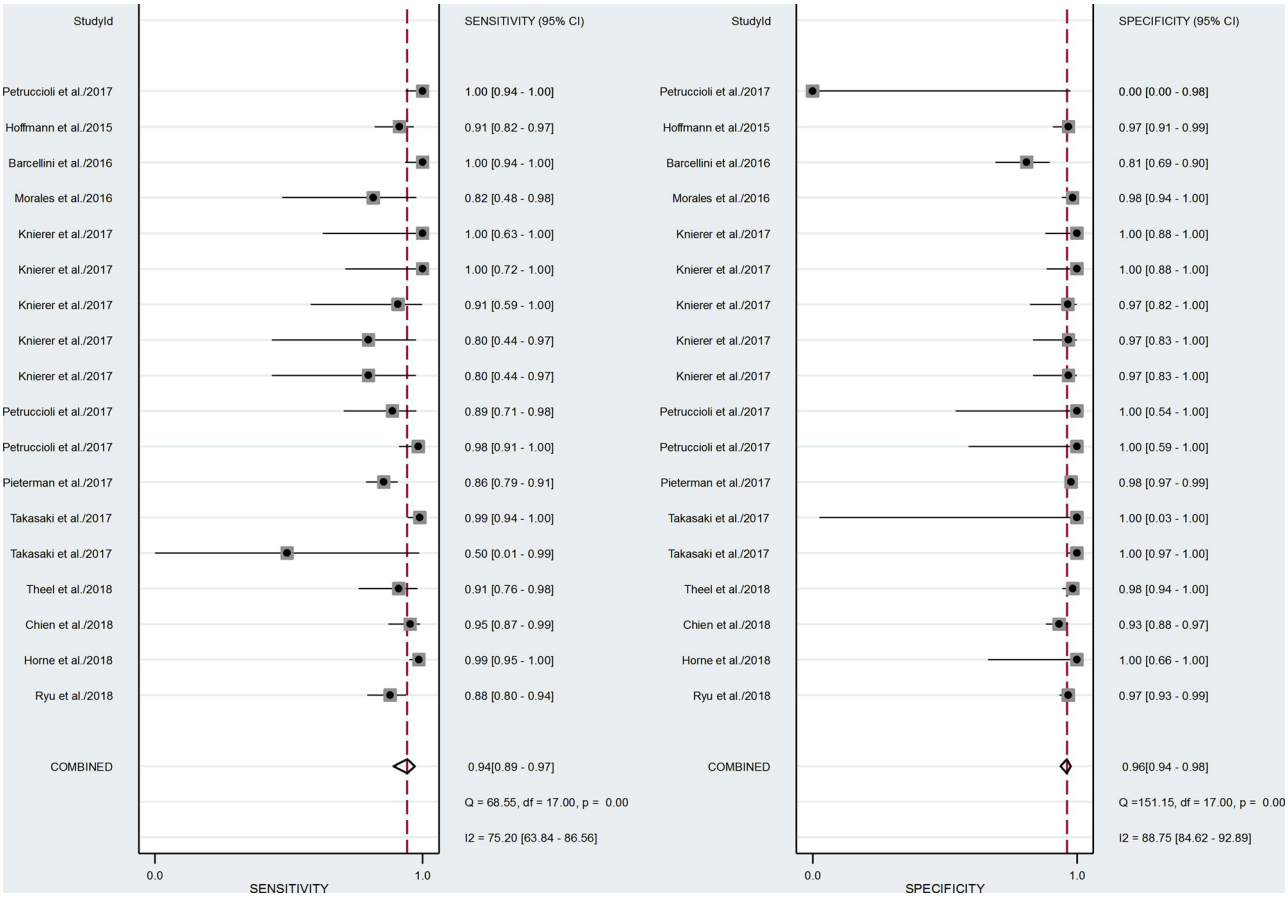

Fig. 2. Forest plot of the sensitivity and specificity of QFT-Plus kit.
The sensitivity and specificity are represented by the circles in squares and the horizontal lines represent the point estimate (95% CI for each included study). Diamonds represent the pooled estimate (95% CI).

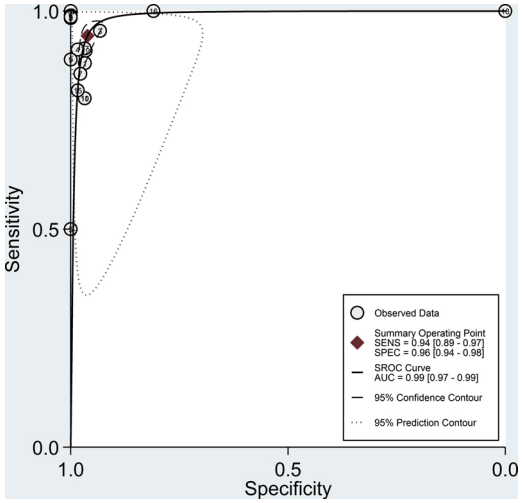

Fig. 3. HSROC plot displaying diagnostic accuracy results of included studies. The circle diameter (study estimate) is proportional to the weight given to each study. Summary sensitivity and specificity is marked by a red diamond.

The pooled proportion of QFT-GIT and QFT-Plus positive was 32% (95% CI 21–44%, ranging from 15% to 100%) for diagnosis of LTBI [11,16,23–29]. The positive proportion of positive results by QFT-Plus was higher than QFT-GIT in cured TB cases (82% vs. 73%) [16]. The pooled proportion of QFT-GIT and QFT-Plus positive for diagnosis of active TB was 93% (95% CI 87–98%, ranging from 88% to 91%) and 94% (95% CI 85–99%, ranging from 88% to 91%), respectively [16,20,21].

The two tests showed a substantial agreement and the majority of the LTBI subjects responded concomitantly to both QFT-Plus and QFT-GIT. However, QFT-Plus showed a stronger association with surrogate measures of TB suspects than QFT-GIT [24,27,29]. In Barcellini et al. study [27], discordant results were found in 12 subjects with negative QFT-GIT and positive QFT-Plus results. Chien et al. [29], reported statistically significantly higher sensitivity (100.0% vs. 89.4%, $p = 0.013$) and similar specificity (95.1% vs. 95.7%) of QFT-Plus compared to QFT-GIT. Among the 66 subjects with definite LTBI, 59 (89.4%) were positive for the QFT-GIT test and all (100.0%) were positive for the QFT-Plus test.

The QFT-Plus test demonstrated a higher sensitivity than QFT-GIT in the older adults. The sensitivity of QFT-GIT decreased with age, especially among the older participants (≥75 years) [29]. Chien et al. reported that 66 (28.8%) and 74 (32.3%) of older adults had positive results of QFT-GIT and QFT-Plus, respectively [29].

It has been found that the majority of LTBI subjects simultaneously responded to both TB1 and TB2 antigens, while in the active TB subjects a higher proportion of patients responded to TB2 and an “only to TB2” response was reported which was more associated with active TB [16,23]. However, Chien et al. reported cases with definite LTBI (n = 13, 5.7%) who had an “only to TB2” response [29].

Some studies reported that absence of the Tb7.7 antigen from the QFT-Plus IGRA does not statistically significantly impact assay performance [16,22,23]. However, these results notably differ from Hoffmann et al. [24] and Horne et al. [20] study which reported statistically significantly higher IFN-γ concentrations in the conventional QFT-GIT than TB1 tube of QFT-plus.

3.1. Overall accuracy of the QFT-Plus kit

After considering the exclusion criteria for meta-analysis, one study [22] was excluded because of the lack of information to calculate sensitivity and specificity.

The sensitivity, specificity, LR+, LR- and DOR overall were 94% (95% CI 89–97), 96% (95% CI 94–98), 24.4 (95% CI 15–39), 0.05 (95% CI 0.03–0.11) and 414 (95% CI 251–685), respectively (Fig. 2).

The graph of the HSROC curves of the analyzed individual studies displaying the diagnostic accuracy of QFT-plus is shown in Fig. 3. The area under summary ROC curve was 0.99 (95% CI 0.97–0.99).

3.2. Publication bias

To estimate the publication bias, the Deek's funnel plot was performed and the results did not reveal any evidence of clear asymmetry and publication bias (p = 0.71) (Fig. 4).

4. Discussion

This study compared the performance of the new FDA-approved QFT-Plus IGRA with the QFT-GIT version of this assay. Evidence suggests that the QFT-Plus performs equivalently to the QFT-GIT for detection of patients at risk for LTBI. However, QFT-Plus in contact screening has an improved performance compared to QFT-GIT due to addition of the second antigen tube, used as an indirect estimate of specific CD8+ activation, which may be more sensitive in detecting new or recent infection with *M. tuberculosis* [27].

Although the sensitivity of TST may diminish with patient's age due to waning immunity, it has been reported that the IGRAs results may be less affected by age than the TST results [30]. According to the recent study performed in Taiwan [29], the sensitivity of QFT-GIT decreased with age, and the QFT-Plus test had higher sensitivity than the QFT-GIT test, with similar specificity, especially among the older participants (≥75 years).

Since few data exist on the use of IGRAs for LTBI diagnosis in older adults, future researches on the utility of these tests particularly QFT-Plus are highly recommended.

Previous studies have found that IGRAs tend to have a high variability with high rates of conversions and reversions in serial testing [11]. The high rate of reversion might be caused by the transient positive results in QFTs [29]. In Chien et al. study, authors used a reproducibility analysis by repeated testing within one month and reported a similar reversion rate (21.6% in QFT-Plus and 22.7% in QFT-GIT) [29]. In Knierer et al. study [11], in four serial measurements at weekly intervals in students with a migration background in Germany, using QFT-GIT kit, a reversion rate of 3.2% (1 of 31 possible reversions, 95% CI 0.2–18.5%) and conversion rate of 2.2% (2 of 91 possible conversions, 95% CI 0.4–8.5%) was reported, while QFT-Plus reversion and conversion rates were slightly higher than for the QFT-GIT (6.9% (2 of 29, 95% CI 1.2–24.2%) and 4.3% (4 of 93, 95% CI 1.4–11.3%), respectively) [11]. In that study, the QFT had a reversion rate of 3.2% and a conversion rate of 2.2% - both rates were slightly higher for the QFT-Plus: 6.9% reversions and 4.3% conversions, however, the sample size of this study was low [11].

Major changes in the QFT-Plus design include the elimination of the TB7.7 peptide from TB1 tube and adding the TB2 tube which contains an additional set of peptides targeted for cell-mediated immune response from CD8+ cytotoxic T lymphocytes which come now as a sticky resin instead of the previous powdery formulation [24]. Some studies reported that the absence of the Tb7.7 antigen from the QFT-Plus does not statistically significantly impact the assay's performance [16,22,23], however, these results notably differ from Hoffmann et al. [24] and Horne et al. [20] studies which reported statistically significantly higher IFN-γ concentrations in the conventional QFT than TB1 tube of QFT-plus.

In Chien et al. study, among 11 subjects with transient positive QFTs results (possible LTBI), 7 cases (63.6%) were transient positive for QFT, and 4 (36.3%) subjects were transient positive in the TB1 tube of the QFT-plus. This might be caused by the slightly higher specificity of the TB1 resulting from the removal of the TB7.7 antigen from the TB1 tube [29].

Petruccioli et al. [16] found that the majority of LTBI subjects simultaneously responded to both TB1 and TB2 antigens, and that an "only to TB2" response was associated with active TB, however, these results are based on one single study and further studies are highly recommended. It has been reported that the response from CD8 + T-cells correlates well with the bacterial load [16,31,32]. TB2-specific CD8 + T-cell responses were more frequently observed in the active TB cases versus patients with LTBI (44% vs. 20%) [23]. Notably, a higher prevalence of *M. tuberculosis*-specific CD8 + T-cells have been reported in smear-positive versus smear-negative patients and in pulmonary TB compared with extrapulmonary TB [33]. Consistent with this paradigm, "only TB2" response after the completion of TB therapy due to decreasing of mycobacterial load was not reported in the study by Petruccioli et al. [16]. Therefore, investigation of the TB1 and TB2 response could serve as a new tool for monitoring the efficacy of TB therapy [16].

Comparing QFT-Plus and QFT-IT in co-infected HIV-TB subjects demonstrated the higher sensitivity of the QFT-Plus compared to QFT-IT [34,35]. This fact may be due to the addition of the TB2 tube which could be potentially useful in conditions of CD4 T-cell impairments [16]. However, the majority of the cases included in this article were immunocompetent and they did not analyze the QFT-Plus performance in immunocompromised subjects separately.

While equivalent performance between the two QFT IGRAs was observed, addition of the TB2 antigen tube to the QFT-Plus improves the diagnostic accuracy of this kit. However, further studies in patients with CD8 + T-cell reliant disease states (e.g. HIV infection with low CD4 counts) are highly recommended.

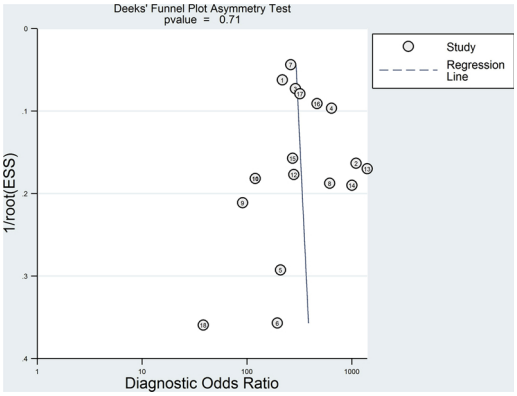

Fig. 4. Deek's funnel plot asymmetry test for publication bias. Deek's funnel plot asymmetry test did not suggest potential publication bias (p = 0.71).

4.1. Limitations of the study

This study has some limitations. First, because of the lack of gold-standard tests for LTBI, we were unable to adequately resolve the discordance between the QFT-GIT and QFT-Plus. Second, the effect of HIV infection was not analyzed. Third, the number of the cured samples was low. The ability of TB1 and TB2 response to monitor the efficacy of TB treatment was based on one single study. Since investigation of the TB1 and TB2 response may be useful to find new tools to monitor the efficacy of TB therapy, further studies on this population are highly recommended.

5. Conclusions

In conclusion, we conducted the first systematic review and meta-analysis concerning the diagnostic test accuracy of QFT-Plus for detection of TB. In summary, QFT-Plus performs equivalently to the QFT-GIT for detection of patients at risk for LTBI, however, QFT-Plus test had higher sensitivity than the QFT-GIT test, with similar specificity among the older participants.

Higher IFN-γ release in TB2 compared to TB1 in diagnosis of active TB was described in the majority of the included studies. On the contrary, declining IFN-γ release in TB2 could serve as a tool for monitoring the efficacy of TB therapy, however, further significance of responses in TB1 and TB2 of QFT-Plus needs to be explored in different population.

Future studies are needed to find whether the discordance results between QFT-GIT and QFT-Plus result from the higher sensitivity or from higher false-positive rates of the QFT-Plus. In addition, it should be further investigated whether the numbers of indeterminate test results are reproducibly lower with the QFT-Plus than with the conventional QFTG-IT.

Since IGRAs have reduced sensitivity in children and immunocompromised subjects, such as HIV-infected individuals [36], further studies on evaluation of QFT-Plus in detecting TB in these groups are highly recommended.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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The author Contribution

Study Design: Shima Mahmoudi.
Data Collection: Shima Mahmoudi, Sepideh Benvari.
Statistical Analysis: Shima Mahmoudi, Babak Pourakbari.
Data Interpretation: Shima Mahmoudi, Babak Pourakbari, Setareh Mamishi.
Manuscript Preparation: Shima Mahmoudi, Sepideh Benvari.
Literature Search: Shima Mahmoudi, Sepideh Benvari.
Funds Collection: Shima Mahmoudi.

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