Diagnostic accuracy of the interferon-gamma release assay in acquired immunodeficiency syndrome patients with suspected tuberculosis infection: a meta-analysis

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Abstract
Purpose The diagnostic accuracy of the interferon-gamma release assay (IGRA) in immunosuppressed patients remains unclear.
Methods A systematic review and meta-analysis were performed for diagnostic test accuracy of IGRA in tuberculosis (TB) infection among people living with HIV (PLWHIV). Summary estimates of sensitivity and specificity were calculated using both univariate and bivariate models.
Results The meta-analysis included 45 of the 1,242 first-screened articles. The total number of PLWHIV was 6,525; 3,467 had TB disease, including 806 cases of LTBI and 2,661 cases of active TB. The overall diagnostic odds ratio (DOR) of IGRA in the diagnosis of TB disease was 10.0 (95% confidence interval (CI) 5.59, 25.07), with an area under the curve (AUC) of 0.729. The DOR was better for QFT (14.2 (95% CI 4.359, 46.463)) than T-SPOT (10.0 (95% CI 3.866, 26.033)). The sensitivity and specificity of QFT and T-SPOT were 0.663 (95% CI 0.471, 0.813), 0.867 (95% CI 0.683, 0.942), and 0.604 (95% CI 0.481, 0.715), 0.862 (95% CI 0.654, 0.954), respectively, in the bivariate model. The sensitivity of IGRA in the diagnosis of LTBI was 0.64 (95% CI 0.61, 0.66).
Conclusion IGRA was useful in the diagnostic of TB disease in PLWHIV, and QFT showed a better tendency of DOR than T-SPOT. IGRA showed a limited effect to rule out LTBI in PLWHIV.

Keywords Interferon-gamma release assay · Tuberculosis · People living with HIV · Sensitivity · Specificity

Introduction

Individuals infected with Mycobacterium tuberculosis (Mtb) may develop symptoms and signs of active tuberculosis (ATB) or may stay in latent tuberculosis infection (LTBI) which have no clinical evidence of the active disease [1]. Mtb is the leading cause of opportunistic infection involved in the death of people living with human immunodeficiency virus (PLWHIV) [2], while the diagnosis is further problematic due to its paucibacillary nature. In addition, human immunodeficiency virus (HIV) infection may cause respiratory problems that can
mimic tuberculosis clinically and/or radiologically. An early diagnosis in this group is thus important.

Until recently, the tuberculin skin test (TST) has been the only method to test for latent infection with Mtb. The TST has well-known strengths and limitations by measuring the delayed type hypersensitivity response to intradermal injection of purified protein derivative [3]. Whereas the TST encompasses antigens recognized by a vast pool of circulating T lymphocytes, the two interferon-gamma (IFN-γ) release assays (IGRAs), the QuantiFERON-TB® assay (Cellestis Limited, Victoria, Australia) and T-SPOT-TB® (Oxford Immuno-tec, London, UK), focus on interferon-gamma responses to epitopes from two specific antigens which is associated with Mtb complex, namely early secretory antigenic-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). No direct tests for LTBI, and therefore no gold standards, are available with which to compare LTBI test characteristics [4]. IGRA rather than TST was recommended by the Centers for Disease Control and Prevention (CDC) in individuals 5 years or older upon the likelihood of infection with Mtb and the likelihood of progression to TB disease if infected [1].

For the IGRA or TST to reliably rule out a diagnosis of Mtb infection and thus TB disease, the sensitivity of the test must be very high (>95%) [5]. The sensitivity and specificity of IGRAs compared with the TST in active TB have been examined in several studies, varying in value and quality [6]. IGRA have a better predictive ability than tuberculosis skin tests. Individuals who are positive on an IGRA might benefit from preventive treatment, but those who are positive by IGRAs will not [7]. The pooled sensitivity (95% confidence interval (CI)) of QFT and T-SPOT, T-SPOT, and TST was: 80% (75–84%), 81% (78–84%), and 65% (61–68%), respectively, in the previous meta-analysis and the sensitivity of IGRAs was too low to support their use as the only method to test for latent infection with Mtb [8]. PLWHIV represents a group to be in the high risk of reactivating LTBI. Furthermore, immunosuppression can lower the spum bacillary load, making the diagnosis of ATB by microscopy more challenging [9].

Study overview

This systematic review and meta-analysis of diagnostic test accuracy was prepared following standard guidelines for systematic reviews of diagnostic test accuracy and registered on the website of the University Hospital Medical Information Network Clinical Trials Registration (UMIN000045715) [11, 12]. Due to the nature of this study, approval of the Institutional Review Board was waived.

Methods

Study overview

This systematic review and meta-analysis of diagnostic test accuracy was prepared following standard guidelines for systematic reviews of diagnostic test accuracy and registered on the website of the University Hospital Medical Information Network Clinical Trials Registration (UMIN000045715) [11, 12]. Due to the nature of this study, approval of the Institutional Review Board was waived.

Study search

Four major online databases, PubMed, Web of Science, Cochrane, and Embase, were searched (September 30, 2021). The following search strategy was used for PubMed: (((interferon-γ release assay) OR (interferon-gamma release assay)) OR (IGRA)) AND (((HIV) OR (Human Immunodeficiency Virus)) OR (acquired immunodeficiency syndrome)) OR (AIDS)).

Two authors (HC and AN) independently screened the titles and abstracts and carefully evaluated the full text to select eligible articles; in cases of discrepancy, they reached a consensus through discussion. Review articles and included original articles were hand-searched (HC and AN) for additional research papers that met the inclusion criteria.

Study selection

Full articles, brief reports, and conference abstracts published in any language that provided data for sensitivity and specificity of IGRA to diagnose TB were included. An article that provided data of both sensitivity and specificity was included in the bivariate analysis [11]. An article that provided data of either sensitivity or specificity was included in the univariate analysis. A case–control study design that consisted of patients with or without TB disease was accepted, though a case–control design may be considered to have a risk of bias according to Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [13].

The target population was PLWHIV with TB and LTBI co-infection. The diagnostic criterion for ATB was spum culture-positive for TB or detection of nucleic acids, both DNA and RNA, which are specific to Mycobacterium tuberculosis, by amplification techniques such as polymerase chain reaction. LTBI is a subclinical mycobacterial infection defined on the basis of cellular immune response to mycobacterial antigens [14]. TST and IGRA are currently used to establish the diagnosis of LTB. The diagnostic criteria for LTBI were either positive on IGRA or TST or a radiograph without clinical findings of active TB. The target IGRA test included T-SPOT and QFT.

Outcomes

Sensitivity, specificity, area under the curve (AUC), and the diagnostic odds ratio were evaluated in studies with both sensitivity and specificity. Univariate analysis was conducted...
for studies with either sensitivity or specificity. Only data from the 3rd and 4th generations of QFT (QuantiFERON-TB-Gold In-Tube and QuantiFERON-plus) were included for test accuracy in this meta-analysis. Studies with test accuracy of the T-SPOT were all enrolled in this analysis. Indeterminate IGRA results were classified as false-negative results.

Data extraction

Two review authors, HC and AN, independently extracted data, including the name of the first author, publication year, publication country, numbers of patients with positive results, numbers of patients evaluated, and QUADAS-2-related information. Risk of bias was appraised by QUADAS-2 in each study [13].

Statistics

A bivariate model was used to obtain pooled sensitivity and specificity and to draw a summary receiver-operating characteristic curve (SROC) [15]. The diagnostic odds ratio (DOR) was obtained by the DerSimonian–Laird random model. The DOR was calculated by the “madauni” command (“netmeta” package of R project, Gerta Rücker, Denmark). Sensitivity, specificity, and AUC were pooled by the “reitsma” command (“netmeta” package of R project, Gerta Rücker, Denmark). AUCs were interpreted as follows: ≥0.97, excellent; 0.93–0.96, very good; 0.75–0.92, good; and 0.5–0.74, fair [16]. The threshold for significance was set at 0.05. Heterogeneity evaluated using $I^2$ statistics was interpreted as follows: $I^2 = 0\%$, no heterogeneity; $I^2 > 0\%$ but $< 25\%$, minimal heterogeneity; $I^2 \geq 25\%$ but $< 50\%$, mild heterogeneity; $I^2 \geq 50\%$ but $< 75\%$, moderate heterogeneity; and $I^2 \geq 75\%$, strong heterogeneity [17].

Results

Study search and study characteristics

A total of 1,242 articles, including 1,239 articles through database search and 3 articles by hand search, were identified; 937, 192, and 47 articles were left after removing duplication, screening, and full-article reading, respectively (Supplementary Figure S1). Finally, 45 reports, comprising 42 full-length articles and 3 conference abstracts, were included (Table 1) [2, 5, 18–60]. All were written in English. Prospective study designs were adopted in 34 articles, and the other 11 were retrospective studies. Of the 47 reports, six were from South Africa, five were from the USA, four were from China, Italy, and the UK, and two were from Brazil and India. Of the 6,525 PLWHIV were enrolled in this study, 3,467 had TB disease, including 806 cases of LTBI and 2,661 cases of ATB. Nine studies discussed diagnostic accuracy including both T-SPOT and QFT, and 22 and 12 studies discussed the test accuracy of only the QFT or the T-SPOT, respectively. Only five studies discussed test accuracy in children, and two studies checked IGRAs in all populations. The remaining 38 studies checked IGRAs in adults, including two studies that checked IGRAs in women only.

Diagnostic accuracy of IGRAs in TB

Nineteen studies checked the diagnostic accuracy of IGRAs with both sensitivity and specificity. Thirty-nine studies checked the sensitivity of T-SPOT or QFT in PLWHIV with suspected TB. The univariate analysis of IGRAs in PLWHIV showed sensitivity and specificity of 0.65 (95% CI 0.63, 0.66) and 0.92 (95% CI 0.91, 0.93), respectively (Fig. 1).

Diagnostic accuracy of IGRAs in ATB

The diagnostic accuracy of IGRAs in ATB was conducted in 49 studies, including in 5,430 participants. On univariate analysis, the sensitivity and specificity were 0.66 (95% CI 0.63, 0.68) and 0.92 (95% CI 0.91, 0.93), respectively (Supplementary Figure S2). On bivariate analysis of the test accuracy of IGRAs in 18 studies, the DOR was 11.84 (95% CI 5.59, 25.07; $I^2 = 0\%$), with AUC of 0.779. This AUC value suggests that IGRA had “good” diagnostic test accuracy for TB disease (Fig. 2) [16]. Using the data from 45 studies of 7,120 specimens, the summary estimates of sensitivity and specificity were 0.631 (95% CI 0.523, 0.727) and 0.866 (95% CI 0.744, 0.934), respectively.

Diagnostic accuracy of IGRAs in LTBI

Since there was no gold standard to diagnose LTBI, seven studies discussed the sensitivity of IGRA in PLWHIV with different diagnostic standards. Five studies defined LTBI by LTBI risk and at least one positive test (TST or IGRA), without clinical evidence of active TB. Two studies calculated sensitivity from supposed presence of LTBI. The univariate analysis yielded a sensitivity of 0.64 (95% CI 0.61, 0.66) in 1,267 patients (Supplementary Figure S3).

Diagnostic accuracy of QFT in ATB

Data of 2,519 samples from nine reports suggested a DOR of 14.2 (95% CI 4.36, 46.46; $I^2 = 0\%$) and an AUC of 0.822, which means that QFT had “good” diagnostic test accuracy for TB disease (Fig. 3). The summary estimates of sensitivity and specificity were 0.663 (95% CI 0.471, 0.813) and 0.867 (95% CI 0.683, 0.942), respectively. The univariate analyses showed sensitivity and specificity of
Table 1 Background characteristics of enrolled studies

| Author/year | Country      | Types of TB | Type of article | Nature of study | Adult | IGRA       | TB patients | All patients |
|-------------|--------------|-------------|-----------------|-----------------|-------|------------|-------------|--------------|
| Aabye 2009  | Tanzania     | AT          | FA              | Retro           | Adult | QFT-GIT    | 161         | 161          |
| Adams 2019  | South Africa | LTBI        | FA              | Retro           | Adult | QFT-GIT    | 496         | 496          |
| Cai 2014    | China        | AT          | FA              | Retro           | Adult | T-SPOT     | 100         | 100          |
| Cattamanchi 2010 | USA | AT       | FA              | pros            | Adult | T-SPOT     | 112         | 212          |
| Chee 2008   | Singapore    | AT          | FA              | retro           | Adult | Q&T        | 280         | 280          |
| Chen 2011   | China        | AT          | FA              | pros            | Adult | T-SPOT     | 38          | 147          |
| Clark 2007  | UK           | AT          | FA              | pros            | Adult | T-SPOT     | 30          | 30           |
| Davies 2009 | South Africa | AT          | FA              | pros            | Children | T-SPOT | 60          | 109          |
| Dheda 2009  | South Africa | AT          | FA              | pros            | Adult | Q&T        | 20          | 20           |
| Elzi 2011   | Switzerland  | LTBI        | FA              | pros            | Adult | T-SPOT     | 64          | 64           |
| Fujita 2011 | Japan        | AT          | FA              | pros            | Adult | QFT-GIT    | 9           | 107          |
| Garcia-Gasalla 2013 | Spain | AT       | FA              | pros            | Adult | QFT-GIT    | 118         | 118          |
| Hormi 2018  | France       | AT          | FA              | pros            | Children | QFT-GIT | 24          | 24           |
| Idr 2010    | Sweden       | AT          | FA              | pros            | Adult | QFT-GIT    | 69          | 69           |
| Jiang 2009  | China        | AT          | &LTBI           | pros            | Adult | T-SPOT     | 100         | 100          |
| Jonnalagadda 2013 | USA | AT       | FA              | retro           | Adult(W) | T-SPOT | 9           | 9            |
| Kabeer 2011 | India        | AT          | FA              | pros            | Adult | QFT-GIT    | 105         | 105          |
| Kaswandani 2018 | Indonesia | TB       | CA              | retro           | Children | QFT-GIT | 10          | 10           |
| Khawcharoenporn 2015 | Thailand | LTBI        | FA              | pros            | Adult | QFT-GIT    | 36          | 36           |
| Klaauan 2018 | Brazil     | LTBI        | FA              | retro           | Adult | QFT-GIT    | 84          | 84           |
| Kussen 2016 | Brazil       | LTBI        | FA              | pros            | Adult | QFT-GIT    | 25          | 25           |
| LaCourse 2017 | USA    | AT          | FA              | pros            | Adult (W) | QFT-GIT | 100         | 100          |
| Lavender 2011 | UK         | AT          | CA              | retro           | Adult | QFT-GIT    | 66          | 326          |
| Lee 2019    | Korea        | TB          | FA              | pros            | Adult | T-SPOT     | 25          | 62           |
| Legesse 2010 | Ethiopia   | AT          | FA              | pros            | Adult | QFT-GIT    | 50          | 50           |
| Leidl 2010  | Uganda       | AT          | FA              | retro           | Adult | Q&T        | 19          | 19           |
| ling 2011   | Canada       | AT          | FA              | pros            | Adult | Q&T        | 127         | 127          |
| Lundtoft 2017 | Ghana     | AT          | FA              | pros            | Children | QFT-GIT | 25          | 25           |
| Markova 2009 | Bulgaria   | AT          | FA              | pros            | Adult | Q&T        | 13          | 90           |
| Oni 2010    | UK           | AT          | FA              | pros            | Adult | T-SPOT     | 85          | 85           |
| Petrucciolli 2020 | Italy    | AT          | FA              | pros            | Adult | QFT-plus   | 32          | 32           |
| Pettit 2020 | USA          | LTBI        | FA              | pros            | All    | Q&T        | 81          | 1520         |
| Raby 2008   | Zambia       | AT          | FA              | pros            | Adult | QFT-GIT    | 96          | 96           |
| Rangaka 2012 | South Africa | LTBI        | FA              | pros            | Adult | QFT-GIT    | 50          | 50           |
| Sanogo 2020 | Burkina      | AT          | FA              | pros            | Children | QFT-GIT | 29          | 58           |
| Sattah 2012 | USA          | AT          | CA              | retro           | Adult | T-SPOT     | 9           | 9            |
| Sauzello 2010 | Italy     | AT          | FA              | pros            | Adult | QFT-GIT    | 30          | 194          |
| Sauzullo 2014 | Italy      | AT          | FA              | pros            | Adult | QFT-GIT    | 44          | 44           |
| Stavri 2009 | Romania      | AT          | FA              | pros            | All    | QFT-GIT    | 36          | 36           |
| Takwoingi 2019 | UK         | AT          | FA              | retro           | Adult | Q&T        | 385         | 911          |
| Tsiouris 2006 | South Africa | AT          | FA              | pros            | Adult | QFT-GIT    | 36          | 36           |
| Vanini 2012 | Italy        | AT          | FA              | pros            | Adult | QFT-GIT    | 58          | 58           |
| Veldsman 2009 | South Africa | AT          | FA              | pros            | Adult | QFT-GIT    | 30          | 60           |
| Vincenti 2007 | India      | AT          | FA              | pros            | Adult | Q&T        | 45          | 111          |
| Yu 2013     | China        | AT          | FA              | pros            | Adult | T-SPOT     | 46          | 120          |

*TB* tuberculosis disease, *AT* active TB; *LTBI* latent tuberculosis infection; *IGRA* interferon-gamma release assay, *QFT-GIT* QuantiFERON-TB-Gold In-Tube, *T-SPOT* T-SPOT.TB, *Q&T* QuantiFERON-TB-Gold In-Tube and T-SPOT.TB
Fig. 1 Forest plot of all enrolled studies including IGRA test accuracy. Pooled sensitivity and specificity are 0.65 (95%CI 0.63, 0.66) and 0.92 (95%CI 0.91, 0.93), respectively.
0.66 (95% CI 0.63, 0.69) and 0.91 (95% CI 0.90, 0.92), respectively, in 27 studies of 3,369 cases of ATB disease in PLWHIV (Supplementary Figure S4).

Diagnostic accuracy of T-SPOT in ATB

Nine studies were included in the bivariate analysis of test accuracy with 2,397 samples that yielded a DOR of 10.0 (95% CI 3.87, 26.03; $I^2 = 2.6\%$) and an AUC of 0.729. This AUC suggested that T-SPOT had "good" diagnostic test accuracy for TB (Fig. 4) [16]. The summary estimates of sensitivity and specificity were 0.604 (95% CI 0.481, 0.715) and 0.862 (95% CI 0.654, 0.954), respectively. The univariate analysis showed that the sensitivity and specificity of T-SPOT were 0.65 (95% CI 0.62, 0.68) and 0.93 (0.92, 0.94), respectively, in 16 studies of 2,810 patients of TB disease in PLWHIV (Supplementary Figure S5).

Diagnostic accuracy of QFT and T-SPOT in LTBI

The sensitivity of QFT and T-SPOT in the diagnosis of LTBI was 0.66 (95% CI 0.63, 0.70) and 0.60 (95% CI 0.56, 0.64), respectively (Supplementary Figure S6, S7). The specificity of QFT and T-SPOT was not estimable.

The risk of bias is shown in Supplementary Figure S8. There were 2 studies with unclear patient selection bias, and 7 studies had a high risk of a reference standard issue. No study showed bias in patient selection applicability concerns, index test, index test applicability concerns, reference standard applicability concerns, and flow and timing.

Discussion

The diagnostic test accuracies of the IGRA QFT and T-SPOT were systematically reviewed. Based on the analysis, QFT showed a better DOR and AUC than T-SPOT in the diagnosis of TB disease, and both of them showed "good" diagnostic accuracy. This systematic review and meta-analysis provided evidence supporting the use of IGRAs in the diagnosis of TB disease in PLWHIV, as in the current guidelines [1, 61]. Although different
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IGRAs were useful in the diagnosis of TB disease in PLWHIV, and QFT showed a better tendency of DOR than T-SPOT. IGRAs showed a limited effect to rule-out LTBI in PLWHIV.

Conclusion

IGRA was useful in the diagnosis of TB disease in PLWHIV, and QFT showed a better tendency of DOR than T-SPOT. IGRAs showed a limited effect to rule-out LTBI in PLWHIV.

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Data availability statement The raw data are available by email on reasonable request to the corresponding author at nseki@med.teikyo-u.ac.jp.

Declaration

Conflicts of interest The authors declare that no conflicts of interests exist.

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