Scientific Research Publishing

Journal of Tuberculosis Research, 2024, 12, 183-192
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Interferon Gamma Release Assay for Latent Tuberculosis Screening in High TB-Endemic Region: A Retrospective Study

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How to cite this paper: Anwar, S., Saleh, A.A., Ahmed, S.A., Farook, S., Udoy, F.M., Islam, M., Siddiqui, T.A. and Ahmed, M.S. (2024) Interferon Gamma Release Assay for Latent Tuberculosis Screening in High TB-Endemic Region: A Retrospective Study. *Journal of Tuberculosis Research*, **12**, 183-192. https://doi.org/10.4236/jtr.2024.124013

Received: October 5, 2024
Accepted: October 27, 2024
Published: October 30, 2024

Abstract

Introduction: Tuberculosis (TB) remains a significant public health challenge, particularly in high-endemicity settings where latent TB infections (LTBI) contribute to ongoing transmission. Early identification and management of LTBI are crucial in limiting the spread of the disease. This study demonstrates the role of Interferon Gamma Release Assay (IGRA) as a screening tool for latent tuberculosis in high-burden region. **Materials and Methods:** This retrospective observational study assessed the detection of LTBI using the QuantiFERON-TB Gold Plus (QFT-Plus) test among 145 patients at the Department of Microbiology & Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from August 2023 to August 2024. The study included patients suspected of TB, those screened before immunosuppressive therapy, organ transplantation, or kidney dialysis. Participants were tested IGRA using QFT-Plus, which detects interferon-gamma (IFN-γ) released in response to *Mycobacterium tuberculosis* antigens. **Results and Discussion:** Among 145 patients tested for the QFT-Gold Plus test, 55.17% (n = 80) were positive for LTBI, with a substantial agreement between TB1 and TB2 responses ($p < 0.05$). Among the study population, 71 (49%) were male, while 74 (51%) were female. The median age of the participants was 37 (5 - 88 years). About 139 of them were BCG vaccinated and all of them were known to be HIV-negative. Notably, 70% of LTBI-positive cases showed a TB1 response, while 22.5% had positive results for both TB1 and TB2. Most patients tested for LTBI were suspected TB cases (122 patients), accounting for approximately 85% of the total. A smaller portion of patients underwent screening before medical procedures such as dialysis (15 patients or 10%) and transplant (8 patients or 5%). Night sweats were the most common symptoms (55.7%), followed by cough and weight loss.

Chest X ray findings were negative for all the patients. **Conclusion:** The results highlight that QFT-Plus may be utilized as a useful diagnostic screening tool for latent TB in regions with a high disease burden, though challenges related to cost and infrastructure persist. With growing global efforts to eliminate tuberculosis, focused screening and treatment of LTBI in high-risk groups could play a vital role in reducing the progression of TB. The study underscores the importance of targeted screening for LTBI to reduce the progression to active TB, particularly in resource-limited settings.

Keywords

Latent Tuberculosis Infection (LTBI), Interferon-Gamma Release Assay (IGRA), High Endemicity Regions, LTBI Risk Factors

1. Introduction

The state of sustained immunological response to stimulation by *Mycobacterium tuberculosis* (Mtb) antigens without clinically evident active tuberculosis (TB) infection is known as latent tuberculosis. Infected persons with latent tuberculosis do not usually exhibit clinical signs and symptoms, but the organism is harbored in macrophage in an inactive stage. LTBI represents a balance between the host and the bacillus, where in most cases, the host's immune response is strong enough to prevent active disease throughout life. However, in some instances, the immune system fails to contain the infection, leading to reactivation and progression to active disease [1]. In 2014, it was estimated that 23.0% of the global population (with a 95% uncertainty interval of 20.4% - 26.4%) had LTBI, equating to about 1.7 billion individuals. The highest prevalence was observed in the WHO regions of South-East Asia, the Western Pacific, and Africa, which together accounted for approximately 80% of the global LTBI population. From this vast reservoir of asymptomatic individuals, 8 to 10 million active tuberculosis cases arise each year, leading to nearly 1.7 million deaths annually [2]-[4]. According to the National Guideline and Operational Manual of Tuberculosis, Bangladesh, 2020, 5% - 10% of infected persons with latent TB may progress to active disease in their lifetime. 90% - 95% remain latently infected without developing active disease or becoming infectious [5]. The potential risk factors that increase their susceptibility to TB include malnourishment, HIV infection, diabetes, prison, tobacco smoking, etc. Host genetic factors, geographic and ethnic clustering of tuberculosis, strain variability, and genetic diversity of Mtb contribute to the risk of developing tuberculosis [1]. Early detection and prevention of latent TB can reduce the progression to active disease by 60% to 90% [4]. In Bangladesh, 292,942 TB patients were notified to the National Tuberculosis Control Programme in 2019, placing Bangladesh in the top ten nations in the world with the most significant TB burden [6]. Consequently, it is essential to target the latent TB population for improved eradication of tuberculosis in such a high-burden region. According to National

Tuberculosis Control Programme (NTP) framework, LTBI screening is suggested for individuals with HIV, household contacts, people undergoing dialysis, organ transplant, or anti TNF treatment, diabetes, smokers, and those with chronic kidney diseases. The national guideline recommends isoniazid (INH) therapy typically for six to nine months for individuals testing positive for LTBI but without active TB. Contact investigations are conducted for those who may have been exposed to TB, especially for close contacts of confirmed TB patients [5]. Till now, no definite studies have been conducted in Bangladesh to identify the load of latent tuberculosis among the general population. The methods used to determine latent tuberculosis available in Bangladesh are TST (Tuberculin Skin Test) and IGRA using QuantiFERON TB gold plus Assay. The antigens used in this assay are encoded by genes deleted in the vaccine strain of BCG and most environmental mycobacteria of clinical relevance [7]. IGRAs cannot distinguish between LTBI and active TB in immunocompetent individuals, in high-risk individuals with immunosuppressive conditions, or in children unaffected by prior BCG vaccination and have no cross-reactivity with most environmental mycobacteria. Although TST has been used for about a hundred years to diagnose latent TB and is widely used in Bangladesh as well, the possibility of cross-reactivity with Bacillus Calmette-Guérin (BCG) and other nontuberculous mycobacteria has rendered QFT-Plus a better diagnostic method to identify latent TB [8]. A study conducted in 2022 among 732 healthcare workers revealed 40% positivity in TST, while 48% was positive in the QFT test [9]. For large-scale screening in low-resource settings, TST might still be preferred due to cost, but for more accurate diagnosis, particularly in specific risk groups, IGRA can often be the better choice [8]. Thus, we aimed to evaluate the detection rate of QFT Plus positive latent tuberculosis infection among suspected and routine cases referred to the Microbiology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

2. Methodology

2.1. Patient Enrollment and Demographics

The study was conducted retrospectively in the Department of Microbiology and Immunology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, over one year (August 2023 to August 2024). Patients suspected of latent TB infection (LTBI) or active TB, particularly those exhibiting symptoms such as a persistent cough, night sweats, or weight loss, as well as immunocompromised individuals, and those undergoing dialysis or organ transplantation, are often prescribed screening tests for LTBI in the outdoor of the hospital. QFT-Plus tests were performed in the Department of Microbiology & Immunology and the results were recorded. Patients with clinical symptoms of TB were screened for TB disease and excluded from this study if active TB disease was diagnosed and if they had received any TB treatment for more than four weeks before screening and 12 weeks before testing. Pregnant women and patients who had their QFT-Plus tests after 12 weeks post-exposure were excluded. A structured questionnaire was

provided to each of the 145 patients to collect demographic information, contact history, clinical features associated with tuberculosis, previous TB history, HIV status, BCG vaccination status, and history of corticosteroid or cancer chemotherapy intake in the past three months before performing QFT-Plus. All participants were also subjected to chest radiography and sputum AFB staining to exclude active tuberculosis. The reports were collected.

Interferon Gamma Release Assay (IGRA)

Blood was collected from each participant using all aseptic precautions in a unique tube coated with a cocktail of tubercular antigens. Blood is stimulated with peptides from Mtb-specific antigens (ESAT-6, CFP-10 for the TB1 tube of QFT-GT with some additions of new peptide for the TB2 tube that stimulate IFN-γ production by CD4+ T cells and CD8+ T cells). The plasma is then tested for IFN-γ in response to tubercular antigen. An aQuantiFERON®-TB Gold (QFT®)Plus (Qiagen, The Netherlands) ELISA test was performed to detect latent TB infection [10]. Individuals infected with Mtb complex organisms recognize these mycobacterial antigens. This recognition process involves the generation and secretion of the cytokine IFN-γ. The detection and subsequent quantification of IFN-γ form the basis of this test. The test was performed according to the manufacturer's instructions, using equal volumes of plasma (50 µl) and conjugate (50 µl) in the first step of the Assay. OD values were measured using an ELISA reader. The QFT Analysis Software was used to analyze raw data and to calculate results. The software made all the calculations, generated a standard curve, and provided a test result for each subject. For the QuantiFERON-TB Gold test to be valid, the nil value must be less than or equal to 8.0 IU/mL, and the mitogen value (positive control for IFN-γ production) must be at least 0.5 IU/mL higher than the nil value. The test is positive for IFN-γ response if the TB antigen minus nil value is at least 0.35 IU/mL [7]. The tests were performed by the routine diagnostic laboratory at Molecular Lab, Microbiology Department, who reported results as QFT plus positive and negative; this result was used to classify the subjects as LTBI positive or negative.

2.2. Statistical Analysis

Descriptive analysis of all relevant variables was done by using frequency, percentage and mean. We calculated the kappa coefficient (κ), which measures the level of agreement between TB2 and TB1 results. We also assessed the statistical significance of the kappa value. Collected data were checked, edited and analyzed using SPSS version-26 (Strata Corporation, College Station, Texas). P value < 0.05 was considered statistically significant.

3. Result

Among 145 patients visiting the laboratory for IGRA test, 71 (49%) were male, while 74 (51%) were female. The median age of the participants was 37 (5-88 years). About 139 of them were BCG vaccinated, and 06 patients could not confirm their BCG vaccination status. All of them were known to be HIV-negative.

The participants experienced certain clinical features such as cough, night sweats, and weight loss which were subjected to latent TB investigation. However, none of the patients experienced an evening rise in temperature and had normal findings in chest radiography. The demographic data along with patient characteristics have been tabulated (Table 1).

Table 1. Characteristics of patients referred for QFT-Plus test.

Characteristics	Number of patients with incidence (n = 145)
Median age (years) (range)	37 (5 - 88 years)
Gender distribution	Male = 71, Female = 74
Number of patients with reason for screening of QFT Plus test	
1. Suspected Tb cases (Chest X-Ray negative)	122
2. Screening before dialysis	15
3. Screening before transplant	8
Symptoms of suspected TB cases:	
1. Cough	62
2. Night sweats	68
3. Weight loss	57
Contact history	7
BCG vaccine	139
Intake of anticancer drugs or corticosteroids or Anti TNF therapy	0

Among QFT Plus results from 145 patients, 80 (55.17%) were positive (≥0.35 IU/mL according to the manufacturer's protocol), and 65 (44.83%) were negative (<0.35 IU/mL). None of the samples were found to be indeterminate. Among 80 QFT Plus positive patients, only TB1 results of ≥0.35 IU/mL were found in 70% patients. Only TB2 positive with cut off more than ≥0.35 IU/mL with a TB1 < 0.35 IU/mL was found to be 7.5%. Using the 0.35 IU/mL cutoff, 22.5% were positive for both TB1 and TB2 (Table 2). The number of observed agreements between the TB1 and TB2 tubes was 57.24%, with a kappa value of 0.27. The agreement was statistically significant ($p < 0.05$).

Table 2. Agreement between TB1 and TB2 results.

Number of patients with TB2 result	Number of patients with TB1 result			
	Negative (<0.35 IU/ml)	Positive (≥0.35 IU/ml)	Indeterminate	Total (145)
Negative (<0.35 IU/ml)	65	56	0	121
Positive (≥0.35 IU/ml)	6	18	0	24
Indeterminate	0	0	0	0

*The cut-off value was used according to the manufacturer's protocol [10].

4. Discussion

Approximately one-third of the world's population is suspected to be infected with *Mycobacterium tuberculosis* [1]. However, not all people infected with the bacteria will suffer from active disease. To prevent the progression of active tuberculosis, it is essential to identify cases of latent tuberculosis and treat them accordingly. To our knowledge, no surveillance study has been conducted in Bangladesh to detect latent tuberculosis.

The study observed a total of 145 participants retrospectively who were referred to the Department of Microbiology and Immunology by the clinicians owing to LTB suspected cases, screening before dialysis, or organ transplantation. Out of 145 subjects, 80 (55%) were positive for IGRA by QFT Plus, with a female predominance of 56.3% (**Table 1**). In a study conducted by Islam *et al.* in 2023 among 731 Bangladeshi healthcare workers, 48% had a positive QFT-GIT result, which agrees with our result [9]. The median age for positive IGRA results was 38 years.

About 23 patients came for routine pre-screening purposes for IGRA before transplantation or dialyses purpose. The rest of the patients had a myriad of symptoms that mimicked tuberculosis, and a few were healthcare workers. However, due to the lack of fever and routine chest radiography, the clinicians mostly suspected other seasonal respiratory tract infections and referred the patients to exclude LTBI. The 80 patients with a positive IGRA result were again referred to the clinician to manage the infection with medicine, according to the National Guideline and Operational Manual for Tuberculosis, 2020 [5]. One limitation of this study was that, despite multiple efforts to inform the patients who tested positive to return for a follow-up IGRA test after completing their drug treatment, none of them attended for a repeat test. Additionally, the study faced challenges due to heterogeneity between participants, the inclusion of small number of study participants and the lack of individual-level data such as lymphocyte counts, TB culture results and other relevant factors. Further research is necessary to explore the link between baseline QFT-Plus responses and the development of incident TB during follow-up in contacts with untreated LTBI. The policymakers are already taking appropriate measures on how to initialize contact investigations of such cases.

The QFT Gold Plus test has recently become famous for detecting interferon-gamma released in response to tubercular antigens. Initially, the QFT-GIT test used three tubes instead of four. Two antigen tubes, TB1 and TB2, are included in the QFT-Plus. It is thought that the difference in IFN-γ between TB2 and TB1 tubes (TB2-TB1) can be used as a proxy for CD8 response [9]. A high CD8 IFN-γ response broadly indicates recent MTB infection and has been correlated with active TB disease [11]-[14]. Some studies have demonstrated that the median level of IFN-γ release is slightly higher in the TB2 tube, suggesting a heightened immune response. However, the TB2 tube's contribution to the diagnosis of active TB or LTBI appears to be limited, as its sensitivity improvement has not consistently translated into significant clinical impact in distinguishing TB stages or

conditions [15].

Applying the 0.35 IU/mL cutoff, the agreement between TB1 and TB2 tubes was fair, with a kappa value of 0.27. This may be due to a very limited number of samples (**Table 2**). A Swedish study conducted a screening study with QFT-Plus with 58,539 subjects, and the agreement between the two tubes was found to be excellent (>95%) with a kappa value of 0.86. The TB1 tube provided a QFT-Plus result above 0.35 IU/mL in 5.1% of cases, whereas the TB2 result uniquely provided a QFT-Plus result of ≥0.35 IU/mL in 6.3% in their study, whereas in our study, it was 70% and 7.5% respectively [11]. The lower kappa value of 0.27 in our study, compared to the much higher kappa value of 0.86 in the Swedish study, highlights the potential impact of sample size and population variation in our study. High TB endemic countries often have a more diverse population of individuals with varying levels of exposure to TB, BCG vaccination, and environmental mycobacteria. These factors can cause greater variability in immune responses [4].

The implementation of LTBI treatment in resource-limited settings is difficult in the identification of those at risk for developing active TB, uncertainty about effectiveness of preventive treatment in high-endemic areas, costs, and fear of enhancing the spread of resistant TB [16]. TST is preferred in Bangladesh than IGRA due to its cost effectiveness, however, the century-old TST has limitations, including low specificity due to false positives in populations vaccinated with the BCG vaccine and in individuals infected with non-tuberculous mycobacteria. Additionally, TST demonstrates low sensitivity in immunocompromised patients. To enhance TB diagnostics and global care, there is a critical need for simple, reliable tests that reduce the false positives and false negatives inherent in TST, providing clinicians with more accurate tools for diagnosing, controlling, and ultimately eliminating tuberculosis [17].

Tackling LTBI with screening and tuberculosis preventive treatment (TPT) is essential for eliminating the TB epidemic by 2035. With the scarce global resources that health ministries have in combating TB, it is essential to evaluate the economic benefits of LTBI screening and treatment approaches to maximize health outcomes with available resources. The cost of QFT-Plus may be difficult for general people to afford in a low-income country like Bangladesh, for which policymakers should take initiatives to reduce the price or make it available from the government, just like Gene-Xpert. According to the National Guideline and Operational Manual for Tuberculosis, 2020, evidence limitations prevent concluding the diagnosis and management of LTB. The higher initial costs of IGRAs compared to the TST, due to more expensive consumables, laboratory infrastructure, and specialized training make IGRAs less likely to be a cost-effective LTBI screening strategy in low- and middle-income countries (LMICs). Additionally, the need for advanced laboratory capabilities and trained personnel poses challenges for health systems in LMICs, which often struggle with inadequate infrastructure. Nonetheless, evidence indicates that targeted LTBI screening using IGRAs in high-risk groups, such as migrants, contacts, and healthcare workers,

can be cost-effective.

5. Conclusion

Latent tuberculosis screening is essential in high-endemic countries like Bangladesh to reduce the risk of active TB cases. With a high TB burden, identifying individuals with LTBI can help prevent the progression to active disease, which poses a significant public health threat. Screening high-risk populations, such as healthcare workers and immunocompromised individuals, is especially critical in preventing outbreaks in these vulnerable groups. Moreover, latent TB screening aligns with global TB elimination efforts by reducing the reservoir of latent infections and minimizing the spread of drug-resistant TB, which is a growing concern in Bangladesh. However, the detection and treatment of LTBI are critical components of the WHO End TB Strategy. Consequently, further surveillance studies utilizing the QFT Gold Plus test to understand the true prevalence of LTB are essential to end the TB burden in highly endemic countries like Bangladesh.

Ethical Considerations

The study was carried out in strict compliance with the Declaration of Helsinki according to which no intervention likely to alter the dignity, integrity, and right to privacy of participants will be implemented. Informed consent was taken from all the participants before the blood collection for their diagnostic tests.

Human ethics and consent to participate declarations: not applicable.

Acknowledgments

We thank the entire technical team of the Molecular Lab, Microbiology & Immunology Department, Bangabandhu Sheikh Mujib Medical University.

Data Availability

The data that support the findings are available from the Microbiology & Immunology Department, Bangabandhu Sheikh Mujib Medical University, but restrictions apply to the availability of these data so are not publicly available. Data are, however, accessible from the authors upon reasonable request and with permission of the department.

Contribution of the Authors

Study design: SA, AAS, SMA, SF.
Laboratory techniques: TAS, MS.
Data analysis: FMU, MI.
All authors acknowledge having read the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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