Diagnostic Utility of QuantiFERON-TB Gold (QFT-G) in Active Pulmonary Tuberculosis

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ABSTRACT

Background: The utility of QuantiFERON-TB Gold In-Tube (QFT-G) test in the diagnosis of tuberculosis disease has been validated in high and low tuberculosis-prevalent (TB) countries. Aim: The aim of this study is to assess the performance of the QFT-G test in the diagnosis of tuberculosis disease among tuberculosis patients in an intermediate prevalent country. Setting and Design: A retrospective study at the King Abdulaziz Medical City-Riyadh (KAMC-R) Materials and Methods: We retrospectively reviewed all the patients with a diagnosis of pneumonia, including tuberculosis, admitted to KAMC-R between 1 January 2009 and 31 December 2013. We included only patients with an available result of the QFT-G test. A total of 142 tuberculosis cases and 226 pneumonia cases were studied, to assess the utility of the QFT-G test in diagnosing tuberculosis cases. Results: Among the tuberculosis (n = 142) cases, the QFT-G tested positive in 68.3%, negative in 23.2%, and indeterminate in 12 cases (8.5%). Of the 226 pneumonia cases, the QFT-G tested positive in only 20.4%, while a majority of 66.4% tested negative, with 30 cases (13.3%) being indeterminate. When we excluded 42 patients with indeterminate results, the QFT-G test achieved a sensitivity of 74.6% [95% CI: 66.09 to 81.65%] and specificity of 76.53 % [95% CI: 69.85 to 82.15%] in the diagnosis of tuberculosis cases. Conclusions: This study concludes that the QFT-G test is a useful tool for detecting tuberculosis disease when used as an adjunct tool for the diagnosis of active TB cases. It certainly cannot be used solely and indiscriminately, separate from other clinical and radiological information, in the diagnosis of active tuberculosis cases.

Key words: Pneumonia, QuantiFERON, QFT-G, Tuberculosis

INTRODUCTION

Tuberculosis remains a major cause of mortality worldwide. It is the second leading cause of death from infectious disease worldwide. The World Health Organization (WHO), in 2012, indicated there were an estimated 8.6 million new cases of active TB and 1.3 million TB deaths.¹ The World Health Organization reported Saudi Arabia as having a moderate TB incidence rate, with 15 for every 100,000.¹ TB remains an important public health problem in Saudi Arabia, affecting all age groups and regions, and is associated with higher mortalities among Saudis.²⁻⁴ Since pulmonary TB can be easily spread, it is a major public health problem. This has become even more important with the development of drug-resistant TB, making effective treatment even more difficult.

Tuberculosis was accepted as a diagnosis if the sputum culture was positive for Mycobacterium tuberculosis (MTB). The interferon alpha release assay (QFT-G) is a new diagnostic test for latent tuberculosis infection (LTBI). QFT-G is similar to the Tuberculin Skin Test (TST), but cannot differentiate between LTBI and active TB. However, despite the limitation of QFT-G in the diagnosis of active disease, it has been recommended by some investigators and it has been used in the diagnosis of active tuberculosis in the private sector.⁵ A meta-analysis by Metcalf J et al.,⁶ using QFT-G, was performed for the diagnosis of active tuberculosis in 13 studies, and there were 13 studies on cases with known active tuberculosis. The overall sensitivity...
of QFT-G in the diagnosis of active tuberculosis was 69-83%.[4] Another meta-analysis by Dai Y et al.[7] revealed the overall sensitivity and specificity of QFT-G in the diagnosis of active tuberculosis to be 85 and 84%. Few other studies recommended the use of QFT-G for ruling out active tuberculosis, especially in high-income countries where the prevalence of tuberculosis was low.[8,9] Legesse M et al.[10] documented in their study that the sensitivity and specificity of QFT-G, using the manufacturer’s cut-off value, was very low in the diagnosis of active tuberculosis in tuberculosis-endemic regions.

The QFT-G-TB Gold kit (Cellestis Limited, Melbourne, Australia) was approved in 2009 for use in King Abdulaziz Medical City-Riyadh (KAMC-R) for the diagnosis of latent TB. Local Saudi guidelines on the management of latent tuberculosis did not recommend using QFT-G for the diagnosis of active tuberculosis.[11] The clinical use of QFT-G has expanded dramatically in the diagnosis of tuberculosis disease. This expanded use was not based on local studies, which confirmed or refuted such practice in Saudi Arabia. It was clear that the use of QFT-G in the diagnosis of active tuberculosis should be based on the local prevalence of the disease, local data, and many other logistic and resource considerations. The aim of this study was to assess the sensitivity and specificity of the QFT-G test in the diagnosis of tuberculosis in patients admitted with pneumonia, when it was ordered to rule out tuberculosis.

**MATERIALS AND METHODS**

A retrospective study was conducted at KAMC-R Saudi Arabia from January 2009 to December 2013. This research was approved by our Institution Review Board (IRB) number RR12/161/R. The study included all patients admitted with a diagnosis of pneumonia, and QFT-G was ordered to rule out active tuberculosis. All cases with pneumonia or a final diagnosis of tuberculosis, but with no QFT-G results available, were excluded. Only patients aged 18 years or older with available QFT-G tests were included in the analysis. The QFT-G results were divided into three categories: Positive, indeterminate, and negative. The procedures for the QFT-G test in our hospitals have been explained in detail in our previous published study.[12] The following data were extracted from the hospital records — demographic and clinical characteristics and QFT-G results. Tuberculosis was accepted as a diagnosis if the sputum culture was positive for MTB. Descriptive statistics such as means and standard deviation, mean ± SD, were used to describe the age of the patients. Frequencies and percentages n(%) were used to describe the gender and the QFT-G test results. The diagnostic performance of the QFT-G test was assessed using sensitivity, specificity, and positive/negative predictive values. We used independent sample t-tests to compare the patients’ ages across the tuberculosis and pneumonia cases. The chi-square tests were used to assess the associations between the demographic characteristics and groups (tuberculosis and pneumonia cases). The percentage of positive QFT-G results in each disease group and gender group was assessed by the chi-square tests. We examined whether the age was significantly different between the positive and negative QFT-G results of the two groups. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

**RESULTS**

Over the study period, 6907 patients were admitted with diagnoses of pneumonia, and 639 (9%) of them were diagnosed with tuberculosis. The results of QFT-G test were available in 368 patients: 142 (38.6%) patients with active TB and 226 (61.4%) patients with pneumonia. Table 1 demonstrates the patients’ demographic and clinical characteristics in relation to the disease status. Out of 368 patients, 188 (51.1%) were female and 180 (48.9%) were male. Most of the 368 patients were Saudis: 363 (98.6%). In both groups (tuberculosis and pneumonia), the results of

| Table 1: Demographic characteristics and QuantiFERON results in relation to disease status (n = 368) |
|-------------------------------------------------|-----------------|------------------|---------------------|----------|
| Characteristics | Overall n = 368 | Pneumonia 226 (61.4%) | Tuberculosis 142 (38.6%) | P-value |
|------------------|----------------|------------------------|-----------------------------|----------|
| QuantIFERON     |                | n %                    | n %                         | n %      |          |
| Indeterminate    | 42             | 11.4%                  | 30 13.2%                    | 12 8.5%  | 0.001*   |
| Negative         | 183            | 49.7%                  | 150 66.4%                   | 33 23.2% |          |
| Positive         | 143            | 38.9%                  | 46 20.4%                    | 57 68.3% |          |
| Gender           |                |                        |                             |          |          |
| Male             | 180            | 48.9%                  | 122 49.6%                   | 68 47.9% | 0.755    |
| Female           | 188            | 51.1%                  | 114 50.4%                   | 74 52.1% |          |
| Nationality      |                |                        |                             |          |          |
| Saudi            | 363            | 98.6%                  | 225 99.6%                   | 138 97.2%| 0.075    |
| Non-Saudi        | 5              | 1.4%                   | 1   0.4%                    | 4 2.8%   |          |
| Age/Year         | Mean±SD        | 60.7±18.8              | 64.4±17.4 (range 18-107)    | 54.9±19.4(range 19-92) | 0.001#   |

*Chi-square/Fisher’s exact test significant at α = 0.05. *Independent t-test significant at α = 0.05
The QFT-G tests were observed to be negative in 183 cases (49.7%), positive in 143 cases (38.9%), and indeterminate in 42 cases (11.4%). When the 368 patients were classified by the disease status, the QFT-G test appeared to have a higher positivity rate among the tuberculosis cases (68.3%) than the pneumonia cases (20.4%), \( P\)-value = 0.001. The result of the QFT-G test was observed to be negative in 150 cases (66.4%) and indeterminate in 30 cases (13.3%) in the pneumonia group [Table 1 and Figure 1]. The patients' ages were significantly higher among the pneumonia group (64.4 ± 17.4, range 19-107 years) than the tuberculosis group (54.9 ± 19.4, range 18-92), \( P\)-value = 0.001. There were no differences between males and females across the two groups (\( P\)-value = 0.755).

Table 2 shows the patients' demographic and disease status in relation to QFT-G results, excluding 42 patients with indeterminate results. The 42 patients who had indeterminate results were excluded because no follow-up QFT-G test was performed on these patients. The mean age for the negative QFT-G (\( n = 183 \)) results was shown to be 62.50 ± 18.0 years, which was significantly higher than that for the positive QFT-G (\( n = 143 \)) results (57.7 ± 19.7 years), \( P\)-value = 0.021. There was no significant difference between the positive QFT-G results comparing males (42.9%) and females (44.7%), \( P\)-value = 0.749. The positive results of QFT-G were higher in patients with tuberculosis disease than in patients with pneumonia disease (74.6 vs. 23.5%, \( P\)-value = 0.001). Table 3 shows the sensitivity, specificity, and positive/negative predictive values of the QFT-G test. The sensitivity of the QFT-G test was 74.6% [95% CI: 66.09 to 81.65%], while its specificity was 76.53% [95% CI: 69.85 to 82.15%]. The positive predictive value of the QFT-G test was 67.83% [95% CI: 59.43%, 75.25%] and the negative predictive value was 81.97% [95% CI: 75.46%, 87.10%]. Among 130 tuberculosis cases, the false negative rate was 25.4% (33/130 tuberculosis cases). Among 196 pneumonia cases, the false positive of the QFT-G test was 23.5% (46/196 pneumonia cases). Furthermore, Figure 2 shows how well the QFT-G test separates the two groups, tuberculosis and pneumonia, with an Area Under the Curve of 75.60% [95% CI: 70.10-81.10%].

**DISCUSSION**

Early diagnosis of active tuberculosis is essential to ensure early treatment and prevention of infection. Sputum culture with microbiological confirmation remains the

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**Table 2: Demographic characteristics in relation to QuantiFERON results, excluding 42 patients with indeterminate results (\( n = 326 \))**

| Characteristics     | Overall \( n = 326 \) | Negative \( 183 \) (56.1%) | Positive \( 143 \) (43.9%) | \( P\)-value |
|---------------------|------------------------|-------------------------------|-------------------------------|-------------|
|                     | \( n \) | %   | \( n \) | %   | \( n \) | %   |        |
| Group               |           |     |           |     |           |     |        |
| Pneumonia           | 196       | 60.1 | 150       | 76.5 | 46       | 32.5 | 0.001*  |
| Tuberculosis        | 130       | 39.9 | 33        | 25.4 | 97       | 74.6 | 0.749   |
| Gender              |           |     |           |     |           |     |        |
| Male                | 156       | 47.9 | 89        | 57.1 | 67       | 42.9 | 0.015*  |
| Female              | 170       | 52.1 | 94        | 55.3 | 76       | 44.7 |         |
| Nationality         |           |     |           |     |           |     |        |
| Saudi               | 321       | 98.5 | 183       | 57.0 | 131      | 43.0 |         |
| Non-Saudi           | 5         | 1.5  | 0         | 0.0  | 5        | 100  |         |
| Age (year)          | Mean±SD   |     | 60.4±18.9 |     | 62.5±18.0 |     | 57.7±19.7 |     | 0.021# |
|                     | (range 18-107) | | (range 19-107) | | (range 38-93) | | | |

*Chi-square/Fisher's exact test significant at \( \alpha = 0.05 \). *Independent t-test significant at \( \alpha = 0.05 \)
The QFT-G test performance excluding 42 indeterminate results (n = 326)

| Statistical measure of the QFT-G test performance | Value (%) | 95% confidence interval (CI) (%) |
|---------------------------------------------------|-----------|---------------------------------|
| Sensitivity                                        | 74.60     | 66.09-81.65                     |
| Specificity                                        | 76.53     | 69.82-81.15                     |
| Positive predictive value                          | 67.83     | 59.43-75.15                     |
| Negative predictive value                          | 81.97     | 75.46-87.10                     |
| Area under the curve                               | 75.60     | 70.20-81.10                     |

There was some evidence that the QFT-G response could be diminished in cases with advanced TB.[20,23] The advantage of our study was having a large number of patients with a confirmed culture positive tuberculosis.

The indeterminate results of the QFT-G tests were not common in tuberculosis (8.5%) compared to pneumonia (13.2%), which was similar to other studies.[21] It is imperative to indicate that there are two commercial QFT-G tests (TB Gold and TB spot). They differ in their positive and negative predictive values, and the concordance of the two tests is modest in both immunocompetent and immunocompromised patients, for both latent and active TB. Although our findings that QuantiFERON TB Gold can be used as an adjunct tool in the diagnosis of active TB, it certainly cannot be used solely and indiscriminately, separate from other clinical epidemiological and radiological factors, and the pre-test probability remains very important for the interpretation of these tests.

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