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

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of QFT-G in the diagnosis of active tuberculosis was 69-83%.[6] 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
		n	%	*n*	%	*n*	%	
QuantiFERON	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	97	68.3	
Gender	Male	180	48.9	112	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 (range18-107)		64.4±17.4 (range 19-107)		54.9±19.4 (range 18-92)		0.001#

*Chi-square/Fisher's exact test significant at $\alpha = 0.05$. #Independent *t*-test significant at $\alpha = 0.05$

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 33 cases (23.2%) and indeterminate in 12 cases (8.5%) in the tuberculosis group, whereas, 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

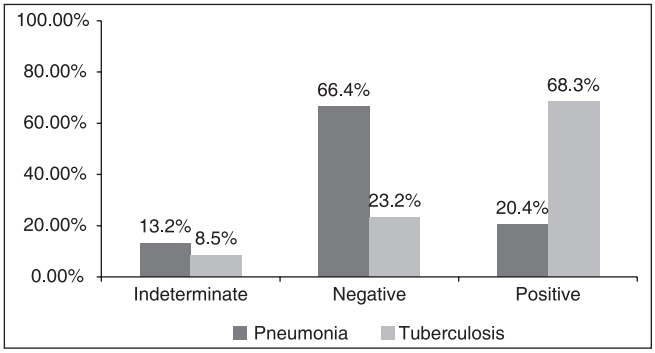

Figure 1: Diagnostic accuracy of the QuantiFERON Test among cases with pneumonia or tuberculosis

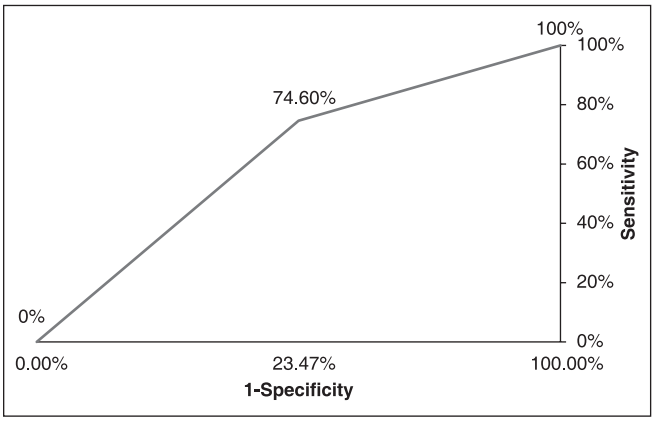

Figure 2: Receiver operating characteristic (ROC) curve of QFT-G test

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	23.5	0.001*
	Tuberculosis	130	39.9	33	25.4	97	74.6	
Gender	Male	156	47.9	89	57.1	67	42.9	0.749
	Female	170	52.1	94	55.3	76	44.7	
Nationality	Saudi	321	98.5	183	57.0	138	43.0	0.016*
	Non-Saudi	5	1.5	0	0.0	5	100	
Age/year	Mean±SD	60.4±18.9 (range18-107)		62.50±18.0 (range 19-107)		57.7±19.7 (range 18-93)		0.021#

*Chi-square/Fisher's exact test significant at α = 0.05. #Independent *t*-test significant at α = 0.05

Table 3: Diagnostic accuracy of the QFT-G test, excluding 42 indeterminate results (*n* = 326)

Statistical measures of the QFT-G test performance	Value (%)	95% confidence interval (CI) (%)
Sensitivity	74.60	66.09-81.65
Specificity	76.53	69.85-82.15
Positive predictive value	67.83	59.43-75.25
Negative predictive value	81.97	75.46-87.10
Area under the curve	75.60	70.10-81.10

gold standard for the clinical diagnosis of active TB, but requires a long follow-up. QFT-G held a promise to provide a rapid and reliable test to diagnose active TB. In this study, the sensitivity of QFT-G for the diagnosis of tuberculosis was 74.6% and specificity was 76.53%. However, several studies subsequently showed only a modest sensitivity of the QFT-G test to detect TB, although it performed better than Tuberculin skin test (TST). Lai CC *et al*. reported 66% sensitivity and specificity (76%), which was comparable to our findings.[13] In their meta-analysis of 26,680 participants, Rangaka *et al*.[14] concluded that QFT-G did not have high accuracy for the prediction of active tuberculosis, although the use of QFT-G in high-risk populations might reduce the number of people considered for preventive treatment. Equally, the QFT-G has suboptimal accuracy for confirming or ruling active tuberculosis disease.[15] In a meta-analysis comparing commercial interferon-gamma release assays for detecting active TB, the authors found that commercial QFT-Gs were superior to TSTs for detecting confirmed active TB disease, especially when performed in developed countries.[16] The overall pooled sensitivity and specificity of QuantiFERON TB Gold was 69-85% and 51-84%,[6,7] which was similar to our study.

A study from China reported a higher overall sensitivity of 81.4% and up to 86.6% in smear-positive cases, while having a specificity of 97%, which was comparable to our findings.[17] Another study from Indonesia revealed the sensitivity of QFT-G to be 88.7% in active TB cases, which was higher than our study.[18] Our study had three advantages: First it was from an intermediate TB-prevalent region and included large numbers of culture-positive, confirmed, TB cases, therefore, it was probably a better representation of the region, with an intermediate prevalence of TB compared to other studies.[7,18-22]

Pre-test probability is a very important factor for a better interpretation of a positive QFT-G test in cases of active TB suspicion. Interferon-γ release assays can be used more reliably in excluding TB, particularly extrapulmonary, in patients originating from areas of low tuberculosis incidence.[9] Other factors influencing discordant results of the QFT-G test in patients with active TB include older age, lower lymphocyte count, total protein and albumin levels, and high CRP levels.[20] In both groups, the elderly patients were more likely to have negative results of QFT-G (62.50 ± 18.0 years) than positive results of QFT-G (57.7 ± 19.7 years). Nevertheless, no gender differences between pneumonia and tuberculosis groups were found in our study.

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 major limitations included the fact that it was a retrospective study with known limitations. We did not include TST as an additional test to the QFT-G and we did not include pre-test probability of active tuberculosis when ordering the QFT-G test.

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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