International Journal of Infectious Diseases 44 (2016) 25–30

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Utility of QuantiFERON-TB Gold In-Tube assay in adult, pulmonary and extrapulmonary, active tuberculosis diagnosis

Mohammed Azghay [a,*], Olivier Bouchaud [a], Frederic Mechaï [a], Pascale Nicaise [b], Olivier Fain [c], Jérôme Stirnemann [d]

[a] Service des Maladies Infectieuses et Tropicales, Hôpital Avicenne – Université Paris 13 Paris Cité Sorbonne, 125 route de Stalingrad, 93000 Bobigny, France
[b] Département d'Hématologie et Immunologie UF Autoimmunité et Hypersensibilités Hôpital Bichat Claude Bernard, Paris, France
[c] Service de Médecine Interne, Hôpital Saint Antoine, Paris, France
[d] Division of General Internal Medicine, Geneva University Hospital, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 22 July 2015
Received in revised form 6 January 2016
Accepted 7 January 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Tuberculosis
Interferon-gamma
QuantiFERON
IGRA
Diagnosis

SUMMARY

Background: Tuberculosis remains a public health problem in France and the diagnosis of tuberculosis disease (TB) is sometimes difficult. The aim of this study was to analyse the contribution of the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) to TB diagnosis.

Methods: Sixty patients hospitalized with TB, for whom a QFT-GIT assay had been performed between June 2008 and June 2011 at the University Hospital of Bondy in the north-east of Paris, were identified retrospectively. Clinical and laboratory data were collected. The sensitivity, specificity, predictive values, and likelihood ratios of the QFT-GIT were all calculated. Furthermore, the characteristics of patients testing positive were compared to those of patients testing negative, as well as the QFT-GIT values according to several different factors.

Results: The sensitivity of the QFT-GIT was 85% (95% confidence interval (CI) 0.73–0.92) and specificity was 73.3% (95% CI 0.68–0.78). The positive predictive value was 39.5% and the negative predictive value was 97.3%. The positive and negative likelihood ratios were 3.2 and 0.20, respectively. The prevalence of TB in this population was 15% (pre-test probability). After a positive test result, the probability of TB increased to 40% (post-positive probability test); after a negative test result, it decreased to 4.5% (post-negative probability test). The combination of the QFT-GIT test with the tuberculin skin test brought no significant improvement in sensitivity. Factors significantly associated with a negative QFT-GIT result included older age, high C-reactive protein, a low lymphocyte count, and immunosuppressant intake. The test value in quantitative terms was significantly higher in those with lymph node TB than in those with pulmonary TB, and in younger patients (<40 years) than in older patients (>40 years old).

Conclusion: On its own, QFT-GIT is an insufficient tool to confirm the diagnosis of TB disease. However, it may form part of an ensemble of tools in combination with clinical, biological, and radiological assessments.

1. Introduction

Tuberculosis (TB) is a major public health problem that affects a third of the world's population and remains the biggest cause of mortality and morbidity through infection.[1] In France, 4975 cases of TB disease were reported to the health authorities in 2012, or 7.6 cases per 100 000 inhabitants. Compared with other parts of the world, this incidence is low, but inter-regional disparities exist. The French administrative area of Seine Saint Denis in the north-east of Paris has one of the highest rates of reported TB in France, with 28 cases per 100 000 inhabitants in 2012.[2]

The tuberculin skin test (TST) has many disadvantages, including many false-positive results in the population vaccinated with bacille Calmette–Guérin (BCG) and in patients infected with atypical mycobacteria. Furthermore, it provides many false-negative results in the elderly and in immunocompromised populations (e.g., people living with HIV).[3]

The GeneXpert PCR technique first became available only a few years ago. This allows the early detection of *Mycobacterium tuberculosis* complex and the detection of multidrug-resistant TB.[4] Its sensitivity varies depending on the origin of the sample and the bacterial load.[5]

* Corresponding author. Tel.: +33 1 48 95 54 55.
E-mail address: mohammed.azghay@avc.aphp.fr (M. Azghay).

http://dx.doi.org/10.1016/j.ijid.2016.01.004

Interferon-gamma release assays (IGRAs) are tests based on the release of interferon-gamma (IFN-γ) by lymphocytes in contact with synthetic peptides specific to *M. tuberculosis*. In France, their use in the diagnosis of latent TB, in place of the TST, is now recommended by the French National Authority for Health and the High Committee on Public Health.[6] However, contradictory results with respect to their use in the diagnosis of TB has been highlighted in many studies, thus doctors are reluctant to prescribe them.[7,8]

The aim of this study was to analyse the performance of the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) in the diagnosis of TB disease using retrospective data obtained from patients with pulmonary or extrapulmonary TB, who were hospitalized in Seine Sainte Denis, a French administrative region with a high TB prevalence.

2. Patients and methods

2.1. Study population

A retrospective study was performed on all adult patients hospitalized for suspected pulmonary or extrapulmonary TB for whom a QFT-GIT assay had been performed in the internal medicine department of the Jean Verdier Hospital in Bondy (district of Seine Saint Denis) between June 1, 2008 and June 30, 2011. Patients who had undergone QFT-GIT screening for latent TB before the initiation of immunosuppressive therapy or chemotherapy were excluded.

2.2. Definitions and diagnosis

A 'certain' diagnosis of TB was based either on bacteriological evidence (direct examination or culture) or histological evidence (identification of epithelioid giant cell granuloma with caseous necrosis). A 'probable' diagnosis was based on clinical, biological, and radiological findings and a favourable TB treatment response. Each diagnosis was reviewed retrospectively. The QFT-GIT was not one of the diagnostic criteria. The diagnosis was rejected when the clinical, biological, and radiological data did not sufficiently validate the need to begin TB treatment, or when a non-favourable disease response while on treatment was observed.

Direct bacteriological examination and culture were performed on sputum or gastric tube samples and/or puncture/organ biopsy samples. Direct examination (Ziehl–Nielsen method) and culture (solid Lowenstein medium and/or liquid culture for positive direct examination or puncture/organ biopsy) were performed in the mycobacterial laboratory of the Jean Verdier Hospital. Identification of the strain and susceptibility testing were performed when the culture was positive. Histological examination of organ biopsies was performed in the pathology laboratory of the Jean Verdier Hospital.

2.3. Data collection

The following data were collected: age, sex, immunosuppressive factors (diabetes, chronic renal failure, progressive cancer, immunosuppressive therapy in the previous 3 months), and biological data (lymphocyte cell count, HIV, hepatitis B virus, and hepatitis C virus status, gammaglobulinemia, albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP)). Data were also collected on the type of TB (pulmonary, pleural, lymph node, bone, peritoneal, liver, urinary tract, uterine, neuromeningeal, miliary, or other) and means of diagnosis.

The study was approved by the Paris Nord University Institutional Review Board (Comité de Protection des Personnes de Paris-Île de France).

2.4. QuantiFERON-Gold In-Tube assay (QFT-GIT)

All QFT-GIT assays on heparinized venous blood samples taken at the Jean Verdier Hospital during the period 2008–2011 were performed by the Autoimmunity and Hypersensitivities Unit at the University Hospital Bichat-Claude Bernard (QuantiFERON-Gold In-Tube; Qiagen, buyer of Australian biotechnology firm Cellestis). Three heparin tubes were collected: (1) negative control tube (NIL tube), (2) antigen tube (AG tube; contained a coating of specific antigens of *M. tuberculosis* (ESAT-6, CFP-10, TB 7.7), which came into contact with the patient's T-cells in the blood sample), and (3) positive control tube containing phytohaemagglutinin-P (PHA) (MIT tube). The concentration of IFN-γ secreted by the cells was measured by ELISA. The results were measured in IU/ml and interpreted in accordance with the manufacturer's recommendations as negative, positive, or indeterminate.

2.5. Tuberculin skin test (TST)

TSTs were performed in the unit using the Mantoux method, with 1 U of tuberculin (Tubertest; Sanofi Pasteur MSD). The result was read at 72 h. A positive test suggested active TB disease or latent TB infection. A cut-off of ≥10 mm of induration was used to define a positive TST in adult BCG-vaccinated or non-vaccinated subjects.[9] In people living with HIV infection, a cut-off of ≥5 mm of induration was considered a positive test result.[10] If there was a skin blister, this was interpreted as suggestive of infection. The TST was always performed after blood samples had been drawn for the QFT-GIT assay. A group of patients who had received both the TST and QFT-GIT ('combined test' group) was created. The result of the combined test was considered positive if either of the two tests was positive, and negative if both tests were negative.

2.6. Statistical analysis

The sensitivity, specificity, and predictive values were calculated for the QFT-GIT. Two specificity calculations were done, one including patients with 'indeterminate' results and the other not including them. The Wilson test was used to calculate 95% confidence intervals (CI). The positive and negative likelihood ratios were also calculated for the QFT-GIT test, having the advantage of being independent of the prevalence of the disease in the population.

Patient characteristics were expressed as the number (%) or as the median (standard deviation (SD)) and were compared between the QFT-GIT-positive group and the combined QFT-GIT-negative/indeterminate group. The Mann–Whitney–Wilcoxon test was used to compare quantitative variables, while Fisher's test was used for qualitative variables. A multivariate analysis was not performed, given the low number of patients with TB.

Finally, quantitative values of QFT-GIT were compared for those variables that were significantly different in the univariate analysis (age and total lymphocyte count) and between the different TB sites (pulmonary vs. lymph node, patients with both TB sites being classified in both groups).

3. Results

3.1. Clinical characteristics

A total of 790 QFT-GIT assays were performed, of which 395 (50%) were done for suspected TB disease (Figure 1): 60 (15.2%) of these patients had TB and received treatment, while 335 (74.8%) did not have TB and were not treated. Half of the patients for whom a QFT-GIT assay was performed were excluded: 297 prior to the initiation of immunosuppressive therapy and 98 for various

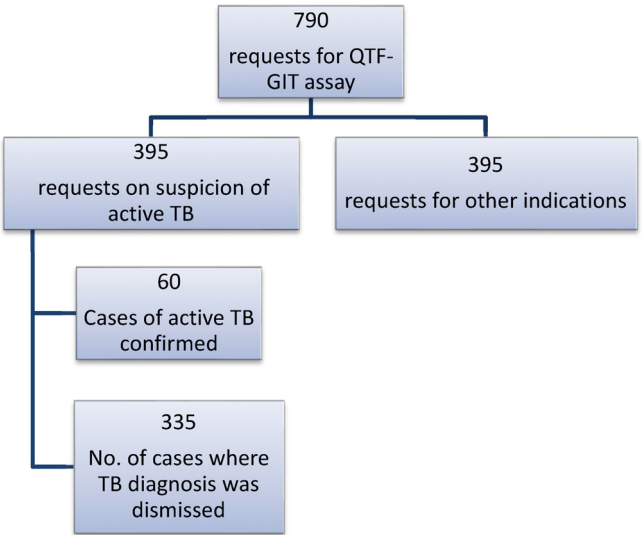

Figure 1. Flow chart of the study population.

reasons (HIV infection, granulomatosis, sickle cell disease, suspected latent TB).

The characteristics of the patients with TB ($n = 60$) are summarized in Table 1. The male to female sex ratio was 1.4, mean age (SD) was 36 (18.75) years, and only 11 cases were of European origin (18.3%), including five from Eastern Europe. Nineteen patients (31%) had isolated pulmonary TB, while 41 (69%) had extrapulmonary TB, including 20 cases of isolated lymph node TB, three cases of hepatic TB, three cases of spondylodiscitis, two cases of miliary TB, three cases of isolated pleural involvement, two cases of peritoneal localization, one of whom had associated pleural involvement, one case with uterine TB, and seven patients with multiple-site TB. Five patients were HIV-positive (recent diagnosis for two of them, all with a CD4 count >200 cells/mm^3).

Three patients were on the following immunomodulators at diagnosis: hydroxyurea, sulfasalazine, and infliximab. Two patients had neoplastic disease (mucinous ovarian tumour, gastrointestinal leiomyosarcoma). Forty-five patients (75%) had a definite diagnosis, based on bacteriological and/or histological data, and 15 patients (25%) had a probable diagnosis. Twenty-three patients had a negative result after direct bacteriological testing and a positive result from culture (Table 1).

Table 1
Characteristics of patients with active tuberculosis, patients with a positive QFT-GIT, and patients with a negative or indeterminate QFT-GIT

Characteristics	Active TB ($n = 60$)	QFT-GIT-positive ($n = 51$)	QFT-GIT-negative/ indeterminate[a] ($n = 9$)	p-Value[b]
Male/female	35/25	29/22	6/3	0.582
Age, years, median (SD)	36 (18.75)	35	63	0.005[c]
Region of origin				
Maghreb	20			
Sub-Saharan Africa	13			
Europe	11			
Haiti	7			
Asia	4			
Other	5			
Type of TB				
Pulmonary	19	15	4	0.443
Extrapulmonary	41	36	5	
HIV[d]				
Positive	5	4	1	0.702
Negative	55	44	7	
Immunosuppressive drugs	3/60	0	3 (QFT-GIT-negative)	<0.0001[c]
Cancer	2/60			
Diabetes	5/60			
Chronic renal failure	0/60			
Lymphocyte count, $\times 10^9$/l				
>1.5	34/60	32	2	
<1.5	26/60	19	7	0.017[c]
Median	1.680	1.790	1.200	
Albumin, g/l, median	35.85	36.35	32.1	0.19
Gamma globulin, median (SD)	15.1 (6.33)	15.2 (6.29)	12.8 (6.79)	0.483
LDH, IU, median	423	411	485	0.195
CRP, mg/l, median	24	23	75	0.009[c]
Microbiology, n				
Direct examination positive	16	13	3	0.822
Culture positive	39	34	5	0.238
Direct examination negative/culture positive	23	21	2	
Histology, n				
Positive	25/42	23/37	2/5	
Negative	17/42	14/37	3/5	0.343
Certain diagnosis[e], n	45	39	6	
Probable diagnosis[f], n	15	12	3	0.531
Tuberculin skin test				
Positive	21/27	19/23	2/4	
Negative	6/27	4/23	2/4	0.148

QFT-GIT, QuantiFERON-TB Gold In-Tube assay; TB, tuberculosis; SD, standard deviation; LDH, lactate dehydrogenase; CRP, C-reactive protein.
[a] Three patients with an indeterminate QFT-GIT are included in this group.
[b] p-Value for the difference between the QFT-GIT-positive group and the QFT-GIT-negative group.
[c] Significant at $p < 0.05$.
[d] One patient had an unknown HIV status.
[e] Certain diagnosis: positive culture and/or positive histology.
[f] Probable diagnosis: negative culture and negative histology.

Table 2
Distribution of QFT-GIT results according to the diagnosis of tuberculosis—confirmed or dismissed

Tuberculosis	QFT-GIT-positive, *n* (%)	QFT-GIT-negative, *n* (%)	QFT-GIT not interpretable, *n* (%)	Total, *n*
TB diagnosis confirmed	51 (85%)	6 (10%)	3 (5%)	60
TB diagnosis dismissed	78 (23.3%)	214 (63.9%)	43 (12.8%)	335
Total	129 (32.7%)	220 (55.7%)	46 (11.6%)	395

QFT-GIT, QuantiFERON-TB Gold In-Tube assay; TB, tuberculosis.

3.2. Diagnostic performance of QFT-GIT

Of the 60 patients who had been tested for TB, 51 (85%) had a positive QFT-GIT result, three (5%) had an uninterpretable result, and six (10%) had a negative result. Among the 335 patients for whom a TB diagnosis was initially suspected but eventually rejected, 78 (23.3%) had a positive QFT-GIT result, 43 (12.8%) had an uninterpretable result, and 214 (63.9%) had a negative result (Table 2). The sensitivity of QFT-GIT for TB diagnosis was 85% (95% CI 0.73–0.92) and the specificity 64% (95% CI 0.58–0.69) when the indeterminate and negative results were combined.

When the indeterminate results were excluded, specificity increased to 73.3% (95% CI 0.68–0.78), the positive predictive value was 39.5%, the negative predictive value was 97.3%, the positive likelihood ratio was 3.2, and the negative likelihood ratio was 0.20. With a prevalence of 15% in the population (61/395), a positive test increased the likelihood of having the disease to 40%, while a negative test decreased it to 4.5%. The TST was performed on 27 patients and was positive in 21 patients, giving a sensitivity of 78% (95% CI 0.57–0.91). The sensitivity of the 'combined test' ($n = 27$) was 92.6% (95% CI 0.74–0.99).

Sensitivity in the group of patients with a certain diagnosis (positive microbiology and/or typical histology) was 86.7% (95% CI 0.74–0.94), whereas the sensitivity in the patient group with a probable diagnosis was 80% (95% CI 0.55–0.93). In the group with a negative direct microbiological result but with positive culture ($n = 23$; included in some diagnoses), sensitivity was 91.3% (95% CI 0.73–0.98) (Table 3).

3.3. Comparison of patient characteristics according to the QFT-GIT result

Table 1 shows the patient characteristics compared according to the QFT-GIT results (positive versus negative or indeterminate). Age was significantly higher in the group with a negative QFT-GIT compared to the group with a positive QFT-GIT (63 (SD 24.9) years vs. 35 (SD 16.2) years; $p = 0.005$). The total lymphocyte count was lower in the QFT-GIT-negative group than in the QFT-GIT-positive group (median 1.200 vs. 1.790 $\times$ 10^9 cells/l; $p = 0.017$). CRP was higher in the QFT-GIT-negative group (75 mg/l vs. 23 mg/l; $p = 0.009$). Finally, all patients taking immunosuppressants had a negative QFT-GIT (3 patients vs. 0 patients; $p < 0.0001$).

Other characteristics were not significantly different between the two groups.

Table 3
Diagnostic performance of QFT-GIT

Sensitivity of QFT-GIT	85% (0.73–0.92)
Specificity of QFT-GIT (with indeterminate results)	64% (0.58–0.69)
Specificity of QFT-GIT (without indeterminate results being included in the negative results)	73.3% (0.68–0.78)
Positive predictive value	39.5%
Negative predictive value	97.3%
Positive likelihood ratio	3.20
Negative likelihood ratio	0.20
TST sensitivity	78% (0.57–0.9)
QFT-GIT + TST group sensitivity	92.6% (0.74–0.99)
Certain diagnosis group sensitivity (45 patients)	86.7% (0.74–0.94)
Probable diagnosis group sensitivity (15 patients)	80% (0.55–0.93)
Direct examination negative/culture positive microbiology group sensitivity (23 patients)	91.3% (0.73–0.98)

QFT-GIT, QuantiFERON-TB Gold In-Tube assay; TST, tuberculin skin test.

3.4. Study of the quantitative results of QFT-GIT

The quantitative QFT-GIT values were significantly higher ($p = 0.03$) in the 24 patients with lymph node involvement (median QFT-GIT of 8.07 IU/ml) with respect to the 22 patients with lung disease (median QFT-GIT of 2.15 IU/ml) (Figure 2A). QFT-GIT values were significantly higher ($p = 0.005$) in patients under 40 years of age (median QFT-GIT of 4.84 IU/ml) compared to those over 40 years old (median QFT-GIT of 1.94 IU/ml) (Figure 2B).

4. Discussion

In France, a very high percentage of TB sufferers are of foreign origin;[11] in the present study only five of the 60 patients were born in Western Europe. Other characteristics, however, were broadly comparable between patients.

The sensitivity value obtained in this study (85%, 95% CI 0.73–0.92) is comparable to those reported in the main meta-analyses performed to date: Diel et al.[7] found a sensitivity of 81%, while Sester et al.[8] found a sensitivity of 80%. In the present study, the sensitivity increased to 92.6% (95% CI 0.74–0.99) when using the combined QFT-GIT and TST test. Of the 27 patients with a TST and QFT-GIT, only two had a positive TST and a false-negative QFT-GIT. One of these patients had a certain diagnosis of TB and the other a probable diagnosis. The advantage of using both tests together is quite low. Moreover, the QFT-GIT sensitivity in the present study cohort (85%, 95% CI 0.73–0.92) did not increase significantly in either the group of patients with a certain diagnosis (86.7%, 95% CI 0.74–0.94) or in the group with a negative direct examination and positive culture (91.3%, 95% CI 0.73–0.98).

The specificity was lower (73%) in the present study than those found in the meta-analyses by Diel et al. (99.2%) and Sester et al. (79%). This can be explained by the fact that latent TB in the study region is high, and therefore the risk of patients with no TB disease having a positive QFT-GIT is greater, since this test does not distinguish between the two forms of TB (active and latent).

In the present study, the positive and negative likelihood ratios were 3.2 and 0.2, respectively. The positive likelihood ratio in the meta-analysis of Diel et al.[7] was 101 and in the meta-analysis of Sester et al.[8] was 3.81, while the negative likelihood ratios were 0.191 and 0.25, respectively. The results of the present study are therefore comparable with those of Sester et al. The difference between the two meta-analyses can be explained by the fact that Diel et al. selected only five studies with patients who had a very low risk of illness: for the 513 patients selected, the QFT-GIT was positive in only four. QFT-GIT specificity was overestimated at 99.2% (95% CI 0.98–1.00), resulting in an artificial increase in the positive likelihood ratio.

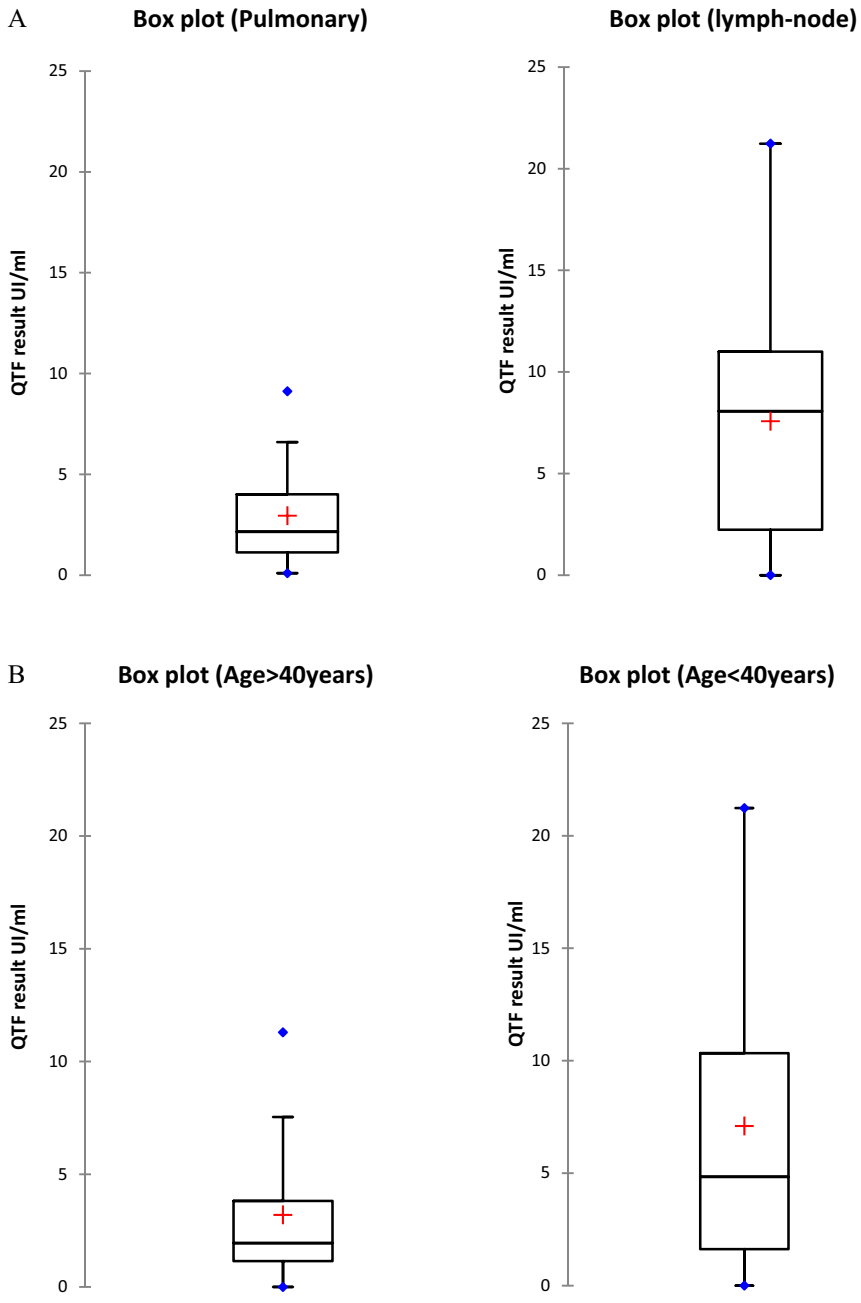

Figure 2. Boxplot of QTF rates according to (A) type of tuberculosis, (B) age.

In another meta-analysis published in February 2013, Davis et al. analysed the performance of microbiological examination of sputum to detect TB. That meta-analysis included 7771 patients. The sensitivity of direct examination of sputum was 64% and specificity was 68%. The positive and negative likelihood ratios were 30 and 0.37, respectively. Direct examination of sputum was therefore much more informative than the QFT-GIT when positive, but less effective when negative.[12]

As highlighted in the literature, elderly age,[13,14] a low level of total lymphocytes,[15] and taking immunosuppressants[16] are three factors that increase the risk of a false-negative QFT-GIT. In the present study a significantly higher CRP result was also found in the negative QFT-GIT group, which may be explained by a possible associated bacterial co-infection leading to a negative QFT-GIT result. This suggestion was made in a South Korean study involving 168 patients that was published in 2013.[17]

Previous studies on the quantitative values of QFT-GIT have shown either higher levels in patients with active TB when compared to those with latent TB,[18] or stable[19] or decreasing[20] values for patients on treatment for TB. In the present study, the QFT-GIT values were found to be significantly higher in patients with lymph node TB than in those with pulmonary TB. This result is interesting, as it is specifically extrapulmonary TB that is linked to difficult diagnosis. This is because of the invasive procedures that are often necessary to obtain bacteriological or histological proof,[21] and also because of the low sensitivity of the tests used (e.g., GeneXpert). In addition, several weeks may be needed for culture results. Furthermore, histology/radiography results often do not provide any further information regarding diagnosis.[22]

A high QFT-GIT level may be of interesting diagnostic value in lymph node TB. This appears to be confirmed by Kyoung-Ho Song et al. who found a QFT-GIT sensitivity of 86% (95% CI 0.64–0.97).

However, these results cannot necessarily be extrapolated to other forms of extrapulmonary TB, such as osseous TB, for which a sensitivity of only 45% (95% CI 0.17–0.77) has been found.[23]

This study had several limitations: (1) there was a high rate of extrapulmonary TB (68.3%), mainly lymph node, whereas this rate is around 30% over the entire French territory, probably because many cases of pulmonary TB did not need a QFT-GIT assay for diagnosis; (2) the number of HIV patients was low and therefore it was not possible to perform a relevant statistical analysis on this population or to extrapolate the results to HIV patients in general, for whom the QFT-GIT is recommended by national health authorities; (3) specificity was probably underestimated because it was calculated on patients with a high prevalence of latent TB; and finally (4) this was a retrospective observational study in which QFT-GIT was not prescribed systematically, especially for those with a clear diagnosis.

In conclusion, the QFT-GIT assay should not be recommended routinely for the diagnosis of TB as the positive and negative likelihood ratios, 3.2 and 0.2 respectively, are of mediocre value. The assay may also produce false-negative results in some situations: elderly age, high CRP, low total lymphocyte count, or when immunosuppressants are being taken. However, the QFT-GIT may be used as an element in the diagnosis of TB in certain situations, particularly for lymph node TB (where the QFT-GIT level is higher) and in low incidence areas (to limit the number of patients with latent TB).

Acknowledgements

Thank you to Nabil Seddiki for his help with the statistical data. Thanks also to Dr Philippe Cruaud for his help with the microbiological data.

Conflict of interest: The authors have no conflicts of interest to declare.

References

1. World Health Organization. Global tuberculosis control. WHO report 2010. Document WHO/HTM/TB/2010.7. Geneva: WHO; 2010.
2. Antoine D, Belghiti F, Guthmann JP, Campese C, Lévy-Bruhl D, Che D. Les cas de tuberculose déclarés en France en 2012. *Bull Epidémiol Hebd* 2014;(20):352–9.
3. Lee E, Holzman RS. Evolution and current use of the tuberculin test. *Clin Infect Dis* 2002;**34**:365–70.
4. Boehme CC, Nabeta P, Hillemann D. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010;**363**:1005–15.
5. Tortoli E, Russo C, Piersimoni C, Mazzola E, Dal Monte P, Pascarella M, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 2012;**40**:442–7.
6. Briere M. Use of interferon gamma release assays in clinical practice: review of QuantiFERON-TB prescription in a French university hospital. *Scand J Infect Dis* 2014;**46**:392–6. http://dx.doi.org/10.3109/00365548.2014.887221
7. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active tuberculosis: a meta-analysis. *Chest* 2010;**137**:952–68.
8. Sester M, Sotgiu G, Lange C, Giehl C, Girardi E, Migliori GB, et al. Interferon-gamma assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2011;**37**:100–11.
9. Bugiani M, Borraccino A, Migliore E, Carosso A, Piccioni P, Cavallero M, et al. Tuberculin reactivity in adult BCG-vaccinated subjects: a cross-sectional study. *Int J Tuberc Lung Dis* 2003;**7**:320–6.
10. Kerkhoff AD, Gupta A, Samandari T, Lawn SD. The proportion of people living with HIV in low and middle-income countries who test tuberculin skin test positive using either a 5 mm or a 10 mm cut-off: a systematic review. *BMC Infect Dis* 2013;**13**:307.
11. Antoine D. Les cas de tuberculose déclaré en France en 2010. *Bull Epidémiol Hebd* 2012;24–5.
12. Davis JL, Cattamanchi A, Cuevas LE, Hopewell PC, Steingart KR. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;**13**. http://dx.doi.org/10.1016/S1473-3099(12)70232–3
13. Kobashi Y, Mouri K, Yagi S, Obase Y, Miyashita N, Okimoto N, et al. Clinical utility of the Quantiferon TB-2G test for elderly patients with active tuberculosis. *Chest* 2008;**133**:1196–202.
14. Hang NT, Lien LT, Kobayashi N, Shimbo T, Sakurada S, Thuong PH, et al. Analysis of factors lowering sensitivity of interferon-gamma release assay for tuberculosis. *PLoS One* 2011;**6**. e23806.1–8.
15. Kobashi Y, Shimizu H, Ohue Y, Mouri K, Obase Y, Miyashita N, Oka M. False negative results of Quantiferon TB-2G test on patients with active tuberculosis. *J Infect Dis* 2009;**62**:300–2.
16. Ferrara G, Losi M, D'Amico R, Roversi P, Piro R, Meacci M, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006;**367**:1328–34.
17. Jeona YL, Nam Y-S, You E, Yang JJ, Kim MJ, Cho SY, et al. Factors influencing discordant results of the QuantiFERON-TB Gold In-tube test in patients with active TB. *J Infect* 2013;**67**:288–93. http://dx.doi.org/10.1016/j.jinf.2013.06.005
18. Kobashi Y, Shimizu H, Ohue Y, Mouri K, Obase Y, Miyashita N, Oka M. Comparison of T-cell interferon-gamma release assays for *Mycobacterium tuberculosis*-specific antigens in patients with active and latent tuberculosis. *Lung* 2010;**188**:283–7.
19. Pai M, Joshi R, Bandyopadhyay M, Narang P, Dogra S, Taksande B, Kalantri S. Sensitivity of a whole blood interferon-gamma assay among patients with pulmonary tuberculosis and variation in T-cell responses during antituberculosis treatment. *Infection* 2007;**35**:98–103.
20. Komiya K, Ariga H, Nagaia H, Kurashima A, Shojia S, Ishii H, Nakajima Y. Reversion rates of Quantiferon TB Gold are related to pre-treatment interferon-gamma levels. *J Infect* 2011;**63**:48–53.
21. Artenstein AW, Kim JH, Williams WJ, Chung RCY. Isolated peripheral tuberculosis lymphadenitis in adults: current clinical and diagnostic issues. *Clin Infect Dis* 1995;**20**:876–82.
22. Brodie D, Schluger NW. The diagnosis of tuberculosis. *Chest Med* 2005;**26**:247–71.
23. Song K-H, Jeon JH, Park WB, Kim S-H, Park KU, Kim NJ, et al. Usefulness of the whole-blood interferon-gamma release assay for diagnosis of extrapulmonary tuberculosis. *Diagn Microbiol Infect Dis* 2009;**63**:182–7.