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Contribution of Quantiferon TB Gold in Tube to the Diagnosis of Tuberculous Pleurisy: A Monocentric Prospective Study

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Abstract

Introduction: The diagnosis of tuberculous pleurisy remainsdifficult because of its paucibacillary character. Several authors have studied the usefulness of IGRAs in the early diagnosis of tuberculous pleurisy, whereas these tests are designed for the detection of latent tuberculosis infection.

Our objective is to study the performance and clinical relevance of QuantiFERON TB Gold in Tube (QFT-GIT) in the diagnosis of tuberculous pleurisy in Algeria.

Patients and methods: QFT-GIT was tested « in vitro » in serum and pleural fluid on a prospective recruitment of 158 immunocompetent patients with pleural effusion.

Results: Of the 158 cases of pleurisy identified, 84 (53.84%) were tuberculosis, diagnosed and proven by conventional methods, and 72 (46.15%) were non-tuberculous, of whom 67 (93%) were proven of neoplasic origin, 5 (7%) secondary to a systemic disease and 2 of non-specific inflammatory origin. Our results showed a high pleural sensitivity of QFT-GIT (97.62%) compared to serum sensitivity (80.95%). In contrast, serum specificity (83.78%) was higher than pleural specificity (72.97%).

When we used the optimal values from the ROC curve analysis, the Area Under The Curve (AUC) of IFN-gamma produced by the QFT-GIT test was significantly higher in the pleural fluid than in the blood. Area under the curve of TB antigen IFN-γ response was 92, 18

(IC 95%=87.56-96.79), nil tube was 95, 71% (IC 95%=92.43-99) and mitogen tube was 65, 34 (IC 95%=57.71-72.98).

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Conclusion, QFT-GIT in pleural fluid appears in our study as a useful test for the diagnosis of tuberculous pleurisy, but its diagnostic accuracy needs to be validated in further large-scale research.

Background

Among extrapulmonary tuberculosis, tuberculous pleurisy occupies the 2nd place after peripheral adenitis in Algeria with an incidence of 31.2% [1,2]. The frequency of tuberculous pleurisy varies according to the country and according to their incidence of tuberculosis, 25% in Spain [3]; 30 to 80% in India [4]; but less than 1% of pleurisy in low-incidence countries [3]. Pleural tuberculosis would represent 3 to 5% of localizations of tuberculosis in countries with low incidence [4,5].

Although part of the accessible locations, the diagnosis of pleural tuberculosis remains difficult. It is based on pleural fluid microbiology and histopathology. However, Bacillus Koch (BK) is only exceptionally found on direct examination, in less than 5.5% of cases[3,5-8], it is only present in 10 to 35% of cases on average on a culture of pleural fluid on Lowenstein medium, and 39 to 45% of cases on a culture of the biopsy specimen. The only diagnostic alternative remains pleural biopsy, which reveals a caseofollicular granuloma in 56 to 82% [9,10] and in 39 to 65% in certain cases [11], explains its unequal sensitivity depending on the diffuse or localized site, it can nevertheless be repeated in the event of failure, which increases its profitability. But this invasive procedure exposes the patient to risks and numerous complications [12-14].

In the absence of a diagnosis, a more invasive exploration such as thoracoscopy is used, which has a significantly higher sensitivity compared to blind pleural biopsies (100% histology, 76% culture and the two combined 100%) [13,15].

Since a definitive diagnosis is not always achieved, empirical anti-tuberculosis medication is frequently administered without supporting evidence. A new class of immunological tests known as IGRAs (Interferon Gamma Release Assay) has been developed [16,17].

T. SPOT test (Oxford Immunotec, Oxford, UK), which is an ELISPOT Assay, the QuantiFERON-TB Gold (QFTG), and finally the QuantiFERON-TB Gold Intube (QFT-GIT); Cellestis, Chadstone, Vic, Australia). IGRAs tests allow the in vitro measurement of Interferon-Gamma (IFN-γ), released by T lymphocytes in response to stimulation by specific antigens of Mycobacterium tuberculosis [18-20]. Their use is increasingly widespread in the context of the diagnosis of tuberculosis disease, while the test is designed for the detection of latent tuberculosis infection. Its use has not yet been validated in the pleural fluid, a compartment whose level of immune activation is higher than in the blood. We want to evaluate the QFT-TB-GIT and study its performance and clinical utility in the diagnosis of tuberculous pleurisy, in Algeria.

Methods

The study was monocentric, prospective, and carried out between May 2010 and June 2013 in the pneumology department of the university hospital of Bab El Oued. Patients with exudative fluid pleural effusion were recruited. All cases were excluded from the study:

- aged under 15 years.
- Transudative pleural effusion, of traumatic and/or haemorrhagic origin.
- Tuberculous pleurisy associated with parenchymal tuberculous lesions.
- Contraindication to pleural biopsy (blood crasis disorder, anticoagulant treatment).
- Condition that can lead to immunodeficiency: renal, hepatic, respiratory insufficiency, unbalanced type I diabetes, decompensated heart disease,
- Pregnancy.
- Current immunosuppressive treatment.
- Anti-tuberculosis treatment received for less than 12 months.
- Positive HIV serology.
- All pleurisy whose diagnosis has not been confirmed by conventional methods.

Clinical data were collected using a standard questionnaire, including demographic characteristics, amount of tobacco and exposure to other physical or chemical risk factors, history, comorbidities, the notion of immunosuppressive treatment, ongoing anti-tuberculosis treatment, clinical history, and finally BCG vaccination status, followed by a thorough physical examination, with routine investigations, HIV serology, liver serology, chest X-ray, bascilloscopies for research of BK, Intradermal Tuberculin Reaction (IDR), an exploratory pleural puncture for the biochemical, cytological and microbiological study of the pleural fluid (direct examination with Ziehl-Nelson staining and culture on Lowenstein medium), then completed with a pleural biopsy at the Abrams needle for the histopathological study and culture of the biopsy specimen on Lowenstein medium, and finally recourse to pleuroscopy if two to three blind biopsies were non-contributory.

The QFT-GIT test was carried out in two stages, before performing the intra-dermal tuberculin reaction and starting anti-tuberculosis treatment.

The first step was to collect a quantity of 1 mL of venous blood and 1 mL of pleural fluid from each patient, collected in each of the three tubes of the QFT-GIT, consisting of a negative control tube (null), a TB antigen tube (ESAT-6, CFP-10 and TB TB7.7) and mitogen control tube (phytohemagglutinin).

The second step consisted of incubating the tubes, within 12 hours of collection. After incubation for 16 to 20 hours at 37°C, the tubes were centrifuged and the supernatants were stored at less than 80°C until the ELISA test was performed. QFT-TB-GIT test results for serum and pleural fluid were interpreted, as recommended, as validated for blood by the manufacturer [16]. Test results were recorded as positive, negative, or indeterminate.

The sample size: The size of the population was calculated from the following formula: P= X/ N (100%)**.** This corresponds to the number of patients having presented sero-fibrinous pleurisy (X=59 cases), hospitalized in the pulmonology department during one year, whatever the etiology, compared to all patients hospitalized in Bab-El-Oued hospital (N=18,059), from the same year, which corresponds to the sample size of 126 cases.

Statistical analysis

Patients were divided into two groups: Tuberculous (TB) and Non-Tuberculous (Non-TB).

Data were analyzed using R software, version 3.6.0.

Values are presented as mean ± standard deviation.

Student's test and chi-square (x^2) were used to compare variables between the two groups. A value of $p<0.05$ was considered statistically significant.

The analysis of the evaluation of the performance of the QFT-TB-GIT test, the area under the curve (AUC: Area Under the Curve) ROC (receiver operation characteristics).

Results

After application of the non-inclusion criteria, of the 208 patients recruited, 50 were excluded; 158 were eligible for the study.

These patients were divided into 2 groups according to the diagnosis retained:

Group 1: Tuberculous pleurisy (n=84).

Group 2: Non-tuberculous pleurisy (n=74).

Patient characteristics, pleural fluid results, and the etiological profile of pleurisy are shown in **Tables 1 and 2.**

Table 1: Demographic and pleural fluid characteristics of patients included in the study.

Characteristics	TB groupn (%)	Non TB groupn (%)	*p Value*
Patients number	84 (53,20%)	74 (46,80%)	0.05
Gender			
-Male	43 (51,20)	34 (46)	0,05
-Female	41 (48,80)	40 (54)	
			0,001
Average age (years)	34,55 ± 15,03	53,58± 13,12	

TB group: Tuberculosis group; Non-TB group: Non-Tuberculosis group

Table 2: Demographic and pleural fluid characteristics of patients included in the study.

Etiologic diagnosis	Number	Percent (%)
Tuberculous pleurisy	84	53,20
Non-tuberculous pleurisy	74	46,80
Malignant pleurisy	67	
lupus pleurisy	4	
Sarcoidosis pleurisy	1	
Non-Specific inflammatory pleurisy	2	

TB pleurisy: Tuberculous; Non-TB pleurisy: Non-tuberculous pleurisy.

Group 1:

-84 cases (53.20%) of tuberculous pleurisy (TB), including 43 men (27.21%) and 41 women (25.94%). The female/male ratio was 1.04, with an average age of 34.55 ± 15.03 years.

67 cases out of 84 (79.80%) tuberculous pleurisy were proven:

• 42 cases (50%) were confirmed exclusively by histology in the presence of a caseofollicular lesion on pleural biopsy.

• 6 cases (7.20%) were confirmed exclusively by bacteriology.

• 19 cases (22.60%) were confirmed by both histology and bacteriology

Seventeen cases out of 84 (20.2%) were presumed to be tuberculous, given the presence of strong evidence: tuberculoid lesions without caseous necrosis on pleural biopsy, simultaneously associated with the notion of contagion and positive IDR including the positivity threshold was greater than or equal to 10 mm, as set by the Algerian recommendations for the fight against tuberculosis [1].

Group 2:

-74 cases (46.80%) of non-tuberculous pleurisy (Non-TB):

• 67 cases (90.55%) were of neoplastic origin, of which 30 (44.80%) were confirmed exclusively by cytology, 19 (28.40%) by histology, and 18 (26.80%) by both cytology and histology. The mean age was higher in the tuberculous pleurisy group (62.56 ± 12.92 years, $p< 0.001$), and the female/male ratio was 1.09.

7 cases of pleurisy of various etiology:

Five cases were secondary to systemic disease (4 cases of lupus diagnosed thanks to the clinical context, and to the immunological assessment which was very in favor, and 1 case of pleural sarcoidosis which had appeared at the same time as pulmonary mediastinal involvement, associated with a multinodular goiter whose histopathological study of the surgical biopsy of the goiter and the endobronchial biopsy was in favor of a granulomatous lesion without caseous necrosis, and which had evolved well under systemic corticosteroid therapy and, two cases of inflammatory origin nonspecific that regressed spontaneously.

-Group 1: 84 patients with proven or strongly suspected tuberculous pleuritis.

-Group 2: 74 patients with pleurisy of various etiologies (67 cases of malignant origin, 5 cases associated with systemic disease, and 2 casesof undetermined origin (non-specific inflammation).

QFT-TB-GIT assay analysis as recommended by the manufacturer IFN-γ was measured simultaneously in serum and pleural fluid by the QFT-TB-GIT assay in all patients. The results of the QFT-TB-GIT test are shown in **Table 3.**

In the TB group, the QFT-TB-GIT tested in the serum of these patients was positive in 68 cases (81%), negative in 11 cases (13%), and indeterminate in 5 cases (6%). The QFT-TB-GIT in the pleural fluid of these patients was positive in 82 cases (97.61%), and indeterminate in 2 cases (2.40%). On the other hand, no negative test was noted in this group of patients.

In the Non-TB group, serum QFT-TB-GIT was negative in 60 cases (81.08%), positive in 12 cases (16.21%), and indeterminate in 2 cases (2.70%).

Pleural QFT-TB-GIT were positive in 20 cases (27.02%), negative in 42 cases (52.2%), and indeterminate in 12 cases (16.21%).

In addition, we studied the sensitivity and specificity, the positive predictive value (PPV), the Negative Predictive Value (NPV), serum, and pleural of the QFT-GIT test with a prevalence of 53.16%, excluding analysis of the indeterminate results (**Table 3**):

Table 3: Results of the QFT-TB-GIT test in pleural fluid and in serum of the TB and Non-TB groups.

QFT- GIT	Serum	Pleural fluid
TB group (n=84)		
Positive	68 (81%)	82 (97,60 %)
Negative	11 (13%)	0
Indeterminate	5 (6%)	2 (2,40 %)
Non-TB group (n=74)		
Positive	12 (16,21 %)	20 (27,02 %)
Négative	60 (81,08 %)	42 (56,75 %)
Indeterminate	2 (2,70 %)	12 (16,21 %)
Sensitivity %	80,95	97,62
Specificity %	83,78	72,97
VPP	85,00	80,39
VPN	79,49	96,43

PPV: Positive Predictive Value; NPV: Negative Predictive Value
TB pleurisy: Tuberculous; Non-TB pleurisy: Non-Tuberculous Pleurisy.

Table 4: IFN-γ responses using the QFT-TB-GIT test (TB Antigen, Mitogen, and Null tubes) in pleural fluid (LP) and in serum (S) of the TB and Non-TB group.

Tube	TB	Non TB	p (Wilcox)	Significance
Pleural fluid				
Mit_LP	9,15 (5,1 - 13,2)	6,94 (-1,25 - 15,13)	1.36E- 4	***
Nul_LP	7,32 (0,07 - 14,57)	0,31 (-0,78 - 1,4)	5.88E-23	****
TB_LP	8,36 (2,4 - 14,33)	1,45 (-3,99 - 6,88)	1.28E-20	****
TB_Nul_LP	2,25 (-6,77 - 11,27)	1,18 (-4,15 - 6,51)	6.88E- 4	***
Serum				
Mit_S	6,66 (-1,06 - 14,37)	6,75 (-0,9 - 14,4)	0.641	ns
Nul_S	0,33 (-1,1 - 1,77)	0,1 (-0,08 - 0,28)	3.61E-11	****
TB_S	4,02 (-3,27 - 11,31)	0,71 (-2,51 - 3,93)	9.48E-14	****
TB_Nul_S	3,77 (-3,48 - 11,01)	0,61 (-2,58 - 3,79)	1.22E-12	****

TB: Tuberculous; Non-TB: Non-Tuberculous

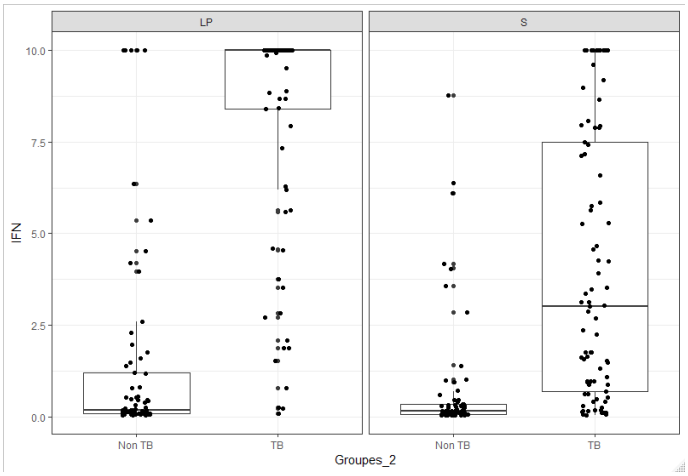

Figure 1a: Serum and pleural levels of IFN-γ produced by specific antigens (TB Antigens tube) in TB and Non-TB groups.

In pleural fluid, the sensitivity and specificity of QFT-TB-GIT were respectively 97.62% (95% CI=82.2 - 99.20) and 72.97% (95% CI=59, 7 - 83.20). PPV and NPV are 80.39% (95% CI=52.5 - 77.6) and 96.43% (95% CI=83.3 - 99.2) respectively.

In serum, the sensitivity and specificity of QFT-TB-GIT were 80.95% (95% CI=70.80 to 87.40) and 83.78% (95% CI=73.40 to 90, 90) respectively.

The PPV and the VPN are respectively 85% (95% CI=74.9 to 91.40) and 79.49% (95% CI=68.5 to 86.6).

Comparison of the serum and pleural level of Interferon-Gamma by the QFT-TB-GIT test (TB antigen, mitogen, and null tubes) in the TB and non-TB group

Table 4 and Figure 1 (1a, 1b, 1c, and 1d), show that the levels of IFN-γ produced in the pleural fluid by the Null tube and by the antigen-TB tube (ESAT-6, CFP-10, and TB7.7) provided with the QFT-TB-GIT assay were significantly higher in the TB group than in the Non-TB group, but with a greater concentration in the null tube.

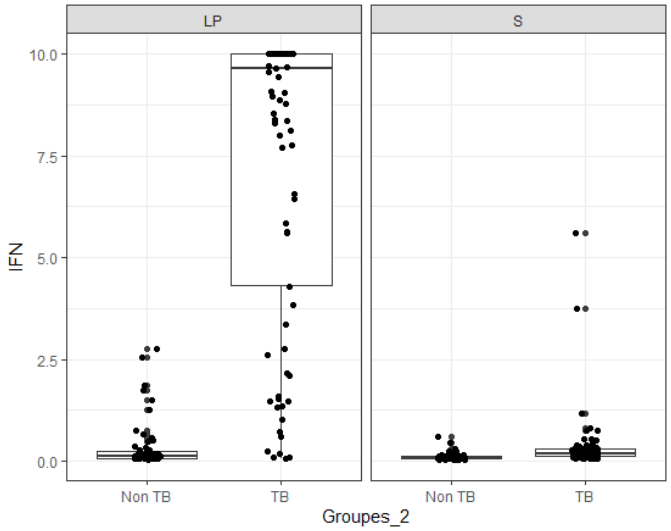

Figure 1b: Serum and pleural levels of IFN-γ produced by the null tube in the TB and Non-TB groups.

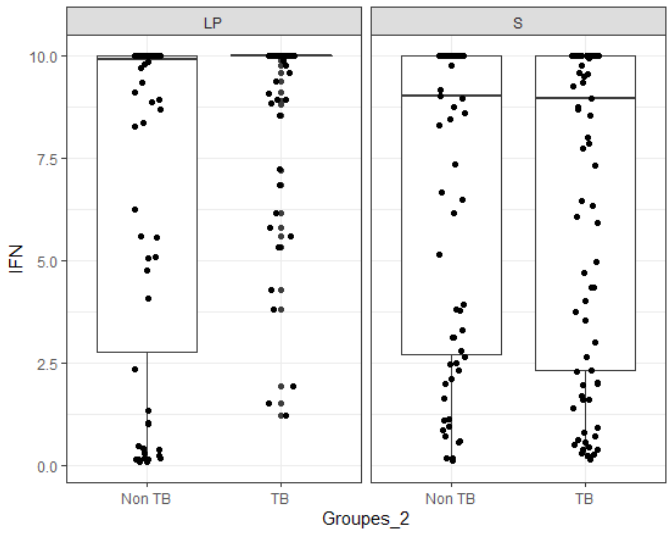

Figure 1c: Serum and pleural levels of IFN-γ produced by the mitogen tube in the TB and Non-TB group.

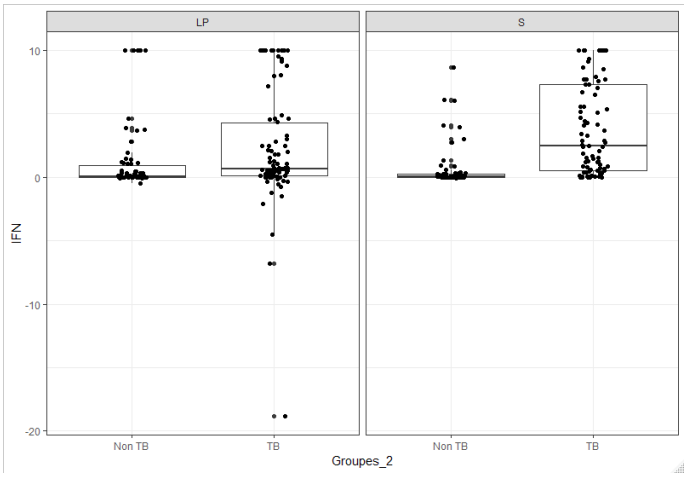

Figure 1d: Comparison of serum and pleural levels of IFN-γ induced by (TB-Ag minus null) in the TB and Non-TB groups.

In order to determine the performance of the QFT-GIT test we performed an analysis of the ROC **(Receiver Operating Characteristics**) curve and calculated the Area Under The Curve (AUC) in the three tubes of the QFT-GIT test as well in the liquid pleural than in serum respectively **(Figures 2 And 3).**

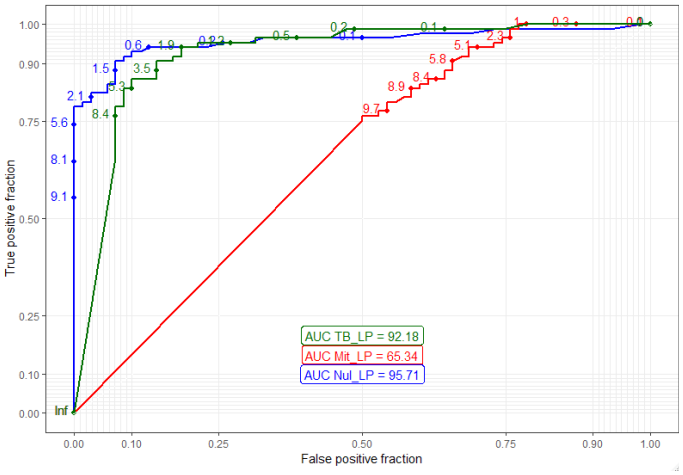

Figure 2: ROC curve analysis showing pleural IFN-γ responses in all three tubes (null tubes, TB antigen, and mitogen).

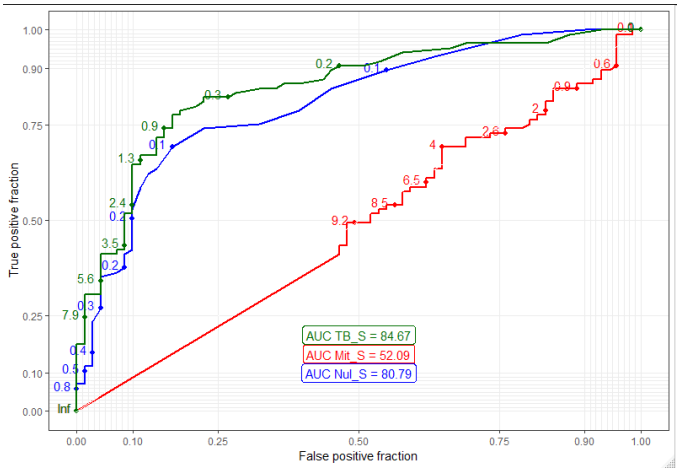

Figure 3: ROC curve analysis showing serum IFN-γ responses in all three tubes (null, TB antigen, and mitogen tubes).

Discussion

This study is the first conducted in our country to assess the clinical utility of the QFT-GIT test in tuberculous pleurisy. The QFT-GIT is based on the measurement of IFN-γ secreted by T lymphocytes, when it is stimulated in vitro by specific M. tuberculosis antigens: Ag ESAT-6, CFP-10, and TB 7.7. This marker was studied with the aim of providing assistance in the diagnostic strategy for tuberculous pleurisy, which poses a real problem of differential diagnosis with exudative effusions, in particular with neoplastic pleurisy, which has clinical and biochemical similarities, and defects of histological evidence.

Several studies have recently been published, in particular on the diagnostic accuracy of IGRAs in pleural tuberculosis [21,22].

A meta-analysis carried out by Rajnish [19,23] in 2008 included 5 studies [1,24-26] classified according to the prevalence of tuberculosis in certain countries, by studying the evaluation and performance of QuantiFERON-TB and T. Spot-TB, which are used for the first time in other compartments than blood, for diagnosis of pleural tuberculosis. These studies have shown dichotomous results. Indeed, the sensitivity of IGRAs tests (two Elispot and one QFT-TB-GIT) carried out in low prevalence countries was 95 to 100% in pleural fluid and 77.7 to 100% in serum [24,25,27], significantly higher than that found in countries with high and intermediate tuberculosis prevalence, which is 44% in pleural fluid and 60-70.8% in serum, where the majority of their patients had positive HIV serology [28,29].Thus, the sensitivity of these tests is low in settings with a high incidence of tuberculosis, due to the high HIV epidemic. Studies conducted in countries with a high prevalence of tuberculosis have reported high serum sensitivity of IGRAs to pleural fluid [28,29].

However, authors from countries with low TB prevalence [24,26,27] conclude that these IGRAs tests are useful in the diagnosis of pleural tuberculosis. These studies also support the argument that the pleura is the site of the immune defense reaction against M. tuberculosis and that these IGRAs tests are promising.

In our study, the overall sensitivity of the QFT-TB-GIT test was 97.62% in pleural fluid versus 80.95% in blood, comparable to those found in countries with a low prevalence of tuberculosis [24-27].

Other more recent studies have been carried out in countries with an intermediate prevalence of tuberculosis [28,32], have objectified that the serum and pleural sensitivity varies from 70 to 81% and from 49 to 57% respectively, and a respective serum and pleural specificity ranging from 51.7 to 71% and from 79.3 to 93.3%, lower than that found in our series (80.95% and 97.62% respectively). The pleural (80.39%) and serum (85%) PPV found in our study is comparable to that observed in previous studies (87% and 76% respectively) [30-32].

On the other hand, the pleural NPV (96.43%) is close to that found in the work of Gungor and Ali Kadri [32,33], serum VPN (79.49%) is significantly higher than previous studies [30-32].

It has been observed in some works [32-35] false positives with these IGRAs tests, especially in the pleural fluid of patients with nontuberculous pleurisy, ranging from 10 to 29.8%. Our results reveal 20 (27.02%) false positives in the pleural fluid of non-tuberculous pleurisy, a percentage comparable to Ali Kadri's study (29.8%) [33,35].

Furthermore, the false positive serum results encountered in non-tuberculous pleurisy are most likely due to latent tuberculosis infection [32].

On the other hand, the false positives observed in the pleural fluid of neoplastic pleurisy are due to a cross-reaction between M. tuberculosis antigens and tumor antigens or with other foreign proteins. It has been shown that by making dilutions, the quantity of these proteins can be reduced and lead to a negative result [32,36]. Moreover, in non-tuberculous pleurisy, these same authors [32-34,37], show high numbers of indeterminate results in pleural fluid, varying from 10 to 15.58%, numbers similar to those of our series (16.21%). The indeterminate results observed in the pleural fluid of the nontuberculous pleurisies of our study are due to the weak response of the ects the immune status of the weakened patients because, in the majority of the cases, it is about elderly subjects whose the immune system is altered, and aggravated by the disease in patients with cancer or autoimmune disease. When we used the optimal values obtained by ROC curve analysis, the Area Under The Curve (AUC) of the IFN-gamma produced in the three tubes supplied with the QFT-TB-GIT as say, was significantly greater. Higher in pleural fluid than in serum. The area under the ROC curve (AUC) of IFN-γ in null tube-induced pleural fluid was 95.71% (95% CI=92.43-99), 92.18% (95% CI= 87.56-96.79) in the antigen-TB tube and 65.34% (95% CI=57.71-72.98) in the mitogen tube. The comparison of the three tubes clearly demonstrated the superiority of the null tube in pleural fluid. On the other hand in the serum, the tubes, antigens-TB and null are better compared to the mitogen tube [37,38]. The high specificity of INF-γ is based on the activity of M.tuberculosis-specific effector T cells at the inflammatory site (pleura) [39,40]. It is known that INF-γ produced by T lymphocytes activates macrophages so that they increase their bactericidal power. Therefore, INF-γ levels in pleural fluid may reflect stimulation of TB antigens by T cells [41,42]. Interestingly, in TB patients, these T cells appear to continue to produce high levels of INF-γ in the absence of added anti-TB antigens [43,44]. This is likely due to a highly activated state that does not require continuous antigenic stimulation. This study demonstrates that INF-γ, produced extensively by the null tube in pleural fluid not stimulated by Mycobacterium tuberculosis-specific antigens, distinguishes between tuberculous and non-tuberculous pleurisy.

The strengths of our study are:

- A fairly representative sampling

- All pleurisies, whatever their etiologies, were proven in the two Tuberculous (TB) and non-Tuberculous (non-TB) groups, by conventional methods, or strongly presumed to avoid any bias in the results obtained. The differences observed, in terms of sensitivity and specificity in the studies cited above [27-30, 33] may be related to many factors:

- Certain recruitment biases in the population studied, which constitute a limitation major (pleurisy was not proven etc.)

- The limited number of the population studied.

- The local epidemiological situation, in countries with low prevalence, these IGRAs tests showed good sensitivity and specificity, whereas the lowest specificity values were obtained in the context of a population with a high endemicity of tuberculosis and in populations at risk (HIV). The prevalence of tuberculosis also influences the PPV and NPV.

The strengths of these tests are:

-The use of tuberculosis-specific antigens has advantages linked on the one hand to their simple in vitro technique, particularly for QFT-TB-GIT,

- Requires a simple sample, so only one visit,

-A standardized analysis method with positive control of the functioning of the immune system and on the other hand:

- The objectivity of the results obtained in less than 24 hours.

On the other hand, these tests are limited by a number of indeterminate results, found mainly in pleural fluid, with false positives and false negatives, and by their cost.

In this case, rigorous large-scale clinical studies should be undertaken, adapting these tests to physiological products less concentrated than blood, such as pleural fluid, in order to reduce the current limits of these IGRAs tests. However, the cost of these tests remains a reality that should not be overlooked, this is all the more important in low-income countries, where access to care is very difficult.

Conclusion

At the end of this work, it seems to us that QFT-GIT measured in pleural fluid is a promising indirect test for a non-invasive diagnosis of pleural tuberculosis. Thus, without claiming to replace the pleural biopsy, which remains the Gold standard, we suggest its use as a complementary test in clinical practice in certain cases, **pending its adaptation to biological fluids:**

- Patients with a clinical picture suggestive of tuberculous pleurisy, whose results of conventional complementary examinations are negative

- Contraindication to pleural biopsy.

The Universal Trial Number (UTN) is U1111-1299-7186

What is already known

- Quanti FERON is a blood test to detect infection with tuberculosis. The test is used as an indirect test for Mycobacterium tuberculosis infection.

- There are relatively few studies have reported a direct comparison between Quanti FERON TB Gold in Tube (QFT-GIT) in serum and pleural fluid in diagnosing tuberculous pleurisy, and the existing studies show that there are important variations in the results and dependant of the prevalence of tuberculosis in these countries.

What is already known on this topic

- This study showed a high pleural sensitivity of QFT-GIT, compared to serum sensitivity.

Conflicts of interests: The authors have no conflicts of interest to declare.

Authors' contribution: RY conceived the study, participated in its design, performed the statistical analysis, helped to draft the manuscript and coordinated the study.

FM conceived the study, participated in its design and helped to draft the manuscript

DH conceived the study, participated in its design and helped to draft the manuscript

RT conceived the study, participated in its design and helped to draft the manuscript

NR conceived the study, participated in its design and helped to draft the manuscript

RA conceived the study, participated in its design and helped to draft the manuscript

KA conceived the study, participated in its design, helped to draft the manuscript

Both authors read and approved the final version of the manuscript.

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