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Comparison of Tuberculosis Skin Testing and QuantiFERON-TB Gold Plus Test in Yazidi Refugees

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ABSTRACT

The aim of this study was to determine the diagnostic value and performance of of the QuantiFERON®-TB Gold Plus (QFT-Plus) test with the tuberculosis skin test (TST) as a screening test for tuberculosis in Yezidi refugees.

The study involved 100 adults who had migrated to our country and were currently residing in refugee camp. The Purified Protein Derivative (PPD) screening test was conducted using the Monteoux method and the size of induration above 15 mm with BCG scars and above 10 mm without BCG scars were considered as positive. The QuantiFERON®-TB Gold Plus test was performed using the interferon-gamma release detection method.

In the study, 49 out of the included individuals (52.1%) tested positive for the QuantiFERON®-TB Gold Plus test, while 59 individuals (62.8%) tested positive for TST. Of the participants, 43 (45.7%) were positive for both TST and QFT-Plus, 9 (9%) were positive for TST but negative for QFT-Plus, and 6 (6%) were negative for TST but positive for QFT-Plus. The study found a positive correlation between the results of the QuantiFERON-TB Gold Plus and TST. The sensitivity and specificity of the test were 82.6% and 85.7%, respectively, when evaluated according to TST.

We can recommend QFT-Plus test for the detection of latent tuberculosis infection as an alternative to TST in refugees populations.

Keywords: Tuberculosis, Quantiferon-TB Gold Plus, Tuberculin Skin Test, Yazidi Refugee

Introduction

Tuberculosis (TB) is a contagious infectious disease caused by Mycobacterium tuberculosis complex. It can affect all age groups and involve many systems, with pulmonary tuberculosis being the most common (1-3). Approximately one third of the world's population is estimated to be infected with tuberculosis bacilli. Latent TB Infection (LTBI) can develop in up to 95% of healthy individuals exposed to tubercle bacilli, with active TB developing in 5% within the first two years. The probability of developing active tuberculosis disease in latently infected individuals in later years is around 5-10% (4). Tuberculosis is a preventable disease and is a significant cause of morbidity and mortality among infectious diseases. Early diagnosis and treatment of tuberculosis are crucial in controlling the disease (5). The gold standard for definitive diagnosis is demonstrating the causative agent or its production in cultures, although diagnosing TB infections can be challenging. Tuberculin skin test (TST) has been used for many years to screen for latent tuberculosis.

Alternative methods have been sought due to difficulties in implementing TST. Undesirable events such as riots, war, and forced migration significantly disrupt healthcare services in countries, negatively affecting public health. Adults who migrated to our country due to civil war and stayed in refugee camps are among the risk groups most affected by these adverse conditions. It is essential to screen refugees for TB and to initiate TB prophylaxis at an early stage for effective TB control (6).

QuantiFERON-TB Gold Plus is the latest generation of interferon gamma release assays to receive approval from the U.S. FDA, replacing its predecessor, QuantiFERON-TB Gold In-Tube (7).

Yazidis are an ethno-religious group scattered across Turkey and nearby regions, including Iran, Iraq, Syria, and Russia. The community comprises approximately 500,000 to 700,000 individuals. Access to health services and vaccination may pose challenges for Yazidis due to their relatively closed society. Additionally, cultural differences may exist both within and between countries regarding health maintenance and seeking medical care (8).

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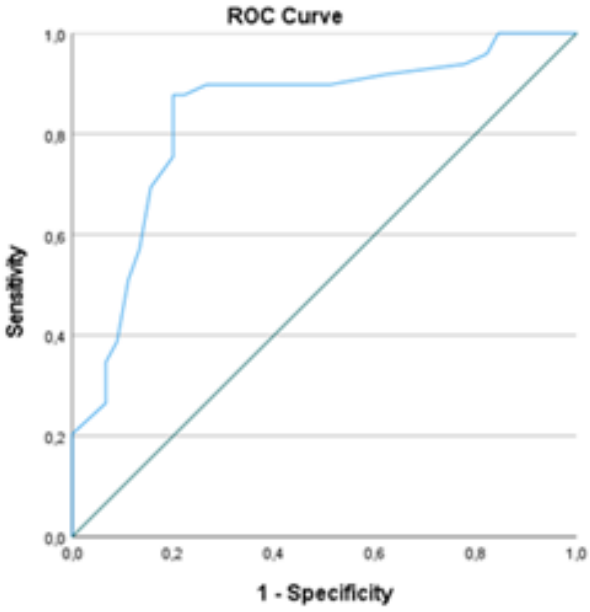

Fig. 1. ROC curve (The area under the curve was 0.835)

The aim of this study was the detection of latent TB in refugees and the comparison of the diagnostic accuracy and sensitivity of the TST and the QuantiFERON®-TB Gold Plus Test.

Materials and Methods

This study involved 100 adults, selected using a systematic random sampling method from a pool of approximately 2500 individuals in the adult age group living in the refugee camp. Informed voluntary consent was obtained from all participants, and a form containing demographic information was completed through face-to-face interviews. The PPD screening test was conducted using the Monteoux method after blood was drawn for the QuantiFERON®-TB Gold Test. All the participants, underwent a TST with 5 tuberculin units of purified protein derivative, according to the intradermal until some time ago, the tuberculin skin test was the only available screening test for the diagnosis of tubercular infection. Mantoux method and a reaction with a diameter >5mm was considered positive. Following the interview, a 1 cc venous blood sample was collected from all participants who agreed to take part in the study under sterile conditions. This was done prior to the PPD test to ensure that the test did not affect the results. The results were then recorded in an Excel table. The calibration curve and results were calculated using the numerical values obtained from the QuantiFERON®-TB Gold Test analysis software provided by Cellestis.

Ethical approval was obtained from the local ethics committee of Dicle University (approval number: 34, approval date: 15/12/2015).

Statistical Analysis: Statistical analysis of the data obtained in this study was performed using IBM SPSS 21.0 (Statistical Package for the Social Sciences) for Windows. Categorical variables were presented as numbers and percentages (%), while measured variables were presented as mean ± standard deviation (SD). Agreement between the results of the TST and QFT-GIT tests was assessed by using kappa (k) coefficients. ROC analysis was performed to determine whether the parameters had diagnostic value. Sensitivity, specificity, positive and negative predictive values were calculated to determine whether the variables were influenced by the prevalence of the disease in the study population. Spearman correlation analysis was performed to determine the relationship between variables. Only results with a P value below 0.05 were considered statistically significant. The statistical power analysis was determined as n=94 with effect size=0.50 (using Cohen's criteria), alpha=0.05 and power 0.95. The hypotheses were considered two-way, and a statistically significant result was accepted when $p \leq 0.05$.

Results

Out of the individuals included in the study, six were excluded due to incorrect and inadequate sampling. Of the remaining individuals, 63 (67%) were female and 31 (33%) were male. The mean age of the participants was 49±17.9 years. In the study, 49 individuals (52.1%) tested positive for the QuantiFERON®-TB Gold Plus Test. Of those who underwent the TST, 52 (55.3%) tested positive for PPD. Please refer to Table 1 for detailed results of the tuberculin skin test. A statistically significant difference was found between TST induration diameter and QFT-Plus test positivity. The rate of QFT-Plus positivity was higher in individuals with a TST induration diameter greater than or equal to 10 mm compared to other TST induration diameters ($p=0.001$).

When evaluating the results of both tests together, 43 (45.7%) individuals had positive results. In this study, 9 individuals with a positive TST had a negative QFT-Plus test, while 6 individuals with a positive QFT-Plus test had a negative TST. When both tests were evaluated together, 36 individuals (38.2%) had negative results. The test results are shown in Table 1.

The QuantiFERON®-TB Gold Test's validity was evaluated according to PPD. The sensitivity was 82.6%, and the specificity was 85.7%. The positive

Table 1: Correlation between TST and QFT-Plus test*

		TDT		
		Positive	Negative	Total
QFT-Plus	Positive	43	6	49
	Negative	9	36	45
	Total	52	42	94

***** QFT-Plus has a sensitivity of 82.6% and the specificity of 85.7%. The positive predictive value was 87.7%, and the negative predictive value was 80%

predictive value was 87.7%, and the negative predictive value was 80%. Figure 1 shows the related ROC curve.

Discussion

Based on the literature review conducted during the planning of this study, it is evident that there are three crucial elements related to this issue. Firstly, screening programs to detect and treat LTBI in migrants have significant health and economic benefits from a societal perspective. Secondly, the most cost-effective strategy for LTBI screening in migrants is a one-step QFT-Plus testing protocol. Thirdly, targeting young migrants from countries with a higher incidence of TB can increase the cost-effectiveness of screening (9-11). This study is the first in the literature to compare the tuberculin skin test and QuantiFERON®-TB Gold Plus in the Yazidi population.

However, it is important to consider various limitations and possible biases in our literature review. It is unclear whether the QFT-Plus testing protocol, which has been reported as the most cost-effective LTBI screening strategy in the majority of studies, maintains this characteristic in all contexts and jurisdictions. This is because the cost and treatment processes are specific to each country. Additionally, we lack the criteria to qualitatively or quantitatively evaluate each study and draw a comprehensive and generalizable conclusion on cost-effectiveness (12).

Oxlade O et al. reported that screening for active TB with postero-anterior chest radiograph is the most cost-effective strategy, whereas QFT-Plus is the least cost-effective way to screen new migrants (13). Pareek M et al. proposed mandatory postero-anterior chest radiographto increase the efficiency and cost-effectiveness of one-step QFT-Plus screening (14).

A study was conducted among healthcare workers in India to determine the agreement between the QFT-Plus test and TST test (TST 10 mm and above). The results showed an 81% agreement among 719 hospital workers. The agreement between these two tests in BCG-inoculated individuals was 80.4% (9). Our study showed similar results.

Convers et al. (15) found a correlation (Spearman's coefficient 0.45, p=0.0001) between TST induration diameter and QFT-Plus test positivity. Our study found a statistically significant higher rate of QFT-Plus positivity in individuals with TST induration diameter equal to or greater than 10 mm compared to other TST induration diameters (p=0.001).

The delay in diagnosing active TB cases in migrants is primarily due to their delayed entry into the healthcare system. This delay contributes to the transmission of the disease to other individuals in the community. Therefore, it is crucial to implement initiatives that ensure regular and timely communication with both migrants and the general population (12,16). However, it is assumed by most of the reviewed economic models that screening and treating LTBI in migrants will prevent active TB cases and solve the problem permanently (17,18). Therefore, we conducted TB screening in refugees to detect LTBI early and provide prompt treatment. Our study identified 69 individuals who tested positive for PPD and/or QFT-Plus as a result of screening. One of the distinguishing features of this study was that Yazidi refugees were not vaccinated with BCG due to their beliefs about health. As all individuals included in the study were BCG negative, there was a high positivity rate for both TST and QFT-Plus. Necessary information was provided to the authorities responsible for providing health services to migrants. Individuals in the risk group were given early treatment according to the Tuberculosis diagnosis and treatment guide.

Our limitations are that we did not plan to follow individuals with a positive TST or QFT-Plus for the development of TB disease, and could not diagnose TB based on microbiological evidence.

In conclusion, the QFT-Plus test is comparable to the TST in detecting Latent TB Infection among screened individuals. However, the QFT-Plus test has several advantages over other tests. It is not affected by BCG vaccination, does not cross-react with non-tuberculous mycobacteria, and is not affected by

factors such as the administration difficulties of TST and reading-related differences in the measurement of induration size.

Conflict of Interest: Regarding the current manuscript, the authors declare that there is no conflict of interest.

Ethics Committee Approval: This study was approved by the Dicle University Faculty of Medicine ethics committee on 15.12.2015 with the decision number 34. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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