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SHORT COMMUNICATION

Diagnosis of Latent Tuberculosis in Liver Transplant Candidates, a Single Center Experience

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SUMMARY

Background: **Tuberculosis is an important cause of mortality and morbidity in liver transplant patients, so it is valuable to diagnose latent tuberculosis in liver transplant candidates by an accurate screening test prior to transplantation. Tuberculin skin test (TST) is the standard test for the diagnosis of latent tuberculosis. Currently interferon-gamma release assays (QuantiFERON-TB Gold (QFT)) have been proposed as the best screening test, especially in the geographic areas with widespread BCG vaccination. In this research, we will compare these two tests in the largest liver transplant center in the south of Iran.**
Methods: **Both TST and QFT were performed in 50 liver transplant patients and 50 normal healthy individuals.**
Results: **TST was positive in 6 cases and 4 controls. QFT was positive in 5 cases and 9 controls. Sensitivity and negative predictive value were higher in QFT but the specificity and positive predictive value were higher in TST.**
Conclusions: **There is no significant difference between QFT and TST in evaluation of latent tuberculosis in liver transplant patients, however TST is less expensive and more feasible in Iran.**
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INTRODUCTION

Active tuberculosis is more prevalent in solid organ transplant recipients. Development of active tuberculosis depends on many factors such as high vs. low endemicity, the type of organ transplanted, and pre-transplant latent tuberculosis infection (LTBI) screening [1]. Liver transplant patients are screened for LTBI as a part of standard of care. One of the challenging issues is the diagnosis of LTBI, especially in endemic geographic regions in which all of the patients have been vaccinated [2,3].

TST (tuberculin skin test) using PPD (purified protein derivatives) and interferon-gamma release assays (QuantiFERON-TB Gold (QFT)) are the main two tests available for the diagnosis and screening of LTBI in liver transplant candidates. In the general population, these two tests have good concordance for detecting latent TB; however, it seems that prior vaccination causes less false positive results in QFT than TST [4].

Another challenge in the patients with chronic liver disease, who are candidates of liver transplantation, is decreased cellular immunity. Both of these screening tests measure cellular immunity, so defective immune cellular responses may cause anergy and false negative results in liver transplant candidates [5].

There is no gold standard test for the diagnosis of LTBI, so in this study we tried to compare TST and QFT tests for screening of LTBI in liver transplant candidates.

MATERIALS AND METHODS

Patients

Patients with chronic liver disease are being evaluated at the pre-liver transplant outpatient clinic at the affiliated hospitals of Shiraz University of Medical Sciences were eligible for inclusion in the study if they were on the waiting list for liver transplantation.

Fifty patients were included between September 2018 and 2019. The study was approved by the local Institutional Review Boards and all study participants provided informed consent.

Fifty healthy volunteers with no prior illness were also included in the study.

It is worthy to note that in our province every neonate is vaccinated with BCG and all of our patients and controls have already been vaccinated.

Tuberculin skin test

TST was performed on the volar side of the forearm according to the Mantoux method using 5 IU of PPD RT-23 by a 27-gauge, one quarter inch needle, 0.1 mL volume was injected intradermally to produce a raised and pale wheal of 6 - 10 mm. The results of the TST was read and evaluated after 48 - 72 hours. Any induration was measured and $\geq$ 5 mm of induration at 48 - 72 h was considered as positive [3].

Interferon-Gamma release assay

The QuantiFERON-TB-plus assay was performed according to the manufacturer's instructions (QIAGEN; Lot No.: 05906561; Germany). One milliliter of whole blood was drawn in each of four separate test tubes: one containing no antigen (nil control), two with TB antigens (TB1 and TB2), and one with phytohemagglutinin (mitogen or positive control). The four tubes were incubated for 24 hours at 37°C. Following incubation, the tubes were centrifuged, plasma was removed from each tube, and IFN-Gamma was measured by ELISA according to the manufacturer's instructions. The analysis of the results was performed according to the standards and controls and the patients' samples with QFT analysis software.

Statistical analysis

Latent tuberculosis lacks a perfect diagnostic tool. Hence, we applied Bayesian latent class model (LCM) to obtain Tuberculin and QuantiFERON tests' diagnostic statistics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Analysis carried out on the Modelling of Infectious Disease Center website (http://mice.Tropmedres.ac) powered by R and WinBUGS programs. It is worth noting that results should be interpreted carefully. First, chains in Bayesian LCM should converge properly and, second, frequencies predicted by Bayesian LCM should fit with or close to the observed data (or frequency observed), that is, the Bayesian p-value should be close to 0.5 or exactly 0.5, as well as having normal posterior predictive distribution of each profile.

Output plots and tables showed Bayesian LCM converged properly and frequencies predicted by Bayesian LCM fit with or close to the frequency observed (Figure 1).

RESULTS

Characteristics of the study population

We tested 100 individuals by TST and QFT. Fifty patients were cirrhotic and liver transplant candidates as part of their pre-transplant evaluation (considered as cases). Fifty were healthy individuals which were considered as control. Table 1 shows the demographic findings of these 100 cases and controls.

TST and QFT results

TST was positive in 3 (6%) and 4 (8%) of liver transplant candidates and healthy individuals, respectively. QFT was positive in 9 (18%) and 5 (10%) of liver transplant candidates and healthy individuals, respectively. Table 2 shows the results of TST and QFT in case and control groups.

Sensitivity and specificity of TST was 33% and 96.8% in comparison with QFT which was 55.9% and 99.5%, respectively. Positive and negative predictive values for TST were 64.5% and 89.1% and for QFT they were 54.2% and 93.4%, respectively (Table 4).

DISCUSSION

Tuberculosis can be a significant cause of morbidity and mortality in the patients on treatment with immunosuppressive drugs [6]. Therefore, it is very important to diagnose it before solid organ transplantations such as liver transplant. Positive screening tests mandate treatment by isoniazid or other anti-tuberculosis medications before performing liver transplantation [7].

Table 1. Demographic findings of cases and controls.

	Cases	Controls
Male/female	**33/17**	**27/23**
Age range	**15 - 69 (43.98 ± 1.9)**	**24 - 57 (38.1 ± 1.5)**

Table 2. Results of TST and QFT in cases and controls.

	Cases		Controls	
	Positive	**Negative**	**Positive**	**Negative**
QFT	**5 (10%)**	**45 (90%)**	**9 (18%)**	**41 (82%)**
TST	**6 (12%)**	**44 (88%)**	**4 (8%)**	**46 (92%)**

Table 3. Agreement between tuberculin skin test (TST) and QFT (QuantiFERON test).

	TST positive	TST negative	Total
QFT positive	**10 (10%)**	**4 (4%)**	**14 (14%)**
QFT negative	**3 (3%)**	**83 (83%)**	**86 (86%)**
Total	**13 (13%)**	**87 (87%)**	**100**

Table 4. Prevalence and diagnostic test estimations (sensitivity, specificity, positive predictive value, and negative predictive value) using imperfect gold standard model (Bayesian latent class model).

Prevalence [1]	**Control 19.6 (1.2 - 90.5)**		**Case 12.1 (1.0 - 94.6)**	
Diagnostic test estimation [2]	**Sensitivity**	**Specificity**	**PPV**	**NPV**
TST	**33.0 (0.1 - 98.7)**	**96.8 (52.0 - 100)**	**64.5 (0.6 - 99.9)**	**89.1 (6.8 - 99.9)**
QFT	**55.9 (0.3 - 99.7)**	**92.5 (44.2 - 100)**	**54.2 (1.2 - 99.8)**	**93.4 (6.5 - 100)**

[1] - prevalence (95% confidence interval), [2] - diagnostic test statistic by median (95% credible interval), Abbreviations: (1) PPV - positive predictive value, (2) NPV - negative predictive value.

There is no general consensus about the best method for the screening of LTBI in pre-transplant patients. The majority of liver transplant centers screen cirrhotic patients before liver transplantation by TST; however, in geographic areas of widespread BCG vaccination, it may create false positive results. Also, reduction of cellular immunity due to chronic liver disease may cause negative results. So, some studies emphasize on the use of QFT as the standard of care for pre-transplant screening [8].

Our center is the largest liver transplant center in the country, and the standard of care for pre-transplant screening of LTBI in our center is TST. In this study, for the first time in Iranian population, we tried to compare the results of TST and QFT tests to find the presence or absence of correlation between these two tests in liver transplant candidates. The sensitivity and specificity of TST and QFT were very close and there was no significant difference.

A systematic review and meta-analysis performed in 2009, confirmed that these two tests have no priority and have the same accuracy [9].

In conclusion, we think that both TST and QFT tests have the same results in cirrhotic liver patients who are

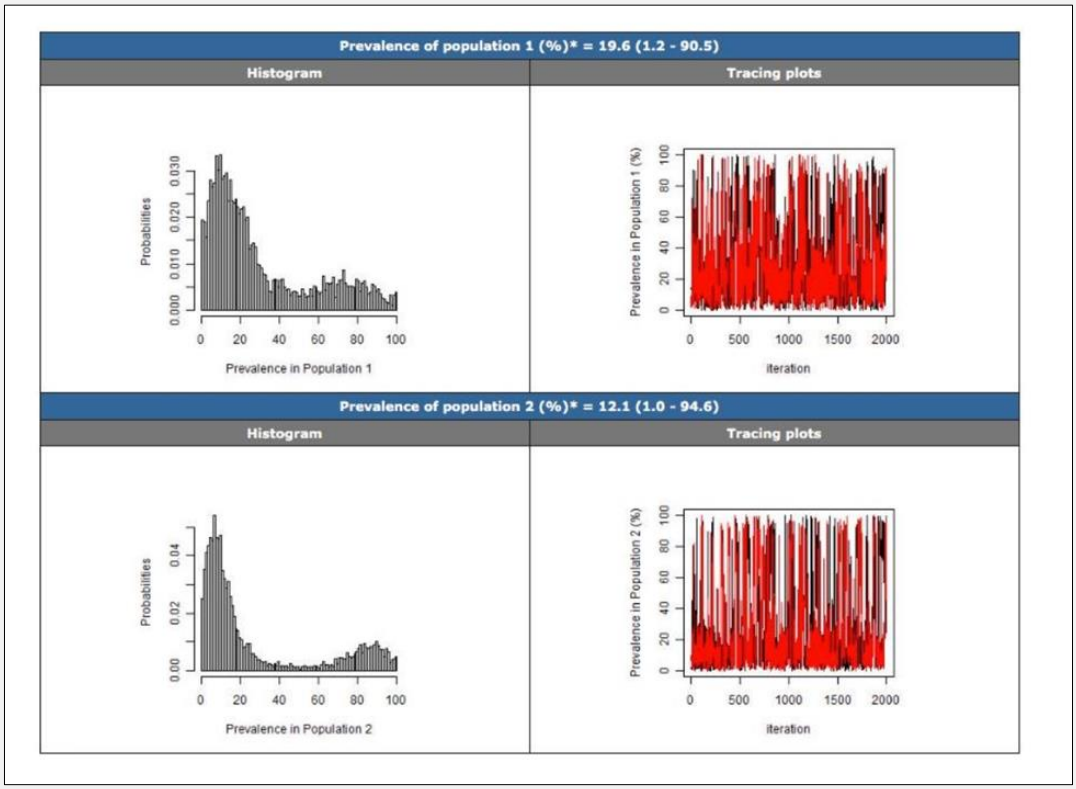

Figure 1. Output plots showed Bayesian LCM converged properly and frequencies predicted by Bayesian LCM fit with or close to frequency observed.

candidates of transplantation. Although in Iran TST is more feasible and less expensive. Therefore, we recommend continuing to perform TST as the standard of care for these patients in Iran.

Declaration of Interest:

There is no conflict of interest for the authors.

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