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Diagnosis of Latent Tuberculosis Infection Using Interferon-gamma Release Assay and Interleukin-2 among Healthcare Workers

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Abstract Background: Latent tuberculosis infection (LTBI) that could be converted to active TB constitutes a major public health problem. LTBI diagnosis is based on TST and/or IGRA. Serum IL-2 may help LTBI diagnosis. Objectives: Current study aimed to estimate the prevalence of LTBI among healthcare workers (HCWs), and to test the agreement between IGRA and IL-2 assay for detection of LTBI. Methods: The study was carried in chest hospitals in Egypt, 89 HCWs were included. Detailed medical history was obtained, and a blood sample was collected to measure IFN-γ and IL-2. Results: High prevalence of LTBI was detected among HCWs (41.57%). This was significantly associated with older age and longer duration of work. Doctors were less exposed to the risk of LTBI. Assessing IL-2 results using ROC curve: AUC was 0.984, optimal cut-off value =13.81 pg/ml, with a sensitivity of 94.59% and 100% specificity. IL-2 responses were higher among participants with LTBI compared to No TB. Conclusions: A high prevalence of LTBI was observed among HCWs. Older age and longer duration of work were associated with higher risk. IL-2/IFN-γ ratios may improve the ability of IGRA to identify individuals with LTBI and those at increased risk of conversion to active disease.

Keywords: *healthcare workers, interferon gamma release assays, interleukin-2, latent tuberculosis infection*

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1. Introduction

Tuberculosis (TB) was identified by the WHO as a major public health problem. One of the most common outcomes of infection with *Mycobacterium tuberculosis* (MTB) is latent tuberculosis infection (LTBI) which is defined as persistent immune response to MTB antigens without evidence of clinically manifested disease. [1] It is estimated that about one quarter of the world population have LTBI that acts as a source for active TB cases. Reactivation occurs in about 5–15% of the individuals with LTBI, leading to the development of active pulmonary or extra-pulmonary TB. [2]

Identification and treatment of LTBI among high risk groups, including Healthcare workers (HCWs), is one of the main components of the World Health Organization (WHO) "END TB strategy" aiming to eliminate TB by 2050. [3]

Two tests are currently used for LTBI screening: Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Comparing IGRAs and TST; IGRAs have higher specificity and sensitivity, give non subjective results and require single visit to the healthcare facility. However, IGRAs may give false positive results, with only three species of the non – tuberculous mycobacteria. They may give an indeterminate test results in immune suppressed patients, in addition to its high cost compared to TST. Both tests, TST and IGRA, are unable to differentiate between active and latent TB, or to predict future development of active TB. [4]

Currently, several biomarkers are being investigated to differentiate between active and latent TB including Interleukin-2 (IL-2) that promotes T-cell replication and is essential for cellular immunity and granuloma formation in MTB infection. Accordingly, several studies suggested measuring IL-2 release following stimulation by MTB specific antigens, to differentiate between active TB and LTBI. [5] Previous research reported higher levels of

interferon gamma (IFN-γ) and IL-2 in active TB and LTBI groups compared to non-infected individuals. In addition, it was found that combining IL-2 with IFN-γ might increase LTBI detection accuracy. [6]

The current study aimed to estimate the prevalence and different determinants of LTBI among HCWs at chest hospitals, using IGRAs and IL-2 assays. Moreover, it aimed to evaluate the diagnostic accuracy of IL-2 for diagnosing LTBI.

2. Materials and Methods

This study was approved by the Institutional Review Board (Ethics' Committee) of High Institute of Public Health Alexandria University, Egypt. (IRB No 128) and performed in accordance with the principles of the Declaration of Helsinki.

The study was conducted, from January to June 2017. HCWs at both Alexandria and Cairo Chest hospitals were included in the study. Blood samples were collected from 94 HCWs who were willing to participate in the study. Five were excluded from the study as they showed IFN-γ indeterminate test results even upon repetition of the test. All professions were included; physicians, nurses, laboratory staff, housekeepers, pharmacists and secretaries. An informed consent was obtained from all eligible participants prior to participation and after explaining the aim of the study.

An interview questionnaire was filled by each participant. The following data were collected: Demographic data (name, age, sex, contact number, profession, smoking status and years spent in the profession), medical history of associated chronic diseases and past history or family history of active TB disease.

Each sample was tested to measure IFN-γ and IL-2 levels. Participants with positive IFN-γ results were subjected to clinical and radiological assessment (Chest x-ray and CT if needed) to exclude active TB disease. All participants with positive IFN-γ results and negative clinical and radiological findings suggestive of TB were classified as LTBI group, and those with negative IFN-γ results were classified as uninfected or No TB group (NTB).

IFN-γ was measured using QuantiFERON®-TB Gold in-tube ELISA (QFT-GIT) produced by QIAGEN (3rd generation). QFT-GIT is an in-vitro diagnostic test that measures whole blood IFN-γ response to peptides simulating those associated with MTB infection. QFT-GIT uses a peptide cocktail that includes a group of TB specific antigens: ESAT-6, CFP-10 and TB7.7. These antigens stimulate IFN-γ response in T-cells from individuals infected with MTB. The test was performed according to manufacturer's instruction and test results were interpreted qualitatively. Results were expressed as positive, negative or indeterminate. All indeterminate test results were repeated with new samples if the participant agreed.

IL-2 was measured using Human Interleukin-2 ELISA (quantitative sandwich ELISA) produced by CUSABIO. This assay employs quantitative sandwich ELISA technique, where antibody specific for IL-2 is pre-coated onto the assay microplate. Professional software "Curve Expert 1.3" was used to make the standard curve to get the final results based on the optical density of each sample. All IL-2 results were assessed using Receiver Operating Characteristic (ROC) curve in order to evaluate the diagnostic performance of IL-2. Youden index was used to choose the cut-off value with best sensitivity and specificity. The chosen cut-off value was used to classify the tested participants as positive or negative for IL-2 response. For further correlation of the relation between IFN-γ and IL-2 among participants with LTBI; Participants with LTBI were stratified into three subgroups, based on IFN-γ response: Low responders (0.35 to <1.0 IU/mL), intermediate responders (1.0-5.0 IU/mL) and high responders (≥5 IU/mL). [7]

2.1. Statistical Methods

Statistical analysis was performed using Statistical Package of Social Sciences version 21 and Medcalc statistical software version 14. [8] D'Agostino test for normality was used to test for the significant deviation from normal distribution across all quantitative variables in all groups. Accordingly, Continuous normally distributed variables were summarized as means and standard deviations, tested for correlation by Pearson's correlation and compared across two subgroups using Student's t-test. Continuous variables significantly deviated from normal distribution where summarized as medians and ranges, tested for correlation using Spearman's rank correlation and compared across two subgroups using Mann-Whitney U test and across two subgroups using Kruskal-Wallis H test. Then significant pairwise comparison across subgroups was carried out according to Conover, 1999. [9]

Nominal variables were summarized in the form of frequency, were analyzed using Fisher's exact test of independence and then unadjusted Odds ratio (OR) was calculated. Binary logistic regression analysis was applied to assess the relationship between LTBI versus NTB and different healthcare professions as a risk factor for LTBI. Adjusted OR were calculated after adjusting for possible confounding factors. Diagnostic performance and accuracy of IL-2 to differentiate between LTBI and NTB were evaluated using ROC analysis, and Youden index was used to determine best cutoff value. Significance level was considered at p-value<0.05.

3. Results

Table 1 shows that 63 out of the 89 HCWs (70.79%) were females and 26 (29.21%) were males, only 2/89 (2.25%) were smokers and 22/89 (24.72%) had associated co-morbidities. HCWs were represented by different professions but the majority were doctors and nurses; 32 (35.96%) doctors and 36 (40.45%) nurses. Other professions included 9 (10.11%) laboratory technicians, 2 (2.25%) laboratory specialists, 7 (7.87%) housekeepers and 3 (3.4%) of both pharmacists and secretary (represented in Table 1 as "others"). The median age of HCWs was 37 (IQR: 30.8 - 44.3) years old. None had past/family history of active TB.

Table 1. Demographic and clinical characteristics of the studied healthcare workers from Alexandria and Cairo Chest Hospitals – Egypt

Characteristic (n=89)		HCWs	
		Number	%
Gender	Female	63	70.79
	Male	26	29.21
Smoker	Yes	2	2.25
	No	87	97.75
Co-morbidity	Yes	22	24.72
	No	67	75.28
Profession			
Doctors		32	35.96
Nurses		36	40.45
Lab technicians		9	10.11
Lab specialists		2	2.25
Housekeepers		7	7.87
Others†		3	3.37
Age in years‡		37 (30.8-44.3)	

HCWs: healthcare workers, n: number, †others include pharmacists and secretaries, ‡ age presented as median (Inter quartile range).

IFN-γ was positive in 37 out of the 89 HCWs (41.57%). None of the IFN-γ positive participants showed clinical or radiological evidence of active TB; therefore, this percentage (41.57%) was considered as LTBI prevalence among HCWs.

Table 2 a. shows qualitative risk factors for LTBI among HCWs. Doctors were less exposed to the risk of LTBI compared to all other professions, OR =0.25 (95% CI: 0.09-0.68), p <0.01, adjusted OR=0.141 (95% CI: 0.036-0.562). Other factors including gender, smoking and co-morbidities were not statistically significant (p >0.05).

Table 2 b. shows quantitative risk factors for LTBI among HCWs. It was observed that HCWs were significantly older in LTBI group, the median age of that group was [43 (IQR: 33.8-49.5) years] compared to NTB group [34.5 (IQR: 28.5-38.5) years], Mann–Whitney U =549, n_{NTB} =52, n_{LTBI} = 37, p<0.0001. Moreover, the median duration of work at chest hospitals was significantly longer among LTBI group [17 (IQR: 10.5-23) years] compared to NTB group [8 (IQR: 2.5-17) years], Mann–Whitney U =510.5, n_{NTB} =52, n_{LTBI} = 37, p<0.0001.

Table 2. Determinants of LTBI among the studied healthcare workers

a. Qualitative determinants.					
Determinant		**LTBI (n=37)**	**NTB (n=52)**	**Fisher's *p*^**	**OR (95%CI)**
Gender	Female	25 (67.57%)	38 (73.08%)	0.64	0.77 (0.31-1.92)
	Male†	12 (32.43%)	14 (26.9%)		1
Smoker	Yes	0 (0%)	2 (3.85%)	0.51	0.27 (0.013-5.78)
	No†	37 (100%)	50 (96.15%)		1
Co-morbidity	Yes	10 (27.03%)	12 (23.08%)	0.80	1.23 (0.47-3.26)
	No†	27 (72.97%)	40 (76.02%)		1
Profession					
Doctor	Yes	7 (18.9%)	25 (48.1%)	< 0.01	0.25 (0.09-0.68)
	No†	30 (81.1%)	27 (51.9%)		1
Nurse	Yes	15 (40.5%)	21 (40.4%)	0.99	1 (0.43-2.38)
	No†	22 (59.5%)	31 (59.6%)		1
Lab technician	Yes	6 (16.2%)	3 (5.8%)	0.16	3.16 (0.74-13.57)
	No†	31 (83.78%)	49 (94.2%)		1
Lab specialist	Yes	2 (5.41%)	0 (0%)	0.17	7.39 (0.35-158.68)
	No†	35 (94.59%)	52 (100%)		1
Housekeeper	Yes	5 (13.51%)	2 (13.5%)	0.12	3.91 (0.71-21.36)
	No†	32 (86.48%)	50 (96.2%)		1
Others	Yes	2 (5.41%)	1 (1.92%)	0.57	2.91 (0.25-33.39)
	No†	35 (94.59%)	51 (98.08%)		1

Data are presented as number (%), †: Subjects in this category served as a reference group with OR=1, OR: Odds ratio, CI: confidence interval, LTBI: latent TB infection, NTB: No tuberculosis infection, *Statistical significance level (p-value < 0.05).

b. Quantitative determinants.				
Determinant (years)	LTBI (n=37)	NTB (n=52)	Mann-Whitney U	*p-value*
Age	43 (33.8-49.5)	34.5 (28.5-38.5)	549	<0.0001*
Duration of work at chest hospitals	17 (10.5-23)	8 (2.5-17)	510.5	<0.0001*

Data are presented as median (Inter quartile range).

The diagnostic performance and accuracy of IL-2 to differentiate between LTBI and NTB was assessed using ROC analysis. As shown in Figure 1, ROC curve is positioned near the upper left corner, AUC equals 0.984 (95% CI: 0.932-0.999), p<0.0001. IL-2 value with the highest "Youden index" was selected as the optimal cut-off (13.81 pg/ml), with a sensitivity of 94.59% (95% CI: 81.8-99.3) and specificity of 100% (95% CI: 93.2-100). The positive predictive value =97.2% (95% CI: 83.4-99.6) and the negative predictive value =96.2% (95% CI: 86.9-99).

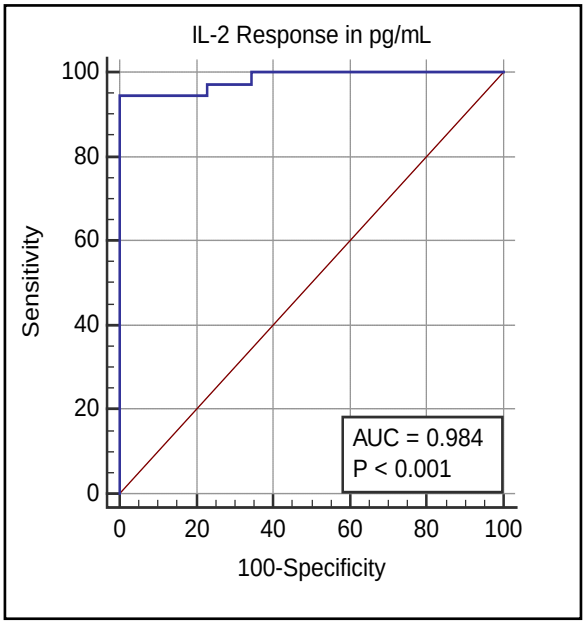

Figure 1. Assessing the diagnostic potential of interleukin-2 among the studied healthcare workers, using Receiver Operating Curve (AUC: area under the curve, IL-2: interleukin-2, statistical significance level (p <0.05))

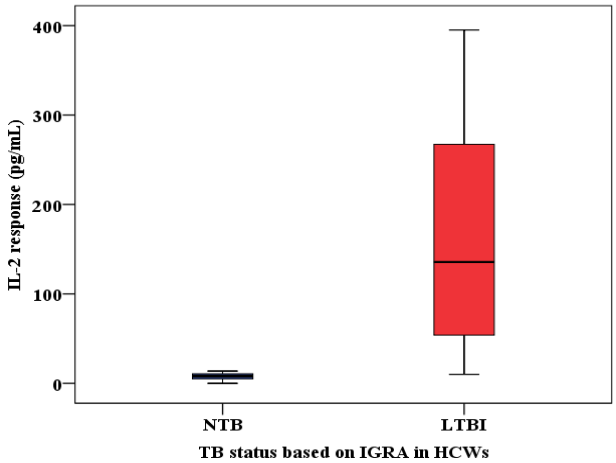

Figure 2. Box plot representing groups with LTBI (n =37) and NTB (n =52) in relation to their IL-2 response (pg//ml) among the studied HCWs (LTBI: latent tuberculosis infection, NTB: No tuberculosis, HCWs: healthcare workers, IGRA: Interferon gamma release assay, IL-2: interleukin-2, IFN-γ: Interferon gamma)

For further correlation of the relation between IFN-γ and IL-2 among HCWs with LTBI, this group was further stratified into three subgroups, based on IFN-γ response: Low responders (0.35 to <1.0 IU/mL), intermediate responders (1.0-5.0 IU/mL) and high responders (≥5 IU/mL). Then IL-2/IFN-γ ratios were calculated for each participant in those subgroups, and the ratios were studied in relation to IFN-γ response among the 3 subgroups. Comparison between the three subgroups showed a statistically significant difference (p <0.0258). A pair-wise comparison across the three subgroups (Low, intermediate, and high responders) showed a statistically significant difference (p <0.05) in IL-2/IFN-γ ratios when comparing IFN-γ low responders with intermediate and high responders' groups, i.e. IL-2/IFN-γ ratio was higher among IFN-γ low responders compared to intermediate and high responders. No statistically significant difference was detected when comparing intermediate to high responders. (Figure 3)

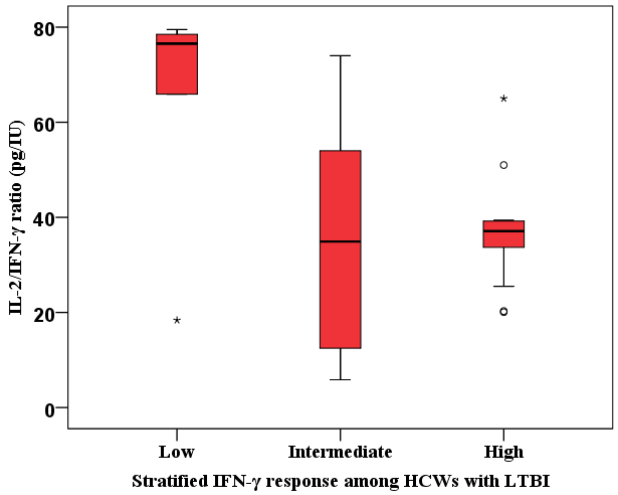

Figure 3. Box plot representing IL-2/IFN-γ ratio (pg/IU) and stratified IFN-γ response (IU/ml) among HCWs with LTBI (n = 37) (LTBI: latent tuberculosis infection, NTB: No tuberculosis, HCWs: healthcare workers, IGRA: Interferon gamma release assay, IL-2: interleukin-2, IFN-γ: Interferon gamma)

4. Discussion

HCWs screening for LTBI is recommended by the WHO and implemented in many high and middle income countries worldwide. [1] In Egypt, there is no routine screening protocols for LTBI among HCWs. A high prevalence of LTBI (41.57%) was observed among HCWs in the current study. Prevalence of LTBI among HCWs could be affected by several factors including the specialty of the studied healthcare facility. Higher prevalence was reported by studies conducted at chest hospitals compared to studies conducted at non-TB facilities. This difference is attributed to the routine and sustained occupational exposure among HCWs in chest hospitals. This observation explains the difference in prevalence between the current study and the prevalence observed in another 3 studies conducted at General University Hospitals in Egypt that reported a prevalence of 28.8%, 19%, and 10.3% respectively. [10,11,12] Similarly, three studies conducted in Georgia, Brazil and Thailand at non-TB facilities reported lower prevalence (31%, 27%, and 18.8% respectively) compared to the current study although these are countries with high TB disease incidence. [13,14,15] Indeed countries with high TB disease incidence and those having HIV associated TB, show higher LTBI prevalence among HCWs. This observation was clear when we compared LTBI

prevalence in the present study with that reported by a similar study conducted in Georgia, a country with high TB disease incidence and high TB/HIV association. Although both studies were carried in TB facilities the prevalence in Georgia (55%) was higher than the current study (41.57%). In addition, the economic level of the country can affect TB prevalence. LTBI prevalence among HCWs at developing countries ranged from 41-63% which is in agreement with the current study. [16,17,18]

Other factors can affect the risk of LTBI among HCWs. In the current study, older age was significantly associated with higher risk of LTBI which was reported in several studies. [11,14,15] On the contrary, two studies in Egypt and Mozambique reported that older age was not significantly associated with LTBI. [12,19] Longer duration of work at chest hospitals was another factor significantly associated with higher risk of LTBI in this study. In general, longer duration of work in healthcare facilities, was reported by several authors as a risk factor associated with LTBI. [10,11,12,14,15] Different healthcare professions have variable risk of exposure to LTBI based on the nature of the profession and the level of patient contact. Several studies reported a significant increased risk of LTBI among nurses compared to other HCWs. [10,14,15] In a study conducted in Cairo University Hospital, in addition to nurses, housekeepers also showed a higher risk of exposure to LTBI. [12] These findings were in agreement with the current study that showed doctors were less exposed to LTBI compared to all other HCWs. On the contrary, neither gender nor co-morbidities affected the risk of LTBI among HCWs in our study.

IGRA, though a highly specific test compared to TST, it cannot differentiate between active and latent TB or predict the conversion among individuals with LTBI. IL-2 was studied to differentiate between different MTB infection outcomes. [5]

In the present study, we tested the agreement between IGRA and IL-2 as screening tests for LTBI considering IGRA as the gold standard. ROC analysis showed that IL-2 has high AUC values (0.984), high sensitivity (94.6%) and specificity (100%) for detection of LTBI. Besides, IL-2 response was significantly higher among HCWs with LTBI compared to those with NTB ($p< 0.0001$). These results indicate high accuracy of IL-2 as a diagnostic marker for LTBI. Rubbo at al reported 100% sensitivity and specificity of IL-2 for the detection of LTBI, and they considered IL-2 as “A marker of interest to improve LTBI diagnosis”. [20] In addition, current study results were in agreement with a meta-analysis aimed to evaluate the diagnostic accuracy of IL-2 for diagnosis of LTBI where they found the pooled IL-2 sensitivity and specificity to be 81% and 95% respectively. [21]

The outcome of MTB infection varies according to body immune response. In addition, the cytokines secreted by activated T-cells vary with different MTB infection outcomes. Three main functional T-cell responses were described: a dominant IL-2 response, a multifunctional response (IL-2 and IFN-γ) and a dominant IFN-γ response. [22] Suter-Riniker et al. and Millington K et al. suggested that the net result of functional T-cell response would be detectable by assessing MTB specific IL-2/IFN-γ ratio. [7,23] In addition, researchers suggested using IL-2 to help proper interpretation of IFN-γ results at or near the test cutoff. In the current study IL-2/IFN-γ ratios were significantly higher among IFN-γ low responders compared to intermediate and high responders. That means participants with IFN-γ results near the cut-off value (low IFN-γ responders) had higher IL-2 levels compared to all other participants with LTBI. Suter-Riniker et al. reported similar findings. They suggested that IFN-γ results around the cut-off with shift towards IL-2 dominant T-cell response may not require LTBI preventive treatment. [7] Similarly, Millington K et al. suggested that IFN-γ/IL-2 ratio could be used to monitor LTBI individuals at high risk of progression to active TB disease to support the decision of initiating LTBI preventive treatment. Those findings may help avoiding unnecessary LTBI preventive treatment that will reduce the financial burden and decrease the possibility of development of drug resistance due to treatment non–compliance. [23] However, one of the current study limitations that we were not able to follow up the studied population for detection of conversion to active TB disease. It would have been idea to monitor the progression to active TB in relation to IFN-γ and IL-2 levels in another study.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Ethical Statement

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission and have contributed significantly to the work. This study has been preapproved by the Ethics Committee of the High Institute of Public Health

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