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Prevalence of Tuberculosis Infection among the Patients Suspected with latent tuberculosis in Baghdad City

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Abstract: The objectives were to estimate the prevalence of latent tuberculosis infection (LTBI) among the patients suspected of the latent tuberculosis referred to the Specialized Chest and Respiratory Disease Center/National Reference Laboratory for Tuberculosis (NRL) in Baghdad, and also to identify their risk factors. A prospective, cross-sectional study was conducted from fifteenth April to fourteenth November 2021. Included all patients referred from Baghdad Specialty Hospitals to the Specialized Chest and Respiratory Disease Center/(NRL) for Tuberculosis in Baghdad of suspected latent TB infected. Quantiferon TB-Gold plus assay (QFT-Plus). Data were analyzed using the Statistical Analysis System (SAS). Among 601 the patients suspected of the latent tuberculosis, 23.8% (143\601) revealed positive QFT-Plus and 76.2% (458\601) negative QFT-Plus. The significant risk factors associated with positive QFT-Plus individuals were (41– 60) years. Specimens were taken both genders: was the percentage positive of the (QFT-Plus) test for females more than male 78(54.6%), 65(45.5%), respectively. The ages of the patients ranged from two to 81 year, and it was divided into six groups. The skin was the highest percentage 44(7.3%) of the rest of the cases, followed by the eye 42(7.0%), joints 34(5.7%), lymph nodes 10(1.7%), digestive system 6(1.0%), respiratory system 6(1.0%) and the lowest percentage was reproductive system1(0.1%). The latent tuberculosis is occur by several risk factors including cigarette smoking and its ratio was 53(37.0%), alcohol consumption 47(32.9%), closed contact with a latent TB patient 32(22.4%) and immunosuppressive therapy 11(7.7%). Where impaired immunity and a higher risk of contracting TB infection are blamed for the issue.

Keywords: Latent TB Infection, IGRA, Prevalence, Contact, Iraq.

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Introduction

Latent tuberculosis infection was the term traditionally used to indicate tuberculosis (TB) infection. This term was used to define "a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens through tests such as the tuberculin skin test (TST) or an interferon-γ release assay (IGRA) without clinically active TB". Recent evidence suggests that subclinical TB is responsible for important *M. tuberculosis* transmission (1). There are two methods for diagnosis of LTBI include the century-old tuberculin skin test (TST) (2) and decade old immunodiagnostic test, interferon gamma release assays (IGRAs). Both these test work on the principle of cell mediated immunity (3). In 1999, the World Health Organization

(WHO) estimated that one-third of the world's population had latent tuberculosis infection (LTBI), which was recently updated to one-fourth. However, this is still based on controversial assumptions in combination with tuberculin skin test (TST) surveys. Interferon-γ release assays (IGRAs) with a higher specificity than TST have since been widely implemented, but never used to estimate the global LTBI prevalence (4). This estimate has since been referred to frequently, but had not been updated until recently. In 2016, a WHO-endorsed estimate updated the global prevalence of LTBI to 23%, corresponding to 1.7 billion people infected worldwide (5, 6).

According to the World Health Organization (WHO) determination, a latent TB infection (LTBI) is described by the lasting immune response to *Mycobacterium tuberculosis* (M.tb) antigens without any TB symptoms, approximately a quarter the world's population infected by Mtb and has a latent TB infection (LTBI) (7). The following factors substantially increase the likelihood of progression of latent infection: suppression of cellular immunity by HIV infection, HIV immunosuppression (8) glucocorticoids, (9) blood or organ transplant (10, 11) and tumor necrosis factor α inhibitors (12). Other factors associated with LTBI include age, positive HIV status, working as physicians/nurses or miners, diabetes and malnutrition (13, 14, 15). The aim of this present study was to locate out how common latent tuberculosis infection in Iraq, where was diagnosed LTBI is diagnosed by detecting memory T-cell response against latent infection with *M. tuberculosis* with the use of interferon-gamma release assays (IGRAs).

Materials and methods

Sample collection

To examine latent tuberculosis infection, 601 diagnostic whole blood collection were obtained from patients referred to Specialized Chest and Respiratory Disease Center / National Reference Laboratory for Tuberculosis (NRL) in Baghdad between fifteenth of April to the fourteenth of November 2021.

Specimens were taken both genders: 65(45.5%) males and 78(54.6%) females, ranging in age from two years to 81 year. After completing the questionnaire, the laboratory technician collected 4–5 ml of venous whole blood from the respondents. Blood samples collected from malty cases of body were divided into seven groups of (LTBI): 226 patients infected in skin, and (132, 166, 19, 38, 18, 2) patient infected in (eyes, joints, lymph nodes, digestive system, respiratory system, reproductive system) respectively, the whole blood was stored in tubes containing heparin. Close contact was defined as those who come in contact with a patient with infectious TB for a long time (more than eight hours) in a closed area (16).

Study criteria included only the patients' cases that who were the referred from hospitals of Baghdad and the other all governorates' hospitals in Iraq's to the (NRL). The patients' ages ranged from two years and over, have no symptoms of active TB.

The diagnosis treating physician that the patients had latent tuberculosis infection, this study was carried out after obtaining consent from the patients by taking a blood sample for an IGRA test.

While health care workers (HCW) were excluded from this study which are other studies that concern health care workers only as they are the most people in direct contact with tuberculosis patients as they are more likely to contract latent tuberculosis.

QFT-Plus ELISA

QuantiFERON-TB Gold Plus Assay blood was drawn using 5 CC syringes. After collection, re-mixing of the tubes by inverting 10 times must be performed immediately prior to incubation at 37°C ± 1°C for 16 to 24 h. The incubator does not require CO2 or humidification. After incubation at 37°C, blood collection tubes may be held between 4°C and 27°C for up to 3 days prior to centrifugation, then separated of plasma is by centrifuging the tubes for 15 minutes at 2500 rpm. the amount of IFN-γ (IU/ml) is measured by ELISA.

Plasma samples can be stored for up to 28 days at 2°C to 8°C or, if harvested, below –20°C for extended periods. For adequate test samples, harvested at least 150µl of plasma. QuantiFERON-TB-Gold-Plus assay (Qiagen) was performed according to the manufacturer's instructions. The specificity and the sensitivity of the test are higher than 95%. All IGRA testing was performed before the patients were prescribed anti-TB medications.

Radiological examination

All patients referred from hospitals to the (NRL) with positive QFT underwent a chest X-ray (CXR) to exclude active TB.

Ethics

Research proposal and consent were reviewed by the Ethics Committee in the Ministry of Health Iraq\ Specialized Chest and Respiratory Disease Center/National Reference Laboratory for Tuberculosis (NRL) in Baghdad written informed consent was obtained from all subjects.

Results and discussion

The studied samples

During a period of seven months, 601 samples were collected from patients who were referred to Specialized Chest and Respiratory Disease Center/National Reference Laboratory for latent tuberculosis screening. Where the proportion of women with latent TB infection was more than males. 78(54.6%) females and 65(45.5%) males, this variation was non-significant (Table 1).

All the cases were sent from specialized hospitals in Baghdad (Baghdad Medical City, Baghdad Teaching Hospital include departments: (Bahgat disease), (Osteoporosis), (Haematology), (renal disease and kidney dialysis) and (Gastroenterology and Hepatology centre), and Ibn Al-Haitham Teaching Eye Hospital) The patients were referred from hospitals the governorates of Iraq. The cases sent include eyes infection, joints, lymph nodes, digestive system, respiratory system and reproductive system, where the number of skin infection represented a 226 patient, while other types of cases represented 375 patients.

Screening and exploration of the determinants of LTBI among patients who are sent from specialty hospitals in Baghdad and the referrals were from all hospitals in Iraq's governorates to the Specialized Chest and Respiratory Disease Center/National Reference Laboratory is an important measure to reduce the incidence of tuberculosis, the subjects included in study were the cases that were transferred to the center were patients with biological factors. The detection of LTBI in this study was performed by IGRA; furthermore, the

study covered the incidence of LTBI among populations belonging to varying age groups, including children, adolescents, and adults. In the present study, LTBI prevalence was evaluated by employing the random effects model since high heterogeneity was encountered among studies.

The existence of high heterogeneity may have possibly been due to variations in study settings, subjects or participants, methodologies involved, exposure to TB patients, and the control measures taken across the studies. Recognizing LTBI among close contacts and identifying the potential risk factors of acquiring the infection is paramount policy toward reducing TB incidence as majority of TB cases result from reactivation of such infections. The gender-based analyses, prevalence of LTBI was found to be in females more than males 54.6%, 45.4% respectively. However, finding a suitable diagnostic tool to determine LTBI is an issue that needs to be confirmed. The current study compares the types of latent TB infections and their prevalence rates among individuals, for both genders and for all ages by IGRA test to diagnosis the population at risk of having LTBI.

The our current study included a different number of men and women which was agreement with the study by Adams *et al*. he had more women compared with less men 241(71%), 98(29%) respectively (17), by contrast this study was not agreement with the prevalence of LTBI in Kenya where there was slightly height among males at 58.8%than females at 54.5%. However, gender was not identified as a risk factor for LTBI (18). In China, men were less susceptible to LTBI (19), while females had a significantly lower risk of LTBI in South Korea (20). A systematic review by Hasan *et al*. studied 38 guidelines published across 16 countries, recommending LTBI screening in immunecompromised hosts (21). It is strongly recommended to systematically test and treat LTBI in patients on biological therapy (22). Overall, immunesuppression is a recognized risk factor for acquiring TB infection and development of the disease (23).

Most of the cases and for both gender, they were from the poor class and the inhabitants of remote areas this study was agree with Lule *et al*., 2020 the several known factors may interact with gender in increasing the risk for LTBI. Lower socio-economic status groups appear to have a higher prevalence of LTBI (24).

Table (1): Distribution of latent tuberculosis patients according to gender.

Gender	No. of specimens	IGRA test diagnosis	
		+Ve	%
Male	272	65	45.4%
Female	329	78	54.6%
Total	601	143	100%
Chi-square-χ 2	---	---	1.181 NS
P-value	---	---	0.277
NS: Non-Significant.			

The ages group of latent tuberculosis infections ranged from two years to eighty-one years for all cases sent, the patients were divided into six age groups show in table (2) based on their age. The age groups (41- 60 years) showed more frequencies of TB cases (45.4%) than other age groups, and the

lest registered age groups was observed in the < 2 years with percentage (1.4%), with highly significant differences between all age groups **(P≤0.01).

As for the age-based prevalence, it was assessed to be 1.4%, 9.8%, in children and adolescents, respectively as for the rest of the ages, it was their percentage 88.8% the ages ranged between (21-81) years, therefore, this systematic review implies this setting not considered a small percentage prevalence of LTBI in the hospitals of Baghdad and the referrals were from all hospitals in Iraq's governorates irrespective gender, and in order to achieve the WHO target of elimination of TB by 2050 and end TB strategy by 2035 could be possible only if the probability of progression LTBI to active TB is drastically reduced below the current lifetime risk of 5–15% (25), LTBI is important to be taken into account when evaluating TB infection control program. Investigating the prevalence of LTBI and the risk factors in the community might improve the health policy.

We noticed that the incidence of latent tuberculosis infection rising with increasing age, our study is in agreement with (26, 27), association with age the LTBI might reflect the increase in cumulative exposure to M.tb with age or the increase in the interferon production in response to mycobacterial antigens in whole blood. In the present study, most patients with positive latent tuberculosis are from poor areas with high intensity people no good health care of those infected, compared with a similar study (28) transmission rates and infectiousness are highly dependent on age distributions, geographical location, drug availability, living conditions and population density. The disparity in the prevalence rate of LTBI at different geographical levels could help target the highest risk countries or regions according to the (29).

Based on IGRA, contacts of index cases of TB in this study had relatively low prevalence of LTBI (23.8%), similar rates have been reported in Iraq (30) a relatively low rate (19.85%) has been estimated, while not agree with high rates have been reported in Ghana: 65% (31). In Oman the prevalence of latent tuberculosis infection (LTBI) was 22.8% among contacts, found higher proportions of LTBI among females than males (28.7% vs. 15%, p = 0.027), This study is agreed with approach to our current study (32).

To compare the prevalence rate of our study with other studies, we observed high prevalence rates of LTBI which were 49% (2008–2009) in Uganda (33), and 41.78% (2000–2018) in the Middle East and North Africa region (34). While reported to be low in Australia (4.6% in 2006 and 5.1% in 2016) (35).

Table (2): Distribution of latent tuberculosis patients according age group

Age group (year)	No. of Specimens	IGRA test diagnosis	
		+Ve	%
< 2	2	2	1.4%
2 – 20	92	14	9.8%
21 – 40	237	42	29.4%
41 – 60	219	65	45.4%
61 - 80	50	20	14.0%
> 81	1	0	0.0%
Total	601	143	100%
Chi-square- χ 2	---	---	18.065 **

P- value	---	---	0.0001
**** (P≤0.01).**			

QuantiFERON-TB gold plus assay

The positive and negative results for latent tuberculosis infection were obtained during our current study period. Where the overall positive result for seven groups of blood samples represented 23.8% (143\601). While the negative samples were 76.2% (458\601).

The skin infection was 226 patients the positive results were 44(7.3%), of them 27(4.5%) males and 17(2.8%) females from the remainder of the studied samples of positive for latent tuberculosis were arranged as follows: eyes infections 132 patients the positive results 42(7.0%), 18(3.0%) males and 24(4.0%) females. The other types of latent infections include joints, lymph nodes, digestive system, respiratory system, reproductive system was arranged positive results as follows, in succession for both males and females: 34(5.7%), 10(1.7%), 6(1.0%), 6(1.0%), 1(0.1%). We noticed there were statistically highly significant differences between seven different types of latent tuberculosis infection **(P≤0.01) as shown in table (3).

We note that the number of cases of cutaneous latent tuberculosis in our study represents the highest percentage about the rest of the other cases 44(7.3%), due to the fact that patients infected with this type of latent tuberculosis because of weak natural immunity cutaneous tuberculosis can be acquired from hematogenous or lymphatic dissemination of a pulmonary focus or by direct inoculation.

The pivotal factor for the clinical presentations prior to contact with bacilli is the host natural immune response, however. Most cases of latent cutaneous TB infections involved infections-granulomatous syphilis, discoid lupus erythematosus, psoriasis, tuberculoid leprosy, actinomycosis, mycetoma, bacterial abscesses, and other skin infections.

Cutaneous tuberculosis is, comprising 1.5-1of all extrapulmonary tuberculosis manifestations، which manifests only in 8.4-13.7% of all tuberculosis cases (36).

Tuberculous uveitis still represents a minority of uveitis cases, with varying prevalence ranging from 1- 4% to 10–26% in different areas of the world (37, 38), where the latent tuberculosis infections of the eye in this study 42(7.0%). As for the remaining cases of latent tuberculosis infection, such as (joints, lymph nodes, digestive system, respiratory system, reproductive system), their proportions were as follows, 34(5.7%), 10(1.7%), 6(1.0%), 6(1.0%), 1(0.1%) respectively. In this study between different patients with the latent tuberculosis infection of different ages and genders, the overall prevalence of LTBI among different person who have been converted to the Specialized Chest and Respiratory Disease Center/National Reference Laboratory was 23.8% by QFT-Plus. This study was a similar with (39) in Kurdistan, Iraq among 521 patients revealed 80 (19.85%) positive QFT-Plus, and in contrast, other studies from Iraq using IGRA showed a higher LTBI prevalence rate ranging from 36.94% - 41.3%, (40, 41). Studies from Iran, a neighboring country with low TB

incidence, showed a prevalence rate of LTBI ranging from 16.5%- 42.8% (42, 43, 44).

Table (3): Determination of the numbers and infected sites for latent tuberculosis for deferent's locations of body in genders.

No.	Tuberculosis infection sites	Total No. of specimens	IGRA test		% of positive IGRA test	Male		Female	
			-Ve	+Ve		(+Ve)	(%)	(+Ve)	(%)
1.	Skin	226	182	44	7.3%	27	4.5%	17	2.8%
2.	Eyes	132	90	42	7.0%	18	3.0%	24	4.0%
3.	Joints	166	132	34	5.7%	13	2.2%	21	3.5%
4.	Lymph nodes	19	9	10	1.7%	2	0.3%	8	1.3%
5.	Digestive system	38	32	6	1.0%	3	0.5%	3	0.5%
6.	Respiratory system	18	12	6	1.0%	2	0.3%	4	0.7%
7.	Reproductive system	2	1	1	0.1%	0	0.0%	1	0.2%
Total		601	458	143	---	65	---	78	---
%		---	76.2%	23.8%	23.8%	---	10.8%	---	13.0%
Chi-square-χ^2		---	165.09 **		14.371 **	---	1.181 NS		
P-value		---	0.0001		0.0001	---	0.277		
** (P≤0.01).									

While in (Table 4) we notice that the percentage according risk factor with the positive prevalence ratio for (QFT-Plus), the cigarette smoking it was the highest value represented as a risk factor strongly associated with latent tuberculosis, and with highly significant differences between all the other risk factor **(P≤0.01).

We observed in the highest rate of latent tuberculosis infection was in people who smoke or alcohol consumption and closed contact with a latent TB patient 53(37.0%), 47(32.9%), 32(22.4%) respectively as they are more susceptible to infection and the lowest rate was for people who were used immunosuppressive therapy 11(7.7%). In countries with high TB prevalence, the WHO expanded program on immunization recommends BCG vaccination during the first week of birth. In Iraq, as a part of national immunization program, BCG vaccine is routinely administered to all newborn babies in the first seven days after delivery (45).

Iraq is one of the seven highest TB burden countries in the WHO–Eastern Mediterranean Region with a TB incidence of 42 per 100,000 people, constituting 3% of the total TB patients.(46). Smoking was significantly related with LTBI in the current study, despite the fact that it was not an independent risk factor by multivariate analysis. Similarly, a systematic review and by Bates *et al*. showed that smoking is implicated in influencing TB infection (Bates *et al*., 2007). Obviously, smoking can damage cilia functions in the airways resulting in an increased risk for acquiring TB infection and disease (47).

Among QFT-Plus individuals, drinking alcohol was a risk factor for LTBI on its own. Indeed, numerous reports (48, 49, 50). Established a connection between drinking alcohol and the development of TB. Impaired immunity and a higher risk of contracting TB infection are blamed for the issue. Failure by auditors to conduct laboratory tests and flop adhere to health prevention guidelines and contact with infected people despite the directives of the Tuberculosis Specialized Chest and Respiratory

Disease Center/National Reference Laboratory for Tuberculosis (NRL) in Baghdad, so the proportion of contacts was high, this is similar to (51), although several guidelines recommend LTBI screening of close contacts of infectious TB only. Most studies show that some high-risk factors (HIV, organ transplantation, silicosis, treatment with tumor necrosis factor-α (TNF-α) blockers, hemodialysis, and close contact with M.tb excreting patients) accelerate the reactivation of TB infection significantly (52,53). Therefore, such patients should be regularly tested for an LTBI (52).

Table (4): Prevalence and population attributable fraction (PAF) for the Latent TB associated risk factors with the QFT-Plus positive results.

Risk factors	Positive Prevalence Ratio for QFT-Plus 143 (23.8%)
Cigarette smoking	53 (37.0%)
Alcohol consumption	47 (32.9%)
Closed contact with a latent TB patient	32 (22.4%)
immunosuppressive therapy	11 (7.7%)
Chi-Square (χ^2)	29.391 **
P-value	0.0001
**** (P≤0.01).**	

Conclusions

The overall rate of LTBI was intermediate 23.8% (143\601). Individuals were the rage among (41– 60) years was smoking, alcoholics or used immunosuppressive therapy they are most susceptible to latent TB.

Recommendations

Screening of LTBI should be routine among people in contact with people with tuberculosis regardless of the site of the disease and age of patient. As it must be screening for latent tuberculosis the patients infected (HIV, organ transplantation, silicosis, treatment with tumor necrosis). An IGRA can overcome the limitation of a BCG vaccinated individual, especially in early life. Further prospective studies with larger sample sizes of close contacts with control group are warranted to better understand the prevalence and associated risk factors.

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