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The Prevalence and characteristic of latent TB in patients on immunosuppressant agents and biological treatment

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Abstract

LTTB is a common condition occurring in one fourth of those who were exposed to mycobacterial bacilli with Medically induced immunosuppression stands as a significant risk factor for having LTTB. Aim of the study: To assess the prevalence and characteristics of LTTB in patients on immunosuppressive agents and biological treatment. A cross-sectional research of 150 patients on immunosuppressants and biological therapy for diverse diseases at Baghdad teaching hospital outpatient rheumatology, dermatology, and TB clinics between 2023 and 2024 was done. All patients were examined with a detailed clinical history, physical exam, and chest x-ray or CT scan. IGRA testing was done per manufacturer instructions and evaluated as positive, negative, or indeterminate. The study involved 149 patients with autoimmune diseases, using immunosuppressants like methotrexate and azathioprine. Significant differences in sex distribution, smoking status, infliximab usage, and disease duration were observed between IGRA-positive and IGRA-negative patients. While univariable analysis showed several factors influencing IGRA test positivity, only disease duration was significant in multivariable analysis. The prevalence of latent tuberculosis in the cohort was 34.9%. In conclusion, High prevalence of latent Tuberculosis (34.9%) was found in patients who were treated with immunosuppressive agents and biological therapies, of them Smoker, male, and infliximab-treated patients were significantly susceptible to LTTB.

Keywords: Latent tuberculosis, Biological therapy, Immunosuppression, Infliximab

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Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (M. tuberculosis), remains a significant global health challenge, with an estimated 10.4 million cases and 1.8 million deaths in 2015. TB infection exists along a spectrum, ranging from latent tuberculosis infection (LTBI), an asymptomatic state that is not transmissible, to active TB disease, which is symptomatic and can affect multiple organs, particularly the lungs. This understanding of TB as a spectrum rather than a binary condition has evolved in recent years, recognizing that only about 5–10% of infected individuals will develop active TB within the first few years after exposure, with the remainder controlling the infection through

their immune response or progressing to LTBI, where the bacterium persists without causing symptoms [1, 2]. The prevalence of LTBI is significant, with roughly one fourth of the global population estimated to be infected, serving as a potential reservoir for active TB [3]. This has underscored the need for effective diagnostic tools not only to identify LTBI but also to gauge the risk of progression to active TB and to monitor treatment responses [4]. Early identification of individuals at risk, especially within the first two years of exposure to active TB, is crucial for preventing disease spread and for better understanding the immune dynamics of TB infection [5]. Over the past decade, the paradigm of LTBI has shifted from viewing it as a stable balance between host immune response and bacterial metabolism, to understanding it as a dynamic interaction where progression to active disease is influenced by various factors including HIV infection, cancer, immunosuppressive therapy, and diabetes—the latter being increasingly relevant in regions where both TB and diabetes are prevalent [6,7]. Innovations in whole-blood transcriptomic profiling have further refined our understanding by identifying immune response patterns that differentiate between LTBI and active TB [8,9]. Diagnosing LTBI involves indirect methods such as the Tuberculin Skin Test (TST) and Interferon-γ Release Assays (IGRA), which detect cellular immune responses to mycobacterial antigens. The TST, a century-old method, involves intradermal injection of purified protein derivative (PPD), with a positive reaction indicating exposure to M. tuberculosis. However, the test's accuracy can be compromised by various factors including immune suppression and prior BCG vaccination, leading to potential false results [10,11]. IGRAs, which measure IFN-γ release by T-cells in response to specific M. tuberculosis antigens, offer better specificity, particularly in BCG-vaccinated populations, though their sensitivity is comparable to TST even in immunocompromised hosts [12,13]. Recent research has also explored other diagnostic avenues, such as identifying specific mycobacterial antigens and the potential role of antibodies in LTBI diagnosis. However, antibody-based tests have not been recommended due to their inadequate sensitivity and specificity [14,15]. The choice between TST and IGRA depends on various factors, including the likelihood of infection, the risk of progression, and the availability of resources [16,17]. The management of LTBI is informed by a thorough evaluation of infection likelihood, progression risks, and the benefits of therapy. The traditional approach of treating LTBI has been with isoniazid; however, rifamycin-based regimens are now often preferred due to better efficacy and shorter treatment durations [18]. Treatment decisions must carefully exclude active TB to avoid drug resistance [19]. Monitoring for adverse effects, especially hepatotoxicity, is crucial, particularly in older patients (20).

Aim of the study: to assess the prevalence and characteristics of LTTB in patients on immunosuppressive agents and biological treatment.

Method

Between 2023 and 2024, a cross-sectional study was conducted at Baghdad teaching hospital / medical city complex involving 149 patients who attended outpatient rheumatology, dermatology, and tuberculosis clinics. The study targeted patients between 5 and 80 years' old who had been on immunosuppressants or biological therapies for at least one year for various diagnoses. Exclusion

criteria included patients outside the age range, those with severe comorbidities such as heart, renal, or hepatic failure, uncontrolled diabetes, unwillingness to participate, undergoing or having indeterminate results on LTTB testing, or showing signs of active TB. The study was approved by the Iraqi Board of Medical Specialization in Respiratory Diseases, and all patients provided verbal consent. Participants underwent a comprehensive evaluation that included a full clinical history, a complete physical examination, and imaging via chest X-ray or CT scan. Demographic and clinical data such as the type and duration of immunosuppressant or biological therapy, the diagnosis and duration of the disease for which therapy was prescribed, and any associated comorbidities were recorded.

The Quantiferon TB-Gold Plus assay (QFT-Plus) was used to diagnose latent tuberculosis infection (LTBI). The IGRA test involved several steps:

1. Explanation and Consent: Patients were briefed on the procedures and provided their consent.
2. Blood Collection and Handling: Blood was drawn using aseptic techniques into a lithium heparin tube, transferred to four QFT-Plus blood collection tubes labeled nil, mitogen, TB1, and TB2. Tubes were shaken to mix the contents thoroughly and then incubated at 37°C for 16–24 hours.
3. Centrifugation: Post-incubation, tubes were centrifuged at 2000–3000 RCF to separate the supernatant.
4. ELISA Testing: The supernatant was then subjected to an enzyme-linked immunosorbent assay (ELISA) to measure interferon-gamma concentrations using an optical density plate reader.

Result Interpretation:

Data distribution was checked for normality using the Shapiro–Wilk test, and statistical analyses were performed using SPSS and Microsoft Excel 2010. Quantitative variables were compared using the Mann-Whitney U test, while qualitative data were analyzed using chi-square or Fisher's exact tests as appropriate. Logistic regression analysis was used to explore the correlation of risk factors with LTBI, with multivariable analysis focusing on factors with a p-value less than 0.1 in univariable models.

Results

The sample consisted of 73 (49%) males and 76 (51%) females with mean age and BMI of 38.49 years and 25.16 kg/m^2 respectively. 49 (32.9%) patients were smoker and 42 (28.2%) patients reported a history of comorbid condition with hypertension being the most commonly recorded Disease (62%). 70 (47%) patients suffered from psoriasis while 47 (31.54%) had rheumatoid arthritis and spondyloarthritis. Multiple sclerosis, Inflammatory bowel disease, and Behçet's disease were found in 8.72%, 8.04%, and 4.7% of patients respectively. Methotrexate and azathioprine were the most commonly (29.53%)and the second most commonly (24.83%) used immunsuppressive agents respectively. Infliximab, prednisolone, etanercept, and adalimumab

were used by 29(19.46%), 27(18.13%), 10(6.71%), and 2(1.34%) patients respectively. Mean time of treatment with immunosuppressants and biological agents was 1.81 years. The sample is generally illustrated in figure 1, figure 2, and table 1.

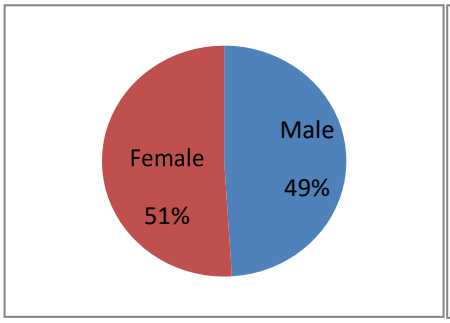

Figure 1 (male to female ratio)

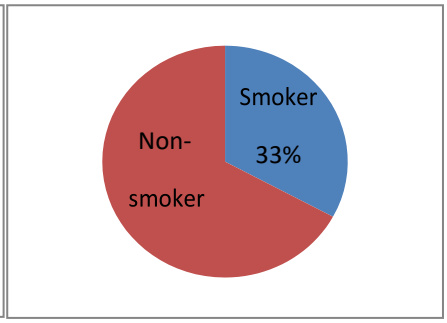

Figure 2 (smoker to non-smoker ratio)

Table 1.

(demographic and clinical parameters of enrolled patients)

Variable	n=149
Mean age(year)	38.49
Sex: n(%)	
Male	73(49%)
Female	76(51%)
Mean BMI (kg/m^2)	25.16
Diagnoses for which Immunosuppressants or biological therapies were being used : n(%)	
Psoriasis	70(47.%)
Rheumatoid arthritis & Spondyloarthritis	47(31.54%)
Multiple sclerosis	13(8.72%)
Inflammatory bowel disease	12(8.04%)
Behçet's disease	7(4.7%)
Mean duration since first diagnosed(year)	4.43
Immunosuppressants or biological therapies: n(%)	
Adalimumab	2(1.34%)
Etanercept	10(6.71%)
Azathioprine	37(24.83%)
Infliximab	29(19.46%)
Methotrixate	44(29.53%)
Prednisolone	27(18.13%)
Mean duration of the treatment with Immunosuppressants or biological therapies(year)	1.81
Smoker status: n(%)	
Yes	49(32.9%)
No	100(67.1%)
Co morbid diseases: n(%)	
No history of comorbid coditions	107(71.8%)
With history of comorbid coditions	42(28.2%)
Diabete mellitus	21(50%)
HTN	26(62%)
HF & IHD	11(26%)

BMI; body mass index, HTN; hypertension, HF; heart failure, IHD; ischemic heart diease, p-value considered significant at less than 0.05

Comparison of IGRA positive and negative patients: Sex, mean duration of auto immune diseases, infliximab using patients and smoker status were significantly different between IGRA-postive and IGRA negative patients (33 males and 19 female's vs 40 males and 57 females; *p*-value 0.009, 6.29 years vs 3.44 years for mean duration of diseases; *p*-value 0.001, 15 vs 14 patients who were using infliximab; *p*-value 0.03, and 23 vs 26 patients who were smokers; *p*-value 0.03 (table 2). Other variables were not markedly different between the two groups (table 2).

(Table 2: Comparison of IGRA positive and negative patients)

Variable	IGRA-positive n= 52	IGRA-negative n= 97	***p-value***
Mean age(year)	41.57	36.83	**0.12**
Sex: n(%) Male Female	 33 (59.6%) 19 (40.4%)	 40 (43.3%) 57 (56.7)	**0.009**
Mean BMI (kg/m^2)	25.5	24.98	**0.44**
Diagnoses for which Immunosuppressants or biological therapies were being used : n(%) Psoriasis	 24 (46.15%)	 46 (47.42%)	 **0.88**
Rheumatoid arthritis & Spondyloarthritis	14 (26.92)	33 (34.02%)	**0.37**
Inflammatory bowel disease	3 (5.77%)	9 (9.27%)	**0.54**
Multiple sclerosis	7(13.46%)	6(6.2%)	**0.13**
Behçet's disease	4(7.7%)	3(3.09%)	**0.2**
Mean duration since first diagnosed(year)	6.29	3.44	**0.001**
Immunosuppressants or biological therapies: n(%) Adalimumab	 1(1.92%)	 1(1.02%)	 **0.12**
Etanercept	4(7.7%)	6(6.2%)	**0.7**
Azathioprine	11(21.15%)	26(26.9%)	**0.71**
Infliximab	15(28.85%)	14(14.9%)	**0.03**
Methotrixate	11(21.15%)	33(33.02%)	**0.1**
Prednisolone	10(19.23%)	17(17.96%)	**0.48**
Mean duration of the treatment with Immunosuppressants or biological therapies(year)	1.84	1.79	**0.77**
Smoker status: n(%) Yes No	 23(44.23%) 29(55.76%)	 26(26.8%) 71(71.2%)	**0.03**
Co morbid diseases: n(%) No history of comorbid disease	 35(67.3%)	 72(72.2%)	**0.37**
history of comorbid disease	17(32.7%)	25(25.8%)	
Diabete mellitus	9(17.3%)	12(12.4%)	
Hypertension	11(21.1%)	15(15.5%)	
Heart failure & ischemic heart disease	3(5.8%)	8(8.2%)	

BMI; body mass index, p-value considered significant at less than 0.05.

Out of 149 52 patients were IGRA-positive as shown in figure 3-3. Prevalence of latent tuberculosis was 34.9% (95%confidence interval: 0.2725, 0.4255). Prevalence was found to be higher in the following: In those with BMI less than 25 kg/m2 (37.93% with 95% confidence interval: 0.2774,

0.4813). Those who are older than 50 years (46.51% with confidence interval: 0.316, 0.6142). Smokers (46.94% with 95% confidence interval: 0.3297, 0.6091). Those who use infliximab (37.93% with 95% Confidence interval: 0.2027, 0.5559). Male patients (45.21% with 95%confidence interval: 0.3379, 0.5662). Patients on prednisolone (40.74% with 95% Confidence interval: 0.2221, 0.5927). Patients with HTN (42.31% with 95%Confidence interval: 0.2332, 0.613). Univariable analysis of factors at positive IGRA test revealed significant effect from Sex, smoking status, treatment type, and the mean duration of autoimmune diseases but none of these factors except the mean duration of diseases showed significant relevance to the positivity of IGRA testing in multivariable analysis. (table 3 and 4).

Figure 3. (ratio of IGRA-positive to IGRA-negative)

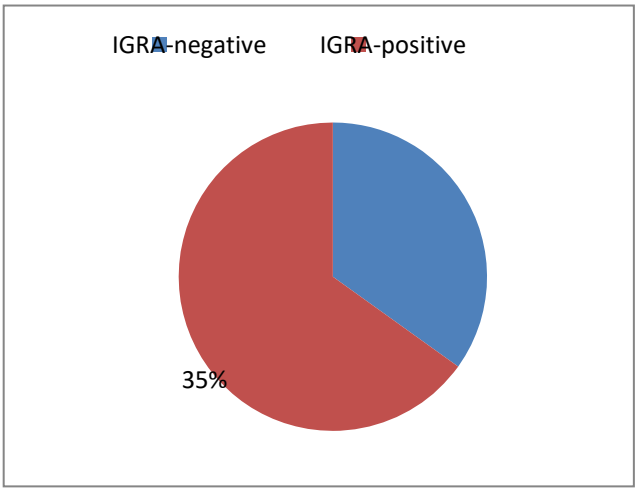

Table 3.

Univariable analysis of risk factors for latent tuberculosis

Variable	*p*-value	Odds Ratio	95% Confidence Interval
Age	0.0856	1.0191	(0.9974,1.0413)
BMI	0.2080	0.9633	(0.9088,1.0210)
Sex	0.0105	2.4750	(1.2361,4.9556)
Smoking	0.0324	2.1658	(1.0669,4.3966)
Diabetes mellitus	0.4111	1.4826	(0.5798,3.7910)
Hypertension	0.3847	1.4667	(0.6184,3.4786)
IHD & HF	0.2415	0.3911	(0.0813,1.8818)
Treatment type	0.0112	2.6081	(1.2433,5.4708)
Treatment duration	0.7240	1.0725	(0.7272,1.5819)
Rheumatoid arthritis & SP	0.4455	0.7484	(0.3554,1.5759)
Psoriasis	0.9779	0.9905	(0.5040,1.9466)
Multiple sclerosis	0.0863	2.8622	(0.8606,9.5195)
IBD	0.4572	0.5986	(0.1548,2.3151)
Behcet' disease	0.2209	2.6111	(0.5616,12.1408)
Disease duration	0.0002	1.3541	(1.1558,1.5865)

Table 4.

Multivariable analysis of risk factors for latent tuberculosis

Variable	*p*-value	Odds Ratio	95% Confidence Interval
Age	0.2460	0.9803	(0.9479,1.0138)
Sex	0.0624	2.5016	(0.9537,6.5616)
Smoking	0.6863	1.2271	(0.4546,3.3128)
Treatment type	0.1251	1.9899	(0.8260,4.7940)
Disease duration	0.0023	1.4305	(1.1367,1.8002)
MS	0.2888	2.2961	(0.4944,10.6648)

Discussion

The prevalence of latent tuberculosis infection (LTTB) identified in our study was 34.9%, which is markedly higher than both the local (24.07%) and global (24.8%) prevalence rates for LTBI, though lower than regional rates in the Middle East and North Africa, which stand at 41.78%. This discrepancy can be attributed to various factors including the high endemicity of TB in Iraq, the widespread use of BCG vaccination, and the nature of the immunocompromised population studied. Our use of the Interferon Gamma Release Assay (IGRA) was justified given its superior accuracy over the Tuberculin Skin Test (TST) in BCG-vaccinated populations and its reliability in immunocompromised individuals, as demonstrated by several studies [21,22]. Our study's demographic composition showed a nearly balanced distribution of males and females, unusual in the context of rheumatic and inflammatory diseases which are predominantly higher in females. This could be attributed to a small sample size and potential selection bias. The higher prevalence of LTTB in our study relative to other studies could be influenced by differences in clinical and demographic variables, study design, and methodology. Factors such as geographical location and the characteristics of the immunosuppressants and biological therapies used play significant roles in the variability of LTBI prevalence observed across studies [23,24]. In particular, age appeared to be a significant factor, with LTTB being more prevalent among individuals over 50 years of age. This association is consistent with other studies and likely stems from immunosenescence, which involves a decline in immune function due to age-related thymic dysfunction, chronic infections, and increased inflammatory cytokines [25,26]. Body Mass Index (BMI) was another notable factor, with a higher rate of LTTB observed in participants with a BMI less than 25 kg/m^2. This finding aligns with other studies indicating that lower BMI is a risk factor for developing LTTB due to impaired immune responses associated with malnutrition [27,28]. Conversely, higher BMI might offer some protective benefits against TB, potentially due to better nutritional status and the immunomodulatory effects of adipose tissue [29,30]. Smoking was identified as a significant risk factor for LTTB, likely due to its impact on immune function and ciliary dysfunction in the respiratory tract. This association has been supported by numerous studies indicating that smoking can impair the immune response necessary for controlling TB infection [31,32]. The role of diabetes in LTTB prevalence was inconclusive in our study, possibly due to the small number of diabetic patients included, which might have led to underreporting and statistically insignificant results. Nonetheless, the relationship between hypertension and LTTB was significant, which could be related to altered immune responses and chronic inflammation commonly seen in hypertensive patients [33]. Furthermore, our findings indicated a significantly higher prevalence of LTTB among patients receiving infliximab therapy. This could reflect the profound impact of TNF-α inhibitors on immune modulation, as they are known to increase susceptibility to infections like TB [34-36].

Conclusion

High prevalence of latent Tuberculosis (34.9%) was found in patients who were treated with immunosuppressive agents and biological therapies. Smoker, male, and infliximab-treated patients were significantly susceptible to LTTB.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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