# PREVALENCE OF LATENT TUBERCULOSIS INFECTION IN PATIENT WITH END-STAGE KIDNEY DISEASE UNDERGOING REGULAR HEMODIALYSIS

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#### Abstract

Background and aim: Tuberculosis, caused by Mycobacterium tuberculosis, causes a condition known as the latent tuberculosis infection (LTBI) that often defined as asymptomatic condition in which tuberculosis organisms present in the lung tissue without any clinical or radiological signs. LTBI can become active TB in hosts who experience immunosuppression caused by comorbid disease or medical therapy. Since immune system alteration occurs, patients with chronic kidney disease (CKD) on routine hemodialysis (HD) have a greater risk for latent tuberculosis infection. Because infection in CKD patients increases the mortality, patients with end-stage renal disease (ESRD) undergoing hemodialysis are at risk of developing active TB 6 to 25 times higher than the general population. The importance of screening LTBI using diagnostic tests such as the OuantiFeron TB-Gold (OFT-G) and proper treatment or regular follow up in hemodialysis patients can prevent development active TB from reactivation of LTBI. Methods: This study conducted as cross sectional study and done in Wasit province. The blood specimens collected from human individuals with chronic kidney disease on regular hem dialysis, the subjects were recruited from September–December 2022. Subjects aged > 18 years at least have undergoing HD in 3 months and twice a week HD were included in this study. Tuberculosis (TB), contact status with TB patients, and history of previous TB was excluded. LTBI was diagnosed using interferon-y release assays (IGRA). All data including age, gender, residence, smoking status, duration of HD, medical history of diabetes mellitus were obtained and recorded in case report form. Results: A total of 91 patients were involved LTBI based on positive result of IGRA was occurred in 28.6% subjects, while 61.5% and 9.9% subjects had negative and indeterminate IGRA, respectively. There is no significant correlation between age, gender, residence, and smoking status of patients with positivity of test. There is no significant correlation of duration of hemodialysis, diabetes as risk factors with positivity of test. Conclusion: the prevalence of LTBI in ESKD patients undergoing regular hemodialysis was high using IGRA in Wasit province.

Keywords: Mycobacterium tuberculosis, TB, Chronic kidney disease, QuantiFeron TB-Gold, Iraq

#### Introduction

Tuberculosis (TB) is an infectious disease usually caused by Mycobacterium tuberculosis (MTB) bacteria, generally affects the lungs, but it can also affect other parts of the body. Infected individuals are classified as either having latent tuberculosis infection (LTBI), an asymptomatic clinical state that is not transmissible, or active TB disease, characterized by the presence of clinical symptoms arising from infection that can occur in multiple organs (Suárez et al., 2019).

While Mycobacterium tuberculosis, the bacterium that causes TB, can infect many parts of the body, pulmonary TB is primarily the transmissible form, Understanding of M. tuberculosis infection as a clear binary condition that is either active or latent has recently shifted, or the more modern view treats infection as a spectrum of disease states (Esmail et al., 2022). The World Health Organization's (WHO) End TB Strategy has set the goal to reduce TB incidence globally by 90% and TB deaths by 95% by 2035, while active TB case detection has been the cornerstone of the public health response to TB, modeling suggests that in order to reach these ambitious targets, reducing the Latent tuberculosis infection (LTBI) reservoir through preventative therapy is essential, preventing the progression of LTBI to active TB disease is an important public health goal that can substantially reduce TB transmission, a key part of the End TB Strategy is targeted treatment of those infected and who are at risk for progression to active TB disease (MacNeil et al., 2020; Chakaya et al., 2022).

Tuberculosis is spread from one person to the next through the air when people who have active TB in their lungs cough, spit, speak, or sneeze, people with Latent TB do not spread the disease, active infection occurs more often in people with immunosuppressed condition and in those who smoke (Patterson and Wood 2019). Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids, diagnosis of Latent TB relies on the tuberculin skin test (TST) or blood tests (Lee et al., 2016). Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with the bacillus Calmette-Guérin (BCG) vaccine, those at high risk include household, workplace, and social contacts of people with active TB, treatment requires the use of multiple antibiotics over a long period of time (Harris 2019). TB infection begins when the mycobacteria reach the alveolar air sacs of the lungs, where they invade and replicate within endosomes of alveolar macrophages (Kumar et al., 2017; Bussi and Gutierrez, 2019). Macrophages identify the bacterium as foreign and attempt to eliminate it by phagocytosis, during this process, the bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome, and the phagosome then combines with a lysosome to create a phagolysosome. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium, however, M. tuberculosis has a thick, waxy mycolic acid capsule that protects it from these toxic substances, M. tuberculosis is able to reproduce inside the macrophage and will eventually kill the immune cell (Bussi and Gutierrez, 2019).

Tuberculosis is classified as one of the granulomatous inflammatory diseases, macrophages, epithelioid cells, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form granulomas, with lymphocytes surrounding the infected macrophages, when other macrophages attack the infected macrophage, they fuse together to form a giant multinucleated cell in the alveolar lumen, the granuloma may prevent dissemination of the mycobacteria and provide a local environment for interaction of cells of the immune system, however, more recent evidence suggests that the bacteria use the granulomas to avoid destruction by the host's immune system, macrophages and dendritic cells in the granulomas are unable to present antigen to lymphocytes; thus the immune response is suppressed, bacteria inside the granuloma can become dormant, resulting in latent infection, another feature of the granulomas is the development of abnormal cell death (necrosis)

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in the center of tubercles, to the naked eye, this has the texture of soft, white cheese and is termed caseous necrosis (Thakur and Muniyappa, 2022). Patients with some type of immunosuppression, such as those with Chronic Kidney Disease (CKD), are more susceptible to TB infection, in those patients, uremia reduces the expression of the co-stimulatory molecule in cells presenting the antigen, which alters the function of the polymorphonuclear cells and interferes in the phagocytic, migration, and chemotactic efficiency, reducing the capacity of cells to kill intracellular microorganisms (Corremans et al., 2022). In patients with CKD on hemodialysis, the risk of developing TB is 6.5 to 52.5 times higher than in the general population (Milburn 2021). These patients present great risk of developing active TB from a previous latent infection and greater risk of reactivating latent TB, or even its atypical presentation (Cahuayme-Zuniga and Brust, 2019). Aim of this study to identify the prevalence of latent TB (LTBI) in patient with chronic kidney disease on regular hemodialysis.

## Material and Method

# Ethical approval

Ethical approval was obtained from The Ethical Committee at scientific research by ethical approval of both ministry of health and ministry of higher education and scientific research in Iraq. Informed consent was obtained from all participants.

## Study design and subjects

This study was conducted as cross sectional study and done in Wasit province. The study consisting of 91 blood specimens collected from human individuals with chronic kidney disease on regular hemodialysis. All specimens were collected from dialysis center in al Zahraa Teaching Hospital, and collected between 20th of September 2022 and 20th of December 2022. The required information was taken from participants based on pre –prepared questions. The medical questionnaires including the following: serial number, name, age, gender, duration of dialysis per months, residence, smoking status, medical history of diabetes mellitus.

#### **Inclusion criteria**

All patient on regular hemodialysis for at least three months and twice a week HD, aged 18 year old and more are eligible for this study.

# **Exclusion criteria**

- 1. Patients with active TB on treatment
- 2. Patient with medical history of previous TB
- 3. Patients close contact with persons with active TB
- 4. Patients with respiratory manifestation at time of collecting blood samples.

In this study QuantiFERON®-TB Gold Plus (QFT®-Plus) was used for detection of interferon- $\gamma$  (IFN- $\gamma$ ) by enzyme-linked immunosorbent assay (ELISA) to identify in vitro responses to ESAT-6 and CFP-10 proteins peptide antigens that are associated with M. tuberculosis infection.

# Statistical analysis

Data were entered and analyzed using the software program Statistical Package for Social Sciences (SPSS) version 26. All numerical variables were represented by means (a measure of central tendency) and standard deviation (a measure of dispersion) while categorical variables were

presented by frequencies and percentages. The Chi-Square test and Fisher's Exact test (when more than 20% of cells have expected frequencies < 5) were used accordingly to assess the presence of an association between categorical variables. The independent samples t-test was used to assess the mean differences of numerical continuous variables. Considering a P-value is equal to or less than 0.05 a significant (Gharban and Yousif, 2021).

## **Results and Discussion**

The results of this research depended on the analysis of data collected from 91 patients who were on hemodialysis machines in the hemodialysis unit. The mean age and standard deviation of the patients were  $49.29\pm14.19$  years old with 33 patients (36.3%) aged 51-65 years followed by 31 patients (34.1%) from the age group 36-50 years old. The males represented slightly more than half of the sample (53.8%) and the majority (76.9%) mentioned living in urban places as shown in table 1.

Continuous variables	(Minimum-	Mean	Standard Deviation
	Maximum)		
Age (Years)	(22-80)	49.29	14.19
<b>Categorial variables</b>	Categories	Frequency	Percentage
Age (Years)	21 - 35	18	19.8
	36 - 50	31	34.1
	51 - 65	33	36.3
	66 - 80	9	9.9
Gender	Male	49	53.8
	Female	42	46.2
Residence place	Urban	70	76.9
	Rural	21	23.1

Table 1: Descriptive statistics of socio-demographic features of the participant patients on
hemodialysis (n=91)

The mean duration patient spent on hemodialysis was  $21.99\pm13.43$  months. The minimum duration was 5 months while the maximum duration was 60 months. Table 2 shows that 38(41.8%) of patients spent between 16-30 months on hemodialysis followed by 35 (38.5%) equal to or less than 15 months. The majority of patients 74(81.3%) never smoked and only 18.7% were smokers. The patients who diagnosed with diabetes mellitus were represented around one-third of the sample (36.3%).

patients

Variables		Frequency	Percentage
Smoking habit	Yes	17	18.7
	No	74	81.3
Presence of DiabetesMellitus	Yes	33	36.3
	No	58	63.7
Duration on hemodialysis	1-15	35	38.5

(months)	16-30	38	41.8
	31-45	9	9.9
	46-60	9	9.9

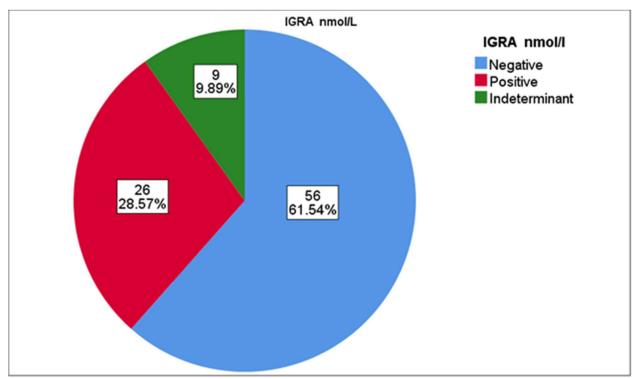


Figure 1: Frequency distribution of IGRA test results among participant patients (n=91)

This study investigated the prevalence of LTBI using the QuantiFERON®-TB Gold Plus (QFT®-Plus) assay as a diagnostic tool in patients with ESKD, focusing on those on regular hemodialysis. In figure 1, there were 56 (61.5%) patients appeared to have negative IGRA test results. Only 26 (28.6%) had a positive IGRA test result while the remaining 9 patients (9.9%) were with an indeterminant result.

The population of patients with CKD is increasing worldwide, and TB is a commonly associated infectious disease (Chou, Li, and Brown 2022; Ríos Burrows, Koyama, and Pavkov 2022). Investigation for LTBI is crucial to identify patients at risk of TB reactivation and offer them LTBI therapy or regular follow up.

The results of this study are consistent with other studies in different part of world where TB is endemic, as IGRA positive rate were reportedly ranges from 21% to 40% in patients with ESKD on regular hemodialysis, whereas 6% to 11% of patients have indeterminate IGRA, in the present study was approximately 28.6%, it is slightly higher than results of studies reported in south east Asia (Wardani and Wicaksi, 2021; Wu et al., 2021; Hayuk et al., 2022). Which reported that the prevalence of LTBI (20.92%) (19.3% conducted in Taiwan) (22.5% conducted in Thiland) receptively. In Middle East, higher results of studies reported (Al Wakeel et al., 2015; Seyhan et

al., 2016). Which reported that the prevalence of LTBI (45.3% conducted in Saudia Arabia) (41%% conducted in Turkey) respectively. Other studies show low prevalence of LTBI (Savaj et al., 2014) 23% conduced in Iran (Abdel-Nabi et al., 2014) 25% conducted in Egypt. This was probably because small population enrolled in these studies as this study. This study IGRA was used to assess prevalence of LTBI, which offers several advantages over TST in term of convenience and accuracy (Hayuk et al., 2022; Al- Ghafli and Al-Hajoj, 2018). Use of TST is limited because of possible cross positivity with BCG strain from child vaccination and an emerging prevalence of non-tuberculous mycobacterial disease. While in IGRA the immune reaction to M.tuberculosis-specific antigens can be differentiated from false positive results due to nonspecific activation and false-negative results due to immunosuppression. Thus, IGRA is a better screening test for LTBI than is the TST. Furthermore, QuantiFERON®-TB Gold although not 100% precise their sensitivity 98% and specificity 99.1% have been proven helpful in immunocompromised patients with T-cell dysfunction particularly those who received BCG vaccination (Hayuk et al., 2022; Wardani and Wicaksi, 2021).

In table 3, there was no significant association (P-value <0.05) between gender and the result of the IGRA test (positive and negative). Only 15 (34.9%) and 11(28.2%) of both males and females respectively had positive IGRA test results. Even though 13(43.3%) of patients aged 51-65 years old were with positive IGRA test, there was no significant association (P-value <0.05) between age groups and positivity or negativity of IGRA test among patients. Only 7 out of 26 (26.9%) patients from the age group 36-50 years old tested positive IGRA test followed by 2 out of 8 (25%) from the age group 66-80 years, which consistent with other studies (Bandiara et al., 2022; Wu et al., 2021). On the other hand some studies reported that positive IGRA significantly correlated with age and gender (Kim et al., 2013) in which male sex and younger age group were associated, Male sex and older age group were significantly associated (Wu et al., 2021), These might be explained by smoking habits .

Socio-demographic variables		IGRA test		P-value (Chi-	
		Positive	Negative	square Test)	
Gender	Male 15(34.9	15(34.9%)	28 (65.1%)	0.516	
	Female	11(28.2%)	28(71.8%)		
Age (years)	21 - 35	4(22.2%)	14(77.8%)	0.382	
	36 - 50	7(26.9%)	19(73.1%)		
	51 - 65	13(43.3%)	17(56.7%)	7	
	66 - 80	2(25.0%)	6(75.0%)		

 Table 3: Association and distribution of socio-demographic features among patients with

 IGRA test positive and negative results (n-82)

IGRA: Interferon-Gamma Release Assay.

In CKD patients, hemodialysis could alter immune response through pro-apoptotic effect due to direct contact to dialysis membrane which affects the nutritional status (Agarwal et al., 2015). In

this study the period on hemodialysis was not associated with being IGRA positive or negative (P-value <0.05). About 34.4% and 27.3% of patients belonging to (16-30) and (1-15) months duration were positively tested IGRA respectively.

This consistent with other studies (Hayuk et al., 2022; Bandiara et al., 2022; Hussein et al., 2017).but it inconsistent with other studies which reported significant association with duration of HD (Wu et al., 2021).

Although DM has known as risk factor for TB, patients with DM also have greater risk for TB reactivation (Remy 2016). Weakening of immune response increases the risk of TB infection development, from latent to active form. In fact, besides TB, DM is also an independent risk for lower respiratory tract infections and predisposing factor to have higher risk for severe complications (Koesoemadinata et al., 2017). Increased pro-inflammatory cytokines is correlated with increased blood glucose. Delayed adaptive immune response including T cell-produced IFN- $\gamma$ , mycobacteria lung-to-lymph dissemination, and leukocytes aggregation has observed in DM patient (Remy 2016).

In this study, diabetes was found to be not significantly related to the test results (P-value <0.05). More than one-third (37%) of patients with diabetes reported positive IGRA test while positive results were reported for 29.1% of those who didn't have diabetes mellitus, this consistent with other studies (Hayuk et al., 2022)in which no significant correlation with diabetes probably because small group of patient has been studied ,delay of patient to start dialysis.

These results are inconsistent with results of other studies in which diabetes regarding significant risk factor for LTBI (Bandiara et al., 2022; Lee et al., 2016). Even smoking has no significant association with the IGRA test (P-value <0.05). Both smokers and non-smokers were found to have around 31% of them with positive IGRA test as shown in table 4.

Variables		IGRA test		P-value (Chi-
		Positive	Negative	square Test)
Duration on	1-15	9(27.3%)	24(72.7%)	0.933*
hemodialysis	16-30	11(34.4%)	21(65.6%)	
(months)	31-45	3(33.3%)	6(66.7%)	
	46-60	3(37.5%)	5(62.5%)	
Diabetes	Yes	10(37.0%)	17(63.0%)	0.467
	No	16(29.1%)	39(70.9%)	
Smoking	Yes	5(31.3%)	11(68.2%)	0.965
	No	21(31.8%)	45(68.2%)	

Table 4: Association and distribution of disease history and smoking habit among patients with IGRA test positive and negative results (n-82)

\*Fisher's Exact Test; IGRA: Interferon-Gamma Release Assay. Conclusion

In this study the prevalence of LTBI in ESKD patient undergoing hemodialysis was high 28.6% using IGRA in Wasit province. There is no significant correlation between age, gender, residence,

and smoking status of patients with positivity of test. There is no significant correlation of duration of hemodialysis, diabetes as risk factors with positivity of test.

# Conclusion

The prevalence of LTBI in ESKD patients undergoing regular hemodialysis was high using IGRA in Wasit province, Iraq. Therefore, furthermore studies are of great importance to provide additional data for other future studies.

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