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Comparison of Sensitivity between Mantoux test, Quantiferon-TB Gold with Bronchoalveolar Lavage for GeneXpert in Renal Transplant for Latent Tuberculosis

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ABSTRACT

Objectives: To compare the sensitivity of the Mantoux test and QuantiFERON-TB Gold plus assay for diagnosing latent tuberculosis in patients of chronic kidney disease being considered for living renal transplant.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Nephrology, Armed Forces Institute of Urology, Rawalpindi and Pak Emirates Military Hospital, Rawalpindi Pakistan, from Sep 2023 to Jun 2024.
Methodology: The study included 306 patients (of both genders) of chronic kidney disease. Mantoux test and QuantiFERON-TB Gold plus assay were performed. GeneXpert analysis of Broncho alveolar lavage was performed for patients who tested positive either for Mantoux or Quantiferon-TB gold assay to confirm the active tuberculosis. Data was analyzed using SPSS.
Results: In the study, out of 306 patients, 6 were (1.96%) tested positive for the Mantoux test and of those, 2 were also positive for GeneXpert analysis of Bronchoalveolar lavage. On the other hand 9 patients (2.94%) tested positive for the QuantiFERON TB Gold plus assay test, with 3 of them were positive for GeneXpert analysis.
Conclusion: This study highlights the critical need for latent TB diagnosis in patients with chronic kidney disease. It suggests that the Mantoux test is less sensitive as compared to QuantiFERON-TB Gold test in our population so it is not recommended for screening of latent tuberculosis in patients of chronic kidney disease.

Keywords: Hemodialysis, Latent Tuberculosis, Renal Transplantation.

How to Cite This Article: *Mustafa G, Kashif N, Nazir R, Sabir S, Islam F, Altaf A. Comparison of Sensitivity between Mantoux test, Quantiferon-TB Gold with Bronchoalveolar Lavage for GeneXpert in Renal Transplant for Latent Tuberculosis. Pak Armed Forces Med J 2026; 76(3): 403-406.*
DOI: https://doi.org/10.51253/pafmj.v76i3.12764

INTRODUCTION

Tuberculosis (TB) is a significant public health concern, contributing high morbidity and mortality worldwide. Many cases remain unaccounted due to incorrect diagnosis. World Health Organization (WHO) reports 10.6 million new cases of TB worldwide in 2021. During 2021, majority of TB cases were reported in regions of South-East Asia (43%).[1] Pakistan is a 5th high-ranked TB-endemic country.[2]

A higher risk of TB is present in patients with chronic kidney disease (CKD).[3] It has been studied that immunocompromised patients with latent Tuberculosis infection (LTBI) are prone to suffer from active tuberculosis infection.[4] The most common techniques used to diagnose TB indirectly are; the tuberculin skin test (TST), and the interferon-gamma release assays (IGRAs). For LTBI detection, the WHO recommended the use of IGRAs or the Mantoux test. Tuberculin skin test has several well documented limitations, including the occurrence of false negatives in immunocompromised individuals.[5] On the other hand, reports showed that Mantoux test has low sensitivity in immunocompromised patients. The latest form of IGRAs is QuantiFERON™-TB gold plus (QTF) introduced in 2015. QFT-Plus Kit consists of 2 vials with TB antigen 1 and TB antigen 2.[6,7] Tuberculosis antigen 1 is used to stimulate an immune response from CD4+ T cells, while TB antigen 2 provokes a response from both CD4+ and CD8+ T cells.[8] T-cell responses make QFT-Plus more useful for diagnosing tuberculosis in immunocompromised renal cases.[9] Although, the Mantoux test is commonly used to identify tuberculosis among kidney patients, but QFT-Plus has higher sensitivity i.e., 72.7% as compared to that of Mantoux test i.e., 34.7%.[10] Therefore, this study aimed to compare the sensitivity of Mantoux test and QFT-Plus in CKD patients within our population with the goal of identifying a more cost-effective and beneficial diagnostic modality.

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Received: 10 Oct 2024; revision received: 05 Mar 2026; accepted: 06 May 2026

METHODOLOGY

This cross-sectional study was conducted at the Armed Forces Institute of Urology and Pak Emirates Military Hospital in Rawalpindi from September 2023 to June 2024. The study was initiated after the official approval of Institutional Review Board (IRB) Armed Forces Institute of Urology Rawalpindi (Uro-Adm-Trg-1/IRB/2023/005, dated;14/09/2023). The sample size came out 306 that was calculated on the basis of sensitivity (34.7%) and specificity (96.3%) of Mantoux test.[11]

Inclusion Criteria: This study included patients of CKD stage G3, G4 and G5 either on conservative management or undergoing hemodialysis being considered for living related transplant.

Exclusion Criteria: Patients with CKD stage G2 and below, patients on immunosuppressive medication and those with previous history of tuberculosis were not included in the study.

A total of 306 subjects (of both genders) were enrolled in the research, all participants were thoroughly briefed about the study, and consent were taken from every participant during enrollment. Participants were selected using the nonprobability consecutive sampling technique.

Mantoux testing (MT) and QuantiFERON-TB Gold plus (QTG) assay were performed for each patient. For Mantoux test, 0.1ml of purified protein derivative (PPD) was injected intradermal into the flexor surface of the forearm, and the reaction was measured in millimeters of the induration (palpable, raised, hardened area or swelling).[12]

Bronchoalveolar Lavage samples were collected after fiber optic flexible bronchoscopy done by certified pulmonologist after consent, of only those patients who tested positive for either Mantoux or Quantiferon TB Gold plus assay for detection of active TB. Essential measures were implemented to safeguard the privacy and invisibility of the data provided by the subjects. Participants had the option to exit the study at any point.

Sensitivity analysis of the Mantoux test was done among the study population using gold standard QuantiFERON-TB Gold plus Assay for detection tuberculosis infection. Sensitivity the proportion of individuals who have a disease and are correctly indicated by a diagnostic test.[13]

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Non-parametric quantitative variable (age) was presented as median with interquartile range, while categorical variables including gender, hypertension, diabetes mellitus, Mantoux test results, QuantiFERON-TB Gold Plus assay results, and GeneXpert findings were expressed as frequencies and percentages. A 2×2 contingency table was constructed to determine the sensitivity, of the Mantoux test. A *p*-value ≤0.05 was considered statistically significant.

RESULTS

This study examined the demographic and clinical features of participants in a specified population. A total of 306 participants with a median age of 45.00 years, (39.00–49.00) were enrolled in this study. The gender distribution showed, 251 participants (82.03%) were male, and 55 females (17.97%) in the study. The results reported 79.74% of participants had DM, while 65.03% had hypertension. Furthermore, screening for latent tuberculosis was done using Mantoux and QuantiFERON TB Gold plus assay. The results observed 6 patients (1.96%) tested positive for the Mantoux test, and 9 patients (2.94%) were positive for QuantiFERON TB Gold plus assay. The details of study population, including gender and clinical conditions, depicted in Table-I.

Table-I: Characteristics of the Study Population (n=306)

Variable(s)	Values
Age (years)	45.00 (39.00-49.00)
Gender	
Male	251(82.03%)
Female	55(17.97%)
Hypertension	199(65.03%)
Diabetes Mellitus	244(79.74%)

Sensitivity analysis of Mantoux test was done in comparison to QuantiFERON TB Gold plus assay. Out of 306 samples, 2 were true positive, 4 were false positive, 293 were true negative whereas 7 were false negative as depicted in Table-II.

Table-II: Analysis of Mantoux Test

		Status of TB According to QuantiFERON TB Gold plus assay	
		Positive	Negative
Mantoux Test	Positive	2	4
	Negative	7	293

Sensitivity of Mantoux Test = True Positive/(True Positive + False Negative)X 100 = 22.22%
Specificity of Mantoux Test = True Negative /(True Negative +False Positive) X 100 = 98.6%

Furthermore, GeneXpert analysis of Bronchoalveolar Lavage (BAL) results showed that among the 6 participants who tested positive for Mantoux test, 2 were BAL positive and 4 were BAL

negative. Conversely, among the 9 participants who tested positive for QuantiFERON TB Gold, 3 were BAL-positive and 6 were BAL-negative

DISCUSSION

In the present study, 306 patients with CKD undergoing evaluation for living renal transplantation were screened for latent TB using both the Mantoux test and QuantiFERON-TB Gold Plus assay. The Mantoux test was positive in 6(1.96%) patients, whereas QuantiFERON-TB Gold Plus assay was positive in 9(2.94%) patients. Furthermore, GeneXpert analysis of bronchoalveolar lavage (BAL) detected active TB in 2 patients from the Mantoux-positive group and in 3 patients from the QuantiFERON-positive group. These findings suggest that QuantiFERON-TB Gold Plus assay identified a greater number of potentially infected patients than the Mantoux test and may therefore provide superior diagnostic performance in this high-risk population.

Our findings are consistent with those reported by Ravi Shankar *et al.,* who evaluated tuberculin sensitivity among patients with chronic renal failure in a TB-endemic region. Their study demonstrated a high prevalence of tuberculin anergy and reduced responsiveness to the Mantoux test among patients with renal impairment. Similar observations in the present study support concerns regarding the limited diagnostic utility of the Mantoux test among patients with advanced CKD.[14]

Altamura et al. described the profound immune dysregulation associated with CKD and emphasized its impact on host defense mechanisms, thereby increasing susceptibility to infectious diseases, including tuberculosis. These immunological alterations may contribute to the reduced sensitivity of the Mantoux test observed in CKD populations.[15]

Chronic renal disease is associated with a multifaceted immune deficiency that significantly elevates the risk of tuberculosis (TB) infection.[16] Evidence suggests that immune dysfunction can manifest as early as stage 3 CKD (characterized by a glomerular filtration rate <60 ml/min).[17,18]

In current research project, we aimed to evaluate the sensitivity of the Mantoux test, considering the QuantiFERON-TB Gold Plus assay as a gold standard test for diagnosing the latent TB infection among CKD patients in local population as in our literature search, no local study was found on the subject topic. Analysis of clinical attributes of 306 participants, highlighted significant metabolic and cardiovascular risks within this population.

This study revealed a significant discrepancy between the Mantoux test and the QuantiFERON-TB Gold Plus assay in terms of sensitivity. The Mantoux test, with a sensitivity of 22.22%, was found to be far less sensitive compared to the QTF assay, that has been previously reported in a study conducted among the patients of CKD.[11] In contrary to our result, Oh *et al.,* 2021 reported that pooled sensitivity of the Mantoux test (70% to 77%) is comparable to of the QuantiFERON-TB Gold Plus assay test's sensitivity (78% to 80%).[17]

The reduced sensitivity of Mantoux test in CKD patients is attributed to T cell mediated immune response, which is impaired in individuals with CKD patients. Primaturia *et al.,* suggested that Mantoux test shows false negative results in immunocompromised individuals because of decreased formation of interferon gamma and tumor necrosis factor, which are responsible for immune response against Mycobacterium Tuberculosis antigen in Mantoux test.[18]

A previous study confirmed that IGRA typically demonstrates specificity rates >96% in low-risk populations, indicating them as a better option for diagnosis of latent TB infection, particularly in individuals who have received BCG vaccination earlier or are immunocompromised.[19] Previous studies have indicated that the sensitivity of the Mantoux test can deviate, depending on the population and their immune status. Similarly, QuantiFERON-TB Gold test results can also vary, depicting high rates of conversion and reversion.[18-19]

LIMITATION OF STUDY

The limitations of our study include a small sample size and a dual center design. A multi-center study would offer more comprehensive insights. Therefore, we recommend a larger multicenter study with an expanded sample size to evaluate the efficacy of the Mantoux and QuantiFERON-TB Gold in patients with chronic kidney disease.

CONCLUSION

The study concludes that the QuantiFERON-TB Gold Plus assay is better diagnostic tool for detecting latent tuberculosis in CKD patients within in our population.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

GM & NK: Data acquisition, data analysis, critical review, approval of the final version to be published.

RN & SS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FI & AA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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