"DETECTION OF LATENT TUBERCULOSIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON RENAL REPLACEMENT THERAPY USING INTERFERON GAMMA RELEASE ASSAY"

By:

DR .KRUTHI .P

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in partial fulfillment of the requirement for the degree of

DOCTOR OF MEDICINE (M.D.)

IN

GENERAL MEDICINE

Under The Guidance Of

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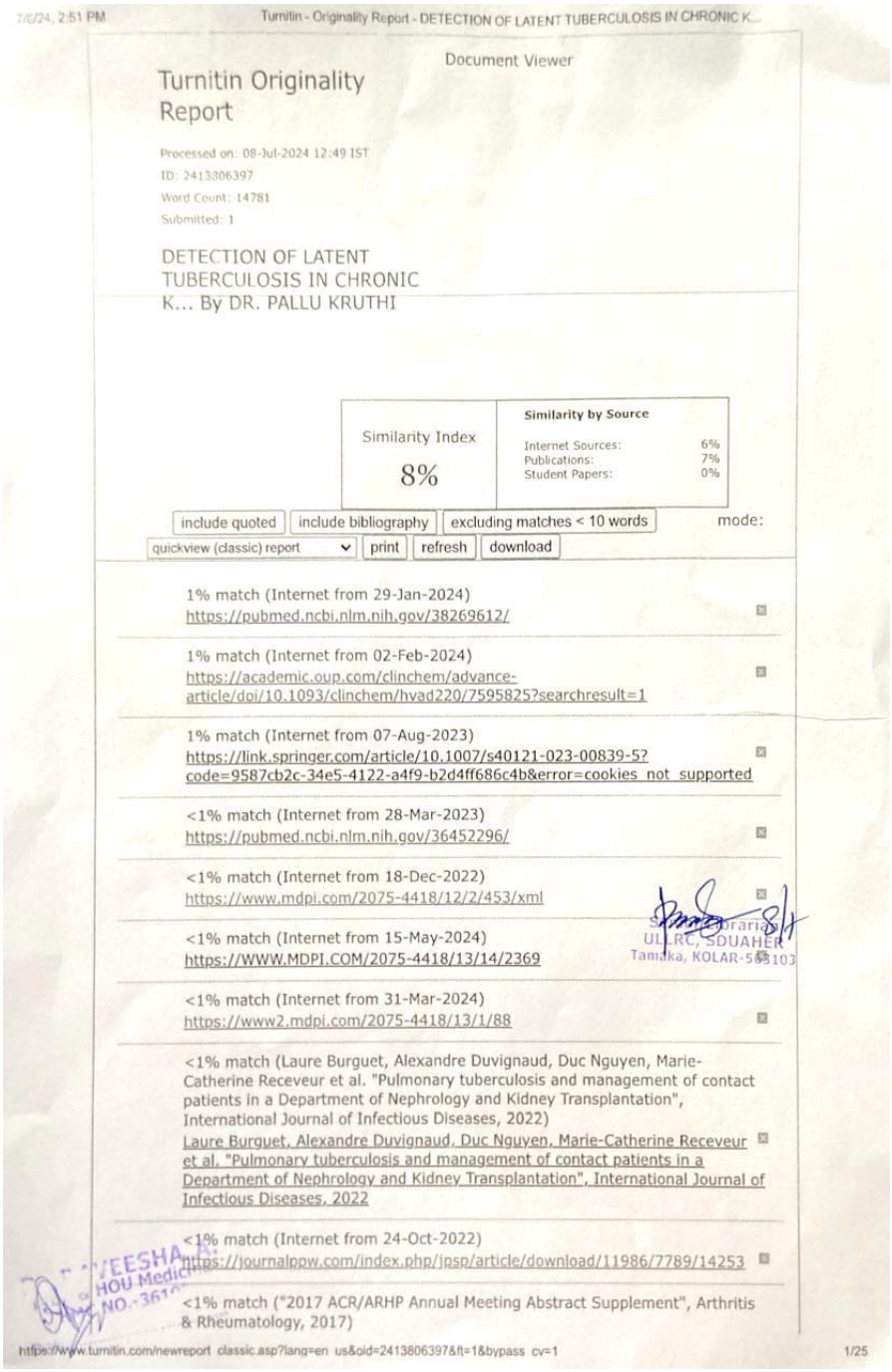

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DR P KRUTHI

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ABBREVIATIONS

Glossary	Abbreviations
LTBI	Latent tuberculosis infection
CKD	Chronic Kidney Disease
RRT	Renal replacement therapy
IGRA	Interferon gamma release assay
TB	Tuberculosis
HIV	Human immunodeficiency virus
TST	Tuberculin skin test
ESKD	End stage kidney disease
QFT -GIT	TB Gold In Tube test
PD	Peritonial dialysis
HD	Hemodialysis

ABSTRACT

Introduction: Latent tuberculosis is presence of immunological response to tubercular antigens without clinical features. Chronic kidney disease patients are more susceptible to developing active tuberculosis from latent tuberculosis infection and are at higher risk of mortality and morbidity.It has been shown that rate of active tuberculosis have been estimated to be 10 times higher than in general population, so our study aims at detecting latent tuberculosis in chronic kidney disease patients who are on maintenance hemodialysis using interferon gamma release assay.

Method of collection of data: At RL Jalappa Hospitals and Research Centre, Kolar, patients diagnosed with CKD who are on hemodialysis were randomly chosen. It is cross sectional observational study with a sample size of 60 subjects. After ruling out active tuberculosis , 5 ml of blood in lithium heparin tube is sent for enzyme linked immunosorbent assay for interferon gamma after harvesting the plasma, along with complete blood count , renal function test , serum electrolytes.

Results: In the study 27 (45%) subjects out of 60 turned out to be positive for interferon gamma release assay and 30 (55%) turned out to be negative. The mean age of patients who tested positive is 49.93 years , with a standard deviation of 14.7 years. Mean Hba1c for subjects turned positive is 7.73%. Alcohol consumption has a statistically significant association with positive interferon gamma release assay (p value – 0) . Smoking did not have effect on igra positivity .

Conclusions: This study highlights significant pevalenc of latent tuberculosis among patients with chronic kidney disease undergoing renal replacement therapy. Using interferon gamma

release assay we were able to detect latent tuberculosis in substantial amount of chronic kidney patients underscores the importance of routine screening .

Key words: IGRA, CHRONIC KIDNEY DISEASE, RENAL REPLACEMENT THERAPY, LATENT TUBERCULOSIS .

INTRODUCTION

CHAPTER 1

INTRODUCTION

1.1 LATENT TUBERCULOSIS

Latent Tuberculosis Infection (LTBI) is characterized by the presence of an immunological response to *Mycobacterium tuberculosis* antigens (Fig 1.1) in the absence of clinical symptoms of active tuberculosis disease. Individuals with LTBI have been infected by the tuberculosis bacteria, but their immune systems have contained the infection, preventing it from progressing to active disease. This condition is significant because it represents a reservoir for potential future cases of active tuberculosis. People with LTBI are asymptomatic and non-infectious, meaning they do not exhibit the common symptoms of tuberculosis, such as a persistent cough, fever, night sweats, or weight loss, and cannot transmit the bacteria to others. However, without intervention, there is a risk that LTBI can reactivate, especially in individuals with weakened immune systems, such as those with chronic kidney disease , HIV, diabetes, or those undergoing immunosuppressive treatments. The diagnosis of LTBI typically involves tests like the Tuberculin Skin Test (TST) or Interferon-Gamma Release Assays (IGRAs), which detect the immune system's response to tuberculosis antigens. While these tests can indicate an infection, they do not distinguish between latent and active disease. Treating LTBI is a crucial component of tuberculosis control strategies worldwide, as it helps to prevent the progression to active tuberculosis and thereby reduces the overall burden of the disease. Treatment regimens include - ISONIAZID 300MG daily or 900mg twice

weekly as monotherapy for 9 months or ISONIAZID 300MG plus RIFAMPIN 600MG daily for 3 months . Public health efforts focus on identifying and treating individuals with LTBI, particularly in high-risk populations, to curtail the spread of tuberculosis and move closer to the goal of tuberculosis eradication. The management of LTBI is thus integral to comprehensive tuberculosis control programs, emphasizing the importance of both medical intervention and public health policies in combating this enduring global health threat.

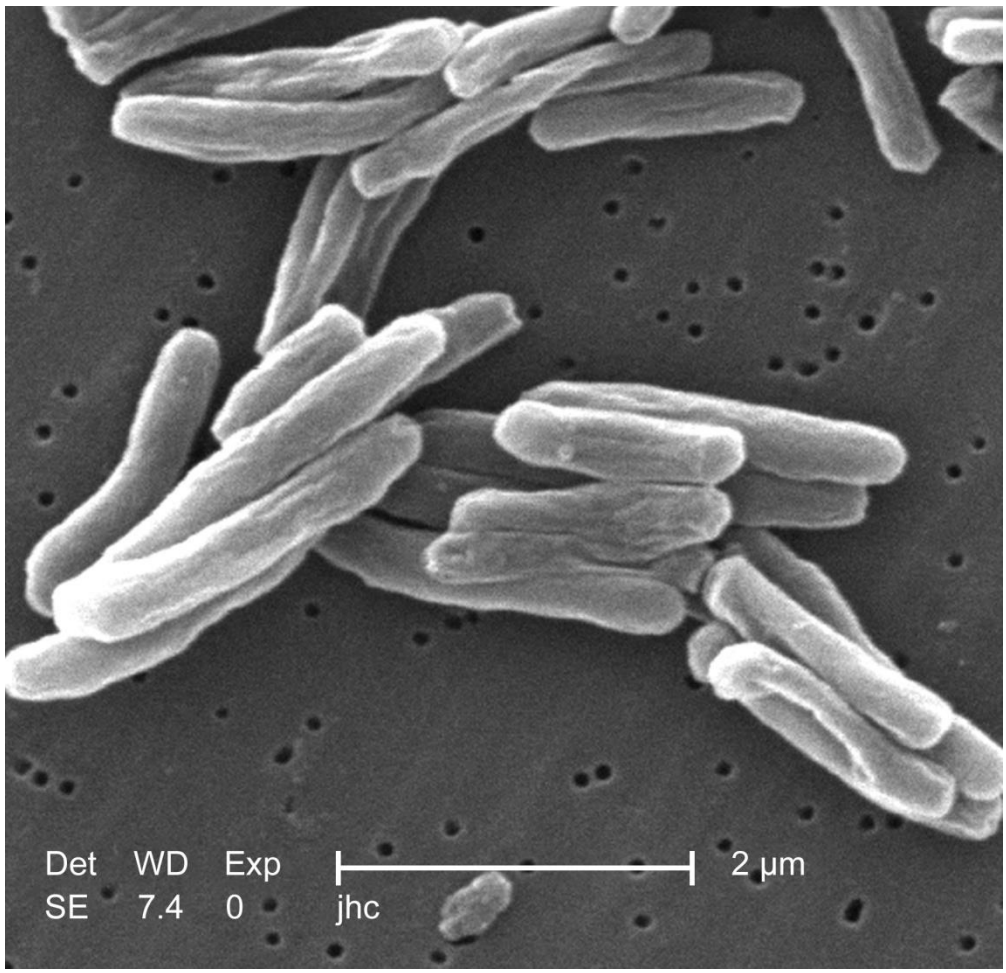


Fig 1.1: Mycobacterium tuberculosis [33][34]

1.2 Global prevalence of LTBI

LTBI is a widespread global health concern, with its prevalence estimated to be nearly 33% of the world's population [1]. This means that approximately one-third of all people worldwide are infected with Mycobacterium tuberculosis but do not show active symptoms of tuberculosis disease. The high prevalence of LTBI highlights the significant burden of tuberculosis and the challenge it poses to global public health efforts. Individuals with LTBI harbor the bacteria in a dormant state, and while they do not exhibit symptoms and are not contagious, they remain at risk for developing active tuberculosis, particularly if their immune systems become compromised. This transition from latent to active TB is a critical concern because it can lead to new outbreaks of the disease. The risk factors for reactivation of LTBI include chronic kidney disease , HIV infection, diabetes, smoking, malnutrition, and the use of immunosuppressive drugs, all of which weaken the immune system.

1.3 Regional Disparities in LTBI Prevalence

The global distribution of LTBI is uneven, with higher prevalence rates in regions with high incidences of active tuberculosis, such as sub-Saharan Africa, Southeast Asia, and parts of Eastern Europe. Socioeconomic factors, healthcare infrastructure, and public health policies significantly influence the management and control of LTBI in these regions. Diagnosis of LTBI is typically conducted using the TST or IGRAs, both of which detect immune responses to TB bacteria but do not differentiate between latent and active infection.

1.4 Management and Treatment Strategies

Effective management of LTBI involves targeted screening and treatment, especially among high-risk populations, to prevent the progression to active tuberculosis. Treatment usually includes a course of antibiotics like isoniazid or rifampin over several months to eradicate the dormant bacteria. Public health strategies aimed at reducing the prevalence of LTBI and preventing active TB include improving living conditions, enhancing nutrition, reducing overcrowding, and increasing access to healthcare services.

TABLE 1

DRUG	DOSE	DURATION	INTERVAL	SIDE EFFECTS
ISONIAZID	300MG	9 MONTHS	DAILY	HEPATOTOXICITY PERIPHERAL NEUROPATHY
RIFAMPIN	600MG	4 MONTHS	DAILY	HEPATOTOXICITY LEUCOPENIA
RIFAMPIN + ISONIAZID	600MG+300MG	3 MONTHS	DAILY	
RIFAPENTIN + ISONIAZID	900MG + 900MG	3 MONTHS	DAILY	

1.5 Global Initiatives and Partnerships

Global initiatives and partnerships, such as those led by the World Health Organization (WHO) and other international health organizations, are crucial in coordinating efforts to combat LTBI. These initiatives focus on increasing awareness, improving diagnostic tools, ensuring the availability of effective treatments, and

supporting countries with high burdens of tuberculosis. The goal is not only to treat those with LTBI but also to reduce the overall incidence of tuberculosis, ultimately moving towards the eradication of this ancient yet persistent disease. The high global prevalence of LTBI underscores the importance of continued vigilance, research, and investment in tuberculosis control programs to protect the health and well-being of populations worldwide.

1.6 The Situation in India

In India, despite being one of the countries with the highest burden of tuberculosis (TB), there are currently no comprehensive estimates regarding the prevalence of Latent Tuberculosis Infection (LTBI) in the general population. This lack of data presents a significant challenge for public health officials and policymakers aiming to control and eventually eradicate TB in the country. LTBI, where individuals are infected with Mycobacterium tuberculosis but do not exhibit active symptoms and are not infectious, is a critical area of focus because it serves as a reservoir for future active TB cases. Without accurate prevalence data, it is difficult to gauge the true scale of the problem and to implement effective screening and treatment strategies.

1.7 Factors Contributing to Data Gaps in India

The absence of LTBI prevalence estimates in India is due to several factors. There is a lack of widespread screening programs for LTBI, limited resources for comprehensive epidemiological studies, and a focus on diagnosing and treating active TB cases, which are more immediately pressing due to their contagious nature. Furthermore, the

diagnostic methods for LTBI, such as the Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRAs), are not routinely used in many parts of India, particularly in rural and underserved areas where healthcare infrastructure is less developed.

1.8 Addressing LTBI in India

The gap in data is particularly concerning given the high incidence of risk factors for TB in India, such as HIV infection, diabetes, malnutrition, and poor living conditions. These factors increase the likelihood of LTBI progressing to active TB, posing a significant public health threat. Addressing LTBI effectively requires targeted screening, especially in high-risk groups, and ensuring that those diagnosed with LTBI receive appropriate treatment to prevent reactivation. However, without reliable prevalence data, it is challenging to prioritize and allocate resources effectively for these interventions.

1.9 Recommendations for Improvement

To combat TB comprehensively, India needs to enhance its public health surveillance systems to include routine screening for LTBI, improve access to diagnostic tools, and integrate LTBI management into national TB control programs. This involves training healthcare workers, increasing public awareness about LTBI, and investing in research to better understand the epidemiology of LTBI in different regions of the country. International collaboration and support from global health organizations can

also play a pivotal role in addressing these challenges by providing technical assistance and funding.

The lack of estimates on LTBI prevalence in India highlights a critical gap in the country's fight against tuberculosis. By addressing this gap through enhanced screening, better data collection, and integrated public health strategies, India can improve its efforts to control both latent and active TB, ultimately reducing the overall burden of this debilitating disease.

1.10 Chronic Kidney Disease

Chronic Kidney Disease (CKD) has emerged as a significant global health concern, with its prevalence estimated to range between 8% and 16% worldwide [2]. This increase in CKD cases over recent years can be attributed to various factors, including the rising incidence of diabetes, hypertension, and obesity—major risk factors for CKD.

Additionally, aging populations in many countries contribute to the higher prevalence, as CKD risk increases with age. The socioeconomic burden of CKD is profound, impacting not only the healthcare system but also the quality of life of individuals. Early stages of CKD often go undiagnosed due to a lack of symptoms, leading to late-stage detection when the disease has already progressed significantly. This delay in diagnosis exacerbates the health impact and increases the likelihood of complications such as cardiovascular diseases. Furthermore, the management and treatment of CKD require substantial healthcare resources, from medications and regular monitoring to

dialysis and kidney transplants in advanced cases. Preventive measures, early detection, and effective management strategies are crucial to addressing this growing health issue. Public health initiatives focusing on lifestyle modifications, better management of underlying conditions like diabetes and hypertension, and increasing awareness about CKD can play a pivotal role in curbing its prevalence and mitigating its impacts. The rising trend in CKD cases underscores the need for a concerted global effort to tackle the underlying causes and to improve healthcare infrastructures for better management and support of those affected by this chronic condition.

1.11 EKSD

End Stage Kidney Disease (ESKD), the final stage of chronic kidney disease, represents a critical health challenge globally, with more than 2.6 million patients currently receiving Renal Replacement Therapy (RRT) such as dialysis or kidney transplants [3]. A striking disparity exists in the distribution of these patients, with over 80% residing in high-income countries. This uneven distribution highlights significant inequities in access to essential healthcare services. High-income countries benefit from advanced medical infrastructure, greater availability of healthcare professionals, and substantial financial resources, enabling them to provide comprehensive RRT to a larger proportion of their populations. In contrast, low- and middle-income countries often face challenges such as limited healthcare funding, insufficient medical facilities, and a lack of trained personnel, which restricts their ability to offer RRT to all patients in need. Consequently, many individuals in these regions either do not receive adequate treatment or have to endure long waiting

periods for life-saving therapies. This situation exacerbates health disparities and underscores the importance of global health initiatives aimed at improving access to RRT in less affluent regions. Addressing these inequities requires a multifaceted approach, including international cooperation to enhance healthcare infrastructure, training programs to increase the number of qualified healthcare providers, and financial assistance to make RRT more affordable and accessible. Additionally, public health policies focusing on the prevention and early detection of kidney disease could reduce the incidence of ESKD, thereby alleviating some of the demand for RRT. The global health community must prioritize efforts to bridge the gap between high- and low-income countries in the provision of renal care, ensuring that all patients with ESKD have the opportunity to receive the life-sustaining treatments they need.

1.12 Increased Susceptibility and Risks of Tuberculosis in CKD Patients

CKD patients are significantly more susceptible to developing active TB from LTBI compared to the general population, and they face increased risks of mortality and morbidity associated with this progression [4]. The immune-compromised state induced by CKD plays a crucial role in this heightened vulnerability. CKD impairs the immune system, reducing the body's ability to contain Mycobacterium tuberculosis in its latent form and making it more likely for the infection to reactivate. Furthermore, CKD patients often require immunosuppressive therapies, such as corticosteroids or immunosuppressive agents used in managing kidney transplants, which further weaken their immune defenses and increase the risk of TB reactivation.

The clinical management of TB in CKD patients is particularly challenging due to the complexity of their medical condition. CKD patients are already at a heightened risk for various infections and complications, and the addition of TB significantly exacerbates their health issues. The symptoms of TB can often be masked by or mistaken for complications of CKD, leading to delays in diagnosis and treatment. Moreover, the treatment of TB in CKD patients is complicated by the potential nephrotoxicity of TB medications, which can further impair kidney function and exacerbate CKD. This necessitates careful monitoring and potential adjustment of TB treatment regimens to avoid worsening kidney damage.

The increased morbidity and mortality rates in CKD patients with active TB are attributed to several factors. The weakened immune system and potential delays in diagnosis contribute to more severe manifestations of TB. Additionally, the interactions between TB medications and treatments for CKD can lead to adverse effects and complicate patient management. CKD patients with active TB are also more likely to experience severe complications, such as disseminated TB, which can affect multiple organs and lead to a higher risk of death.

Public health strategies aimed at preventing TB in CKD patients are crucial. This includes routine screening for LTBI in CKD patients, especially those undergoing dialysis or awaiting kidney transplants. Prophylactic treatment for LTBI in these high-risk groups can significantly reduce the risk of progression to active TB. Additionally,

healthcare providers need to be vigilant in monitoring CKD patients for signs of TB and promptly initiating appropriate diagnostic and therapeutic interventions.

Addressing the heightened risk of TB in CKD patients requires a multifaceted approach involving close collaboration between nephrologists, infectious disease specialists, and public health officials. By implementing comprehensive screening programs, optimizing treatment protocols, and enhancing patient education on the risks and symptoms of TB, the healthcare system can better manage and mitigate the impact of TB on CKD patients. The increased susceptibility of CKD patients to TB and the associated higher risks of morbidity and mortality underscore the need for targeted strategies to protect this vulnerable population and improve their overall health outcomes.

1.13 Need for study

- In the CKD population, rates of active TB have been estimated to be 10 times higher than in general population [5].
- This increased risk appears to be due to impaired cellular immunity that CKD people experience and is further compounded by co morbid conditions such as diabetes and other demographic factor
- Detection of latent TB early in the disease course helps in limiting patient morbidity, mortality and potential for TB spread.

- It may also enable the initiation of LTBI preventive therapy for patients at the highest risk of the development of active disease while avoiding unnecessary complications of treatment in low-risk individuals
- So, detection of latent tuberculosis and early treatment in CKD ON RRT patients reduces mortality and morbidity associated with it.

AIMS AND OBJECTIVES:

AIMS AND OBJECTIVES:

1.14 Objectives

The novel objectives of this study are:

1. To detect latent tuberculosis among chronic kidney disease patients on renal replacement therapy using interferon gamma release assay.

1.15 Summary

Introduction chapter sets the context by discussing the prevalence of CKD globally, the increasing number of patients on RRT, and the significance of latent tuberculosis infection in this population. It highlights the increased risk of active TB in CKD patients, emphasizing the importance of early detection of latent TB to reduce morbidity and mortality. Next chapter deals with review of existing literatures.

REVIEW OF LITERATURE:

CHAPTER 2

LITERATURE REVIEW

Chapter 2 of thesis deals with review of literature of the topic "Detection of latent tuberculosis in patients with Chronic Kidney Disease on renal replacement therapy using interferon gamma release assay". This chapter provides an overview of previous studies establishing the link between CKD and TB, along with the role of IGRAs in diagnosing TB infection.

2.1 Review of Literature

The link between active tuberculosis (TB) and chronic kidney disease (CKD) was first reported in a 1974 case series involving dialysis patients (Pradhan et al. [6]). Numerous publications have since confirmed this link, with hospital-based cohorts and regional registries consistently showing that dialysis is associated with an increased risk of TB (Dobler et al. [7]).

Magdi M Hussein et al [8] in their study proved there is an increased risk (6.9- to 52.5-fold) of tuberculosis (TB) in patients with chronic renal failure and on dialysis as compared to the general population.

Uditruzangi et al [9] in their comparative cohort study in England which concluded CKD is associated with an increased risk of TB diagnosis in a UK General Practice cohort and that this group of patients should be considered for testing and treating for latent TB.

Kamila Romanowski et al [10] in their retrospective study on effectiveness of latent TB screening on patients initiating dialysis and concluded that systematically

screening and treating people initiating dialysis is associated with significant decrease in active TB in these high risk population. The increased risk might be because CKD is associated with an acquired immunodeficiency state as a result of functional abnormalities of neutrophils, reduced T and B cell function and compromised monocyte and natural killer cell function.

25-Hydroxyvitamin D insufficiency, common in stages 3-5 CKD, may also have an important role through impaired monocyte function, reducing production of cathelicidin, a peptide capable of destroying Mycobacterium tuberculosis (Ganimusa et al. [11]). The risk of developing TB is compounded further by associated comorbid conditions, immunosuppressive drugs and socioeconomic factors.

2.2 Interferon-Gamma Release Assays

Interferon-Gamma Release Assays (IGRAs) are whole-blood tests that can aid in diagnosing Mycobacterium tuberculosis infection. They do not help differentiate latent tuberculosis infection (LT BI) from tuberculosis disease (Al-Efraij K et al. [5])

Two IGRA`S are available:

QuantiFERON® – TB Gold In-Tube test (QFT–GIT)

SPOT® TB test (T–Spot)

2.3 QuantiFERON gold

- It measures a person's immune reactivity to M. tuberculosis. White blood cells from most persons that have been infected with M. tuberculosis will release interferon-gamma (IFN-g) when mixed with antigens (Single mixture of

synthetic peptides representing ESAT-6, CFP-10 and TB7.7) (Hussein et al. [8])

- Prior BCG vaccination does not cause false positive IGRA test result.
- Agarwal et al. [12] in a comparative study of interferon gamma release assay & tuberculin skin tests for diagnosis of latent tuberculosis in patients on maintenance haemodialysis have concluded that more number of patients on haemodialysis were positive for QuantiFERON Gold In-Tube test as compared to TST.

In Hayuk et al. [13], all patients with CKD were prospectively recruited from September 2020 to November 2021 and retrospectively reviewed from December 2020 to November 2021. The prevalence of LTBI was determined using IGRA by CKD stage and dialysis type. Predictors of LTBI were assessed by logistic regression analysis. In total, 199 patients with CKD were enrolled (102 prospectively, 97 retrospectively). Of these, 173 patients were evaluable (mean age, 53 ± 16 years; 44% male). Ninety-five (55%) patients had ESKD and were maintained on renal replacement therapy. Overall, 39 (22.5%) patients had LTBI with a prevalence of 25.0%, 12.5%, 25.0%, 25.0%, and 24.2% among patients with CKD stage 1, 2, 3a, 3b, and ESKD, respectively (p=0.89). Among patients with ESKD, the prevalence of LTBI was higher in those on hemodialysis than in those on peritoneal dialysis (28.9% vs. 5.3%, p=0.03). In the multivariable analysis of patients with ESKD, drinking alcohol was significantly associated with LTBI (odds ratio, 8.51; 95% confidence interval, 1.24–58.38; p=0.029), and hemodialysis was marginally associated with LTBI (odds ratio, 8.14; 95% confidence interval, 0.95–69.91; p=0.056). In TB-

endemic settings, 20% of patients with CKD and 25% of patients with ESKD may have LTBI. Alcohol consumption and hemodialysis can help to identify high-risk patients with ESKD and potentially screen for LBTI.

Park et al. [14] clinically evaluate the effect of T-cell dysfunction in hemodialysis (HD) patients with latent tuberculosis (TB) infection (LTBI) who were false-negatives in the QuantiFERON-TB Gold In-Tube (QFT-GIT) test. Whole blood samples from a total of 20 active TB patients, 83 HD patients, and 52 healthy individuals were collected, and the QFT-GIT test was used for measuring *Mycobacterium tuberculosis* (MTB)-specific interferon gamma (IFN-γ) level. The positive rate of the IFN-γ release assays (IGRAs) in HD patients was lower than the negative rate. The mean value of MTB-specific IFN-γ level, which determines the positive rate of the IGRA test, was highest in active TB, followed by HD patients and healthy individuals. Among HD patients, phytohemagglutinin A (PHA)-stimulated IFN-γ levels of approximately 40% were 10.00 IU/mL or less. However, there was no low level of PHA-stimulated IFN-γ in the healthy individuals. This reveals that T-cell function in HD patients was reduced compared to healthy individuals, which leads to the possibility that QFT-GIT results in HD patients are false-negative. The clinical manifestations of TB in patients on HD are quite non-specific, making timely diagnosis difficult and delaying the initiation of curative treatment, delay being a major determinant of outcome.

Chinen et al. [15] performed Adjuvant diagnosis of tuberculosis in hemodialysis patients using fourth generation interferon γ releasing assay. Hemodialysis patients aged 20 years or older who underwent QFT-plus measurement in our hospital were

included, inclusion criteria being fever above 37°C, high inflammatory response, and infiltrative pulmonary shadows. Forty-six patients were enrolled. Of these, 15% were QFT positive, 4% were diagnosed with active TB, 76% were QFT negative, 8% had inconclusive results. Sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 87.5%, 28%, and 100%, respectively.

Bandiara et al. [16] determine the risk factors that associated with LTB among CKD on routine HD patients. It was a cross-sectional study conducted in Haemodialysis Unit, Hasan Sadikin General Hospital, Bandung. The subjects were recruited from March–May 2020. Subjects aged > 18 years at least have undergoing HD in 3 months and twice a week HD were included in this study. Patients with active tuberculosis (TB) suspected, malignancy, or immune compromised were excluded. LTB was diagnosed using interferon-γ release assays (IGRA). All data including age, sex, CKD etiologies, smoking status, HD adequacy that assessed using KT/V and urea reduction ratio (URR), and contact status with TB patients were obtained and recorded in case report form. A total of 120 subjects were involved. LTB based on IGRA was occurred in 39.2% subjects, while 56.7% and 4.1% subjects had negative and indeterminate IGRA, respectively. Adequacy of HD based on KT/V value was not significantly different between positive and negative IGRA subjects. Positive IGRA subjects had lower URR ($p = 0.042$). Smoking status had significant association with LTB (OR = 2.5[95%CI 1.2–5.4, $p = 0.017$). Furthermore, URR < 73% also had significant association with LTB (OR = 2.6[1.2–5.6, $p = 0.013$). Smoking status and HD adequacy based on URR < 73% are associated factors that contribute to LTB among CKD on HD patients.

Burguet et al. [17] described the investigation, follow-up, management, and outcomes in a cohort of chronic kidney disease (CKD) and kidney transplant recipients (KTR) exposed to a case of pulmonary tuberculosis (TB). Contacts were investigated following a concentric circles approach and followed-up according to their level of priority. In those with evidence of latent TB infection, treatment decision was based on the level of exposure, individual vulnerability, as well as the results of an interferon-gamma release assay. A total of 130 patients with CKD and 180 KTR were identified as contacts and followed-up over a 2-year period. Few vulnerable high-priority contacts received anti-TB treatment, including the two (100%) highly exposed patients in circle 1, 11/78 (14.1%) CKD patients and 4/142 (2.8%) KTR in circle 2, and 10/52 (19.2%) CKD patients and 2/36 (5.6%) KTR in circle 3; all had a positive interferon-gamma release assay result. No incident cases of TB disease occurred. These findings suggest that latent TB treatment, as recommended in European guidelines, might be reasonably avoided in vulnerable high-priority contacts of circle 2, with a negative interferon-gamma release assay and in countries with low prevalence of TB.

Yang et al. [18] summarized the diagnostic value and clinical recommendations of IGRAs for different immunocompromised populations, including peoplewith physiological factors (pregnant and puerperal women, children, and older people), as well as people with pathological factors (solid organ transplantation recipients, combination with human immunodeficiency virus infection, diabetes mellitus, end-stage renal disease, end-stage liver disease, and chronic immune-mediated inflammatory diseases). Though the performance of IGRAs is not perfect and often

requires a combination with other diagnostic strategies, it still has some value in the immunocompromised population. Hopefully, the newly developed IGRAs could better target this population.

Wang et al. [19] investigated the protective effect of BCG vaccination against LTBI in adult patients with end-stage renal disease (ESRD) and renal transplants. Patients aged ≥ 20 years with ESRD who received hemodialysis (HD), peritoneal dialysis (PD) or kidney transplant were enrolled from January 2012 to December 2019 at a medical center and a regional hemodialysis center. Patients with active tuberculosis (TB), previously treated TB, active immunosuppressant therapy or human immunodeficiency virus infection were excluded. LTBI status was determined by QuantiFERON-TB Gold In-tube (QFT-GIT). After the exclusion of indeterminate results of QFT-GIT, 517 participants were enrolled and 97 (18.8%) were identified as having LTBI. Participants with LTBI were older (55.1 ± 11.4 vs. 48.5 ± 14.6 years, $p < 0.001$) and had a significantly higher proportion receiving HD than those without LTBI (70.1% vs. 56.7%, $p = 0.001$). The percentage with BCG scars was higher in the non-LTBI group than in the LTBI group (94.8% vs. 81.4%, $p < 0.001$), whereas the neutrophil-to-lymphocyte ratio (NLR) (≥ 2.68) was significantly higher in the LTBI group (62.8% vs. 45.5%, $p = 0.02$). By multivariate logistic regression analysis, presence of BCG scar and high NLR were independent protective factors against LTBI [adjusted OR: 0.19 (0.063–0.58, $p = 0.001$) and 0.50 (0.28–0.89, $p = 0.02$)]. The prevalence of LTBI was as high as 18.8% in patients with end-stage kidney disease or kidney transplant. BCG vaccination and high NLR might have protective effects against LTBI in patients with renal failure or transplant.

Yamatani et al. [20] assessed the association between intrathoracic calcification and IGRA results. They retrospectively included consecutive patients who concurrently underwent chest X-ray, chest computed tomography (CT), and an IGRA. Patients with a current diagnosis of active TB or treatment history of active TB or latent tuberculosis infection (LTBI) were excluded. The association between calcification according to the chest X-ray or CT and IGRA results were analyzed using binomial logistic regression. The study included 574 patients, and 38 (7%) patients had a positive IGRA result. Patients with a positive result were significantly older and had a higher proportion of comorbidities, and history of tuberculosis exposure compared to those with a negative result. Calcification of the lung field and mediastinal lymph nodes according to chest CT was more frequently observed in patients with a positive IGRA result, whereas no significant difference was observed concerning the proportion of lung field calcification on chest X-ray between patients with positive and negative IGRA results. In multivariate analysis, calcification of mediastinal lymph nodes alone (adjusted odds ratio [OR] = 3.82, 95% confidence interval [CI] = 1.76–8.26) and the combination of lung field and mediastinal lymph node calcification (adjusted OR = 4.12, 95% CI = 1.51–11.76) on chest CT was independently associated with positive IGRA results. The finding of mediastinal lymph node calcification, with or without lung field calcification, on chest CT was associated with positive IGRA results independent of TB exposure history. Previous TB infection including eliminated TB infection and LTBI can be suspected when calcified lymph nodes in are observed the mediastinum on chest CT.

Binay et al. [21] determine the frequency of latent TB infection in HD patients and to compare the effectiveness of the tests used. The files of 56 HD patients followed between 1 January 2021 and 1 October 2022 were retrospectively analyzed. Demographic data, the presence of the Bacillus Calmette-Guerin (BCG) vaccine, whether or not the patients had previously received treatment for TB before, the status of encountering a patient with active TB of patients over 18 years of age, without active tuberculosis and who had a T-SPOT.TB test or a Tuberculin Skin Test (TST) were obtained from the patient files. The presence of previous TB in a posterior–anterior (PA) chest X-ray was obtained by evaluating PA chest X-rays taken routinely. Of the patients, 60.7% (n = 34) were male and their mean age was 60.18 ± 14.85 years. The mean duration of dialysis was 6.43 ± 6.03 years, and 76.8% (n = 43) had 2 BCG scars. The T-SPOT.TB test was positive in 32.1% (n = 18). Only 20 patients (35.7%) had a TST and all had negative results. While the mean age of those with positive T-SPOT.TB results was higher (p = 0.003), the time taken to enter HD was shorter (p = 0.029). T-SPOT.TB test positivity was higher in the group that had encountered active TB patients (p = 0.033). However, no significant difference was found between T-SPOT.TB results according to BCG vaccine, albumin, urea and lymphocyte levels. Although T-SPOT.TB test positivity was higher in patients with a previous TB finding in a PA chest X-ray, there was no statistically significant difference (p = 0.093). The applicability of the TST in the diagnosis of latent TB infection in HD patients is difficult and it is likely to give false-negative results. The T-SPOT.TB test is not affected by the BCG vaccine and immunosuppression.

Therefore, using the T-SPOT.TB test would be a more appropriate and practical approach in the diagnosis of latent TB in HD patients.

In Canney et al. [22], TB was validated in an external cohort linked to the Provincial TB registry at the BC Centre for Disease Control (BCCDC). Standardized incidence ratios were calculated using the age-matched general population. Risk factors for active TB were identified using Cox proportional hazards regression analysis. The sensitivity and specificity of the outcome definition of active TB were 87.6% and 99.5%, respectively. During a median follow-up of 6.2 years, 41 patients developed active TB with an incidence of 197 of 100,000 person-years, approximately 23 times as high as the general population and >6 times higher than the threshold of 30 per 100,000 used to define high TB incidence. A high incidence was observed in all glomerular diseases (range, 110-403 per 100,000), in both Canadian- and foreign-born patients (range, 124-424 per 100,000), and in patients exposed or not to immunosuppression (282 vs 147 per 100,000). Factors associated with higher TB risk included immigration from a high-incidence country (HR, 3.90 [95% CI, 1.75-8.68]), diminished eGFR (HR, 2.81 [95% CI, 1.18-6.69]), higher levels of proteinuria (HR, 1.15 [95% CI, 1.04-1.27]), lupus nephritis (HR, 2.79 [95% CI, 1.37-5.68]), and immunosuppression use (HR, 2.13 [95% CI, 1.13-4.03]).

Song et al. [23] assess the performance of an interferon-gamma release assay blood test (QuantiFERON-TB Gold Plus [QFT-Plus]) in various clinical contexts and identify conditions that affect its results. They conducted a retrospective analysis of 31 000 QFT-Plus samples collected from 26 000 subjects at a tertiary hospital in South Korea over a 4-year period and compared the rates of positivity and

indeterminate results across diverse clinical situations. We also analysed the contribution of the QuantiFERON TB2 tube to the test's sensitivity and determined optimal cutoff values for 3 hematologic parameters to distinguish false-negative results. These cutoff values were validated in a separate cohort of subjects with microbiologically confirmed subclinical TB. Rates of QFT-Plus positivity and indeterminate results were disparate across diagnoses. The TB2 tube increased QFT-Plus sensitivity by 4.1% (95% CI, 1.1%–7.0%) in patients with subclinical TB. Absolute lymphocyte count $\leq 1.19 \times 10^9$/L, absolute neutrophil count $\geq 5.88 \times 10^9$/L, and neutrophil-to-lymphocyte ratio ≥ 4.33 were effective criteria to discriminate false-negative QFT-Plus results. Application of the hematologic criteria, individually or combined with mitogen response <10 IU/mL, substantially improved performance in the main study cohort and the validation cohort. These findings highlight the influence of clinical context and patient hematologic profiles on QFT-Plus results. To minimise neglected latent TB infections due to false-negative QFT-Plus results, serial retesting is advisable in patients with severe lymphopenia or neutrophilia, particularly when the mitogen response is <10 IU/mL.

Sivanandam et al. [24] considered screening tests such as IGRA (interferon gamma release assay) and TST (tuberculin skin test), for tuberculosis in CKD patients with a risk of infection, thereby increasing the awareness of tuberculoma in CKD and ensuring early treatment which would eventually decrease the morbidity and mortality rates in such patients. CKD associated with tuberculoma represents one of the rarest conditions occurring worldwide. Among tuberculous patients, only 1% show central

nervous system involvement. We present a case of a 45-year-old male with CKD who presented with a seizure and was diagnosed to have tuberculoma.

Pakfetrat et al. [25] found that solid-organ transplant recipients with pretransplant tuberculin skin test (TST) indurations of ≥5 mm had higher tuberculosis rates. Analyzing 334 patients from 2009 to 2019, it revealed that those completing treatment for latent tuberculosis had significantly lower rates of conversion to active tuberculosis compared to those who did not (8.6% vs. 43.7%). Higher TST results (≥10 mm) were also associated with greater active tuberculosis development. The study recommends adjusting the TST positivity cutoff for transplant candidates in Iran to ≥10 mm to reduce morbidity and mortality.

Hamada et al. [26] conducted an individual participant data meta-analysis to directly compare the predictive performance for incident TB disease between TST and IGRA to inform policy. The meta-analysis of 13 studies (N = 32,034) found that the QuantiFERON Gold in-Tube (QFT-GIT) had a higher pooled hazard ratio (HR) for predicting active tuberculosis compared to the tuberculin skin test (TST), particularly in low-incidence countries. Both tests showed higher predictive performance in countries with TB incidence rates below 100 per 100,000 population.

In Ayers et al. [27] diagnostic study of 22 020 participants, 2 US-approved interferon-γ release assays (IGRAs) demonstrated significantly superior performance in predicting progression to TB disease compared with the tuberculin skin test. Estimated positive predictive value (PPV) ratios from generalized estimating equation models were used to compare test performance in predicting incident TB.

Incremental changes in PPV were estimated to determine whether predictive performance significantly improved with the addition of a second test. Case patients with prevalent TB were examined in sensitivity analysis. Findings suggest that IGRA performance may enhance decisions to treat TBI and prevent TB.

Xu et al. [28] compared QFTPlus, which has an additional TB antigen 2 (TB2) tube to induce cell-mediated ($CD8^+$ T cell) immune responses, with QFT-GIT. We conducted this study to assess the agreement of the QFT-GIT and QFT-Plus assays in immunocompromised patients in a clinical setting. A total of 278 immunocompromised patients and 175 immunocompetent patients from different departments were continuously enrolled from August 2020 to March 2021, and each patient underwent both tests. Correlations between QFT-GIT and QFT-Plus assays showed good agreement (κ value $= 0.859$). Patients receiving long-term immunosuppressant therapy had the lowest concordance between QFT-GIT and QFT-Plus assays; 9 out of 11 positive latent tuberculosis infection (LTBI) cases were diagnosed by the QFT-Plus assay, implying that QFT-Plus may detect more LTBI than QFT-GIT does in these patients. Indeterminate results were associated with lower lymphocyte, $CD4^+$ T cell, and $CD8^+$ T cell absolute counts, and with lower CD4/CD8 ratios. In conclusion, we found that the QFT-GIT and QFT-Plus assays had high agreement not only in immunocompetent patients but also in immunocompromised patients. QFT-Plus may detect more LTBI than QFT-GIT in patients receiving long-term immunosuppressant therapy. Thresholds were established for lymphocyte absolute counts of $>1.15 \times 10^9$ cells, and for $CD4^+$ T cell absolute counts of

>467.7 × 10^6 to 478.5 × 10^6 cells, which may lessen the incidence of indeterminate results.

Pai [29] compare the efficacy of tuberculin skin testing (TST) and interferon gamma release assay (IGRA) in detecting latent tuberculosis in patients with human immunodeficiency virus infection (HIV). The diagnosis of latent TB infection in HIV patients is critical to the disease's overall control. Individuals with latent tuberculosis infection (LTBI) who get anti-tubercular medication have a lower risk of developing active tuberculosis. Because LTBI testing is used to identify people who will acquire active TB and would benefit greatly from treatment, the accuracy of these tests can only be determined by measuring their ability to predict active TB development. A study that evaluates the sensitivity,specificity and predictive values of two techniques may help clinician to personalize the treatment in HIV patients with latent TB, hence better clinical outcome.

Prasad et al. [30] conducted a retrospective single-center study to analyze the safety of kidney transplantation and its outcomes in patients undergoing transplantation while on the continuation phase of ATT. Between 2013 and 2022, 30 patients underwent kidney transplantation while on ATT. Median age was 38 years and 70% were males. Majority of the patients (86.7%) had extrapulmonary tuberculosis, most common site of involvement being tubercular lymphadenitis. 14/30 patients had microbiological/histopathological diagnosis of TB and the rest were diagnosed by ancillary tests. Patients were treated with 4 drug ATT (isoniazid, rifampicin, pyrazinamide, ethambutol) before transplantation for aminimum of 2 months. Post-transplantation fluoroquinolone-based non-rifamycin ATT was used (median duration

11 months). All patients completed therapy. At 2 years, there was 100% patient survival and 96.7% graft survival. Median eGFR at 6, 12, and 24 months post-transplantation was 71.9, 64.7, and 67 mL/min/1.73m^2, respectively. The percentage of patients suffering a biopsy proven acute rejection at 6, 12, and 24 months was 3.3%, 6.7%, and 6.7%. Kidney transplantation can be done in patients with TB who have a satisfactory response to the intensive phase of the ATT. The decision for transplantation while on the continuation phase of ATT should be individualized. In our experience, there is excellent patient and graft survival in these patients with a low risk of failure of ATT or relapse of TB.

Kobayashi et al. [31] investigated the potential risk factors, including T-SPOT.TB test results and routine laboratory markers of inflammation, associated with death during hospitalization due to TB. A retrospective analysis was conducted on 244 hospitalized TB patients. Demographic data, clinical characteristics, T-SPOT.TB results, and laboratory parameters were collected. Univariate and multivariate analyses were performed to identify independent risk factors for in-hospital mortality. Among the patients, 206 survived and 38 died during hospitalization. Multivariate analysis revealed that age (HR: 1.08, 95% CI: 1.02–1.15, $p = 0.001$), a negative T-SPOT.TB test result (HR: 4.01, 95% CI: 1.78–9.01, $p < 0.001$), elevated C-reactive protein (CRP) levels (HR: 1.04, 95% CI: 1.01–1.08, $p = 0.007$), and increased neutrophil-to-lymphocyte ratio (NLR) (HR: 1.04, 95% CI: 1.00–1.07, $p = 0.025$) were independent risk factors for mortality. The study identified age, a negative T-SPOT.TB result, elevated CRP levels, and a high NLR as significant independent risk factors for death in hospitalized TB patients. Those findings underscore the

importance of these parameters in the risk stratification and management of hospitalized TB patients. Further research is warranted to elucidate the mechanisms behind these associations and to validate these results in different populations.

Table 2: Summary of Research gap

Ref Num	Author	Methodology	Key Findings	Research Gap
[5]	Al-Efraij K et al.	Review of Interferon-Gamma Release Assays (IGRAs) in diagnosing Mycobacterium tuberculosis infection	IGRAs do not help differentiate latent tuberculosis infection (LTBI) from tuberculosis disease	Further investigation needed to develop diagnostic tools that can distinguish between LTBI and active TB
[6]	Pradhan et al.	Case series involving dialysis patients reporting the link between active TB and chronic kidney disease (CKD)	Dialysis is associated with an increased risk of TB	Research on optimizing TB screening and treatment strategies for CKD patients
[7]	Dobler et al.	Analysis of hospital-based cohorts and regional registries confirming the increased risk of TB in dialysis patients	Dialysis is consistently associated with an increased risk of TB	Investigation needed on TB prevention strategies tailored to dialysis patients
[8]	Magdi M Hussein et al.	Study on the increased risk of TB in patients with chronic renal failure and on dialysis compared to the general population	Chronic renal failure and dialysis increase the risk of TB by 6.9- to 52.5-fold	Research on interventions to mitigate the increased risk of TB in patients with chronic renal failure and on dialysis
[9]	Uditruzangi et al.	Comparative cohort study in England examining the association between CKD and TB diagnosis	CKD is associated with an increased risk of TB diagnosis in a UK General Practice cohort	Further investigation needed on TB screening and treatment strategies for CKD patients
[10]	Kamila Romanowski et al.	Retrospective study evaluating the effectiveness of latent	Systematic screening and treating people initiating dialysis	Research on optimizing TB screening strategies and treatment outcomes in

		TB screening in patients initiating dialysis	decrease active TB incidence	high-risk populations
[11]	Ganimusa et al.	Study on the role of 25-Hydroxyvitamin D insufficiency in TB risk among CKD patients	Vitamin D insufficiency may contribute to increased TB risk in CKD patients	Investigation needed on the impact of vitamin D supplementation on TB risk in CKD patients
[12]	Agarwal et al.	Comparative study of IGRA and tuberculin skin tests for LTBI diagnosis in patients on maintenance haemodialysis	IGRA shows higher positivity compared to tuberculin skin tests in dialysis patients	Further research needed to optimize LTBI diagnosis and management in dialysis patients
[13]	Hayuk et al.	Prospective study on LTBI prevalence in CKD patients stratified by dialysis type in TB-endemic areas	Hemodialysis patients have a higher prevalence of LTBI compared to peritoneal dialysis patients	Investigation needed on interventions to reduce LTBI prevalence and progression in dialysis patients
[14]	Park et al.	Clinical evaluation of T-cell dysfunction in HD patients with false-negative QFT-GIT test	T-cell dysfunction may lead to false-negative results in QFT-GIT test among HD patients	Research on improving TB diagnostic accuracy in HD patients with compromised immunity
[15]	Chinen et al.	Adjuvant diagnosis of TB in hemodialysis patients using fourth-generation interferon gamma releasing assay	QFT-Plus demonstrates high sensitivity and negative predictive value in diagnosing TB among HD patients	Investigation needed on implementing QFT-Plus as a diagnostic tool for TB in HD patients
[16]	Bandiara et al.	Cross-sectional study on risk factors for LTBI among CKD patients on routine HD	Smoking and HD adequacy are associated with LTBI risk among CKD patients on routine HD	Further investigation needed on interventions to mitigate LTBI risk in CKD patients on HD
[17]	Burguet et al.	Investigation, follow-up, and management of CKD and KTR exposed to a case of pulmonary TB	Vulnerable high-priority contacts in CKD and KTR may not require latent TB treatment if they have a negative interferon-	Further research needed to validate the approach of avoiding LTBI treatment in high-priority contacts with negative IGRA results

			gamma release assay result	
[18]	Yang et al.	Summary of diagnostic value and clinical recommendations of IGRAs for immunocompromised populations	IGRAs have value in diagnosing TB in immunocompromised populations	Further investigation needed to improve the performance of IGRAs in immunocompromised populations
[19]	Wang et al.	Investigation of BCG vaccination's protective effect against LTBI in adult patients with ESRD and renal transplants	BCG vaccination and high neutrophil-to-lymphocyte ratio are protective against LTBI in patients with ESRD or renal transplants	Research on optimizing BCG vaccination strategies and evaluating their effectiveness in preventing LTBI in renal failure or transplant patients
[20]	Yamatani et al.	Assessment of the association between intrathoracic calcification and IGRA results	Mediastinal lymph node calcification on chest CT is independently associated with positive IGRA results in patients without active TB	Further investigation needed to explore the predictive value of intrathoracic calcification for LTBI diagnosis
[21]	Binay et al.	Determination of latent TB infection frequency and comparison of diagnostic test effectiveness in HD patients	T-SPOT.TB test is more practical and accurate than TST in diagnosing LTBI in HD patients	Research on improving diagnostic strategies and evaluating their effectiveness in detecting LTBI in HD patients
[22]	Canney et al.	Validation of TB cases in an external cohort linked to the Provincial TB registry. Standardized incidence ratios were calculated. Risk factors identified using Cox proportional hazards regression analysis.	High TB incidence observed in CKD patients, particularly those with glomerular diseases, and factors associated with higher TB risk identified	Further investigation needed to explore the effectiveness of TB screening strategies in CKD patients and evaluate preventive interventions
[23]	Song et al.	Retrospective analysis of QFT-Plus	Clinical context and patient hematologic	Further research needed to validate the identified

		samples to assess performance in diverse clinical situations. Contribution of TB2 tube to sensitivity evaluated. Optimal cutoff values for hematologic parameters determined.	profiles influence QFT-Plus results. Serial retesting advisable in patients with severe lymphopenia or neutrophilia	cutoff values and assess their applicability in different patient populations
[24]	Sivanandam et al.	Retrospective consideration of IGRA and TST for TB screening in CKD patients. Case presentation of a CKD patient with tuberculoma.	Increased awareness of tuberculoma in CKD patients and importance of early treatment highlighted	Further investigation needed to determine the optimal TB screening strategy in CKD patients and assess the prevalence of tuberculoma in this population
[25]	Pakfetrat et al.	Analysis of pretransplant TST indurations and TB rates in solid-organ transplant recipients. Comparison of TB rates between treated and untreated patients.	Adjusting TST cutoff may improve TB detection and reduce morbidity and mortality in transplant recipients	Further research needed to validate the proposed TST cutoff and assess its effectiveness in different transplant recipient populations
[26]	Hamada et al.	Individual participant data meta-analysis comparing predictive performance of TST and IGRA for incident TB.	QFT-GIT had higher predictive performance for active TB compared to TST, particularly in low-incidence countries	Further research needed to assess the performance of TB screening tests in different epidemiological settings and populations
[27]	Ayers et al.	Diagnostic study comparing the predictive performance of IGRAs and TST for incident TB.	IGRAs demonstrated superior performance compared to TST in predicting progression to TB disease	Further research needed to validate these findings and assess the cost-effectiveness of IGRA-based screening strategies
[28]	Xu et al.	Comparison of QFT-Plus and QFT-GIT assays in	QFT-Plus may detect more LTBI than QFT-GIT in	Further validation needed to confirm the diagnostic superiority of QFT-Plus

		immunocompromised patients. Evaluation of agreement and diagnostic performance.	immunocompromised patients. Thresholds established for hematologic parameters to reduce indeterminate results	and assess its clinical utility in diverse patient populations
[29]	Pai	Comparison of TST and IGRA in detecting LTBI in HIV patients. Evaluation of sensitivity, specificity, and predictive values.	Study findings may help personalize LTBI treatment in HIV patients and improve clinical outcomes	Further research needed to validate the findings in larger and more diverse HIV patient populations and assess long-term outcomes
[30]	Prasad et al.	Retrospective single-center study analyzing safety and outcomes of kidney transplantation in patients undergoing ATT continuation phase.	Kidney transplantation feasible in patients on ATT continuation phase with excellent patient and graft survival	Further research needed to determine optimal timing and safety of kidney transplantation in patients with TB undergoing ATT continuation phase
[31]	Kobayashi et al.	Retrospective analysis of TB patients to identify risk factors for in-hospital mortality.	Age, negative T-SPOT.TB result, elevated CRP levels, and high NLR identified as significant risk factors for mortality in hospitalized TB patients	Further investigation needed to elucidate underlying mechanisms and validate findings in different patient populations

2.4 Research gap

Despite significant advancements in understanding TB diagnostics and management in various patient populations, several research gaps remain. The effectiveness of TB screening strategies, particularly in immunocompromised patients and those with chronic conditions like CKD, needs further investigation to optimize early detection and intervention. There is also a need for validating the proposed cutoff values for

hematologic parameters in different populations to minimize false-negative results in TB tests like QFT-Plus. Additionally, the superiority of IGRA over TST in predicting active TB, especially in low-incidence countries, warrants further exploration to confirm these findings and assess cost-effectiveness. Lastly, the safety and timing of kidney transplantation in patients undergoing anti-tubercular therapy (ATT) continuation phase require more comprehensive studies to ensure patient and graft survival. Addressing these gaps could significantly improve TB management and outcomes in vulnerable patient groups.

2.5 Problem statement

The challenge of accurately diagnosing and managing latent and active tuberculosis (TB) in immunocompromised patients, such as those with chronic kidney disease (CKD) or undergoing kidney transplantation, remains unresolved. Current screening methods include interferon-gamma release assays (IGRAs) and tuberculin skin tests (TSTs), show variability in sensitivity and specificity, often leading to false negatives or unnecessary treatments. Furthermore, the optimal timing and safety of kidney transplantation in patients on anti-tubercular therapy (ATT) are not well-established. Addressing these issues is critical to improving patient outcomes and preventing TB progression in high-risk populations.

2.6 Summary

Chapter 2 of thesis dealt with review of literature of the topic “Detection of latent tuberculosis in patients with Chronic Kidney Disease on renal replacement therapy using interferon gamma release assay”. This chapter provided an overview of previous

studies establishing the link between CKD and TB, along with the role of IGRAs in diagnosing TB infection. Next chapter deals with materials and methods that outlines the study design (cross-sectional observational), study period, data collection methods, inclusion and exclusion criteria, and sample size estimation.

MATERIALS AND METHODS

CHAPTER-3

MATERIALS AND METHODS

The third chapter deals with materials and methods that outlines the study design (cross-sectional observational), study period, data collection methods, inclusion and exclusion criteria, and sample size estimation.

3.1 Source of data

The study is conducted in the department of Internal Medicine at RL JALAPPA HOSPITAL a teaching facility of SRI DEVRAJ URS MEDICAL COLLEGE , a constituent college of SRI DEVARAJ URS HIGHER ACADEMY AND RESEARCH – A tertiary care centre Tamaka , Kolar .

3.2 Study design

A Cross sectional observational study

3.3 Study period

September 2022 to December 2023

3.4 Method of collection of data

All consecutive patients presenting to RL Jallapa hospital with following inclusion criteria are included into our study

3.4.1 Inclusion Criteria:

1. End stage renal disease patients initiated on renal replacement therapy for at least 90 days.
2. With no clinical features suggestive of active tuberculosis.
3. Chest x ray showing no features suggestive of active tuberculosis

3.4.2 Exclusion Criteria:

Patients with any of the following are excluded from the study:

1. Patients with past history of tuberculosis.
2. Patients previously treated for latent tuberculosis.
3. Age <18 years

3.5 Sample size

- Sample size was estimated by using the proportion of Latent TB infection in subjects who underwent 3HP treatment was 19.3% from the study by Chien using Wu et al. [32] using the formula:

$$\textbf{Sample Size} = \frac{Z_{1-\alpha/2}^{2}\, P\,(1-P)}{d^{2}}$$

- Using the above values at 95% Confidence level a sample size of 54 subjects are included in the study. Considering 10% Non-response, a sample size of 54+6 ≈ 60 minimum subjects are included in the study

3.6 Methodology

This study has been meticulously planned and executed with a strong emphasis on ethical considerations and methodological rigor. Before commencing the research, ethical clearance was obtained from the institutional ethical committee, ensuring that the study adheres to established ethical guidelines and safeguards the rights and well-being of the participants. Additionally, informed consent was obtained from all study subjects, emphasizing their voluntary participation and understanding of the study's objectives, procedures, and potential risks.

The study recruited a minimum of 66 subjects who met the predefined inclusion and exclusion criteria, ensuring a representative sample for analysis. Detailed and thorough histories were recorded, and comprehensive examinations were conducted to gather comprehensive baseline data and assess relevant clinical parameters. This meticulous approach enhances the reliability and validity of the study findings by ensuring that potential confounding factors are adequately addressed and controlled for.

Furthermore, all study participants underwent a series of necessary investigations to assess various aspects of their health status. As part of this process, 3ml of blood was collected in lithium heparin tubes to facilitate further laboratory analysis. Specifically, enzyme-linked immunosorbent assays (ELISAs) for interferon-gamma (IFN-γ) were performed using harvested plasma, following the manufacturer's protocol (Qiagen). This involved meticulously following standardized procedures, including the addition of enzyme-conjugate solution, reconstitution of IFN-γ standards, loading of samples

into microplates, and subsequent incubation and washing steps. The optical density of each well was measured at 450 nm, providing quantitative data on IFN-γ levels.

Importantly, collaboration and consultation with the department of microbiology were undertaken to ensure appropriate storage and handling of blood samples during the incubation period, maintaining the integrity and stability of the specimens for accurate analysis. This interdisciplinary approach underscores the importance of collaboration and expertise from various fields to ensure the successful execution of the study objectives.

This study exemplifies a systematic and rigorous approach to scientific inquiry, incorporating ethical considerations, meticulous methodology, and interdisciplinary collaboration. By adhering to established protocols and standards, the study aims to generate robust and reliable data that contribute to our understanding of the underlying mechanisms and clinical implications of IFN-γ in the context of the research question at hand.

3.7 Statistical analysis

3.7.1 Data entry

Software Used: Data are entered into a Microsoft Excel spreadsheet.

Organization: Data are organized into appropriate columns and rows, categorizing patient demographics, test results, and other relevant information.

3.7.2 Data Analysis

Software Used: The data are analyzed using SPSS version 22 software.

3.7.2.1 Categorical Data

Representation: Categorical data (such as gender, presence or absence of a condition, etc.) are represented as frequencies (the number of occurrences) and proportions (the percentage of occurrences within the total sample).

Example: If analyzing the presence of a symptom, the number of patients exhibiting the symptom are counted and expressed as a percentage of the total number of patients.

Rate of Detection:

Purpose: Used as a test of significance to determine how often a particular condition or result is identified within the study population.

Example: The rate at which a specific complication is detected in patients with CKD are calculated and analyzed to assess its prevalence and significance.

3.7.2.3 Continuous Data

Representation: Continuous data (such as age, blood pressure levels, test results) are represented as rates, ratios, and proportions.

Example: Average age of participants, mean serum electrolyte levels, or the ratio of male to female participants.

This approach allows for a detailed and structured analysis of the data collected from the investigations and interventions. Using frequencies and proportions for categorical data helps in understanding the distribution and commonality of different variables, while the analysis of continuous data through rates, ratios, and proportions provides insights into the quantitative aspects of the study. The rate of detection as a test of significance helps highlight important findings and trends within the study population.

3.8 Requirement for Investigations or Interventions on Patients or Animals

The proposed study requires the following investigations or interventions to be conducted on patients or other humans:

3.8.1 Interferon Gamma Release Assay (IGRA):

Description: A blood test used to detect latent tuberculosis infection by measuring the immune response to Mycobacterium tuberculosis.

Purpose: Identifies patients at risk for tuberculosis, especially important in immune-compromised populations such as those with CKD.

3.8.2 Chest X-Ray as Part of Routine Investigations in CKD:

Description: An imaging test that provides visual information about the lungs, heart, and chest wall.

Purpose: Assesses potential pulmonary complications, infections, and other abnormalities in patients with CKD.

3.8.3 Complete Blood Count (CBC):

Description: A blood test measuring various components including red and white blood cells, haemoglobin, haematocrit, and plateletsusing an automated machine with fluorescent flow cytometry, cyanide-free SLS hemoglobin method, and DC sheath flow detection.

Purpose: Evaluates overall health, detects a wide range of disorders such as anemia, infection, and many other diseases in CKD patients.

3.8.4 Serum Electrolytes:

Description: A blood test measuring levels of sodium (Na^+) and potassium (K^+) using an automated machine and VITROS chemistry Na^+ and K^+ slides.

Purpose: Monitors electrolyte balance and detects imbalances which are common in CKD and can lead to serious health issues.

3.8.5 Renal Function Test:

Description: Blood tests measuring levels of blood urea nitrogen (BUN), urea, and creatinine using an automated machine and VITROS chemistry BUN/UREA/CREA slides.

Purpose: Assesses kidney function and monitors the progression of CKD.

3.8.6 Other Relevant Investigations:

Description: Any additional tests deemed necessary based on patient condition, including but not limited to liver function tests, lipid profiles, and specific biomarkers relevant to CKD.

Purpose: Provides a comprehensive assessment of the patient's health status and identifies any other underlying conditions that may affect CKD management.

All investigations follow ethical guidelines and obtain necessary approvals to ensure patient safety and data integrity.

3.9 Summary

In Methodology Chapter, the study was conducted at RL Jalappa Hospital, affiliated with Sri Devraj Urs Medical College, as a cross-sectional observational study from September 2022 to December 2023. A total of 60 subjects meeting inclusion criteria, including end-stage renal disease patients on renal replacement therapy for at least 90 days without active tuberculosis, were included. Detailed histories, examinations, and necessary investigations were conducted. Blood samples were collected for IFN-γ ELISAs, following ethical clearance and consent procedures.

Next chapter deals with Statistical Analysis. It describes the statistical methods planned for analyzing the data collected during the study. It lists the investigations and interventions to be conducted on patients, including IGRA, chest X-ray, CBC, serum electrolytes, renal function tests, and others.

RESULTS

CHAPTER-4

STATISTICAL ANALYSIS

4.1 Introduction

Chapter 4 describes the statistical methods planned for analyzing the data collected during the study. It lists the investigations and interventions to be conducted on patients, including IGRA, chest X-ray, CBC, serum electrolytes, renal function tests, and others. It confirms that ethical clearance will be obtained before initiating the study.

The data in this study are analyzed using SPSS version 22 software. Categorical data, such as gender or the presence or absence of a condition, are represented as frequencies and proportions, illustrating the number and percentage of occurrences within the total sample. For example, if analyzing the presence of a symptom, the number of patients exhibiting the symptom is counted and expressed as a percentage of the total number of patients. The rate of detection serves as a test of significance, determining how often a particular condition or result is identified within the study population. For instance, the rate at which a specific complication is detected in patients with chronic kidney disease (CKD) is calculated and analyzed to assess its prevalence and significance.

Continuous data, such as age, blood pressure levels, and test results, are represented as rates, ratios, and proportions. This includes the average age of participants, mean serum electrolyte levels, or the ratio of male to female participants. This approach allows for a detailed and structured analysis of the collected data, with frequencies and proportions helping to understand the distribution and commonality of different variables. The analysis of continuous data through rates, ratios, and proportions provides insights into the quantitative

aspects of the study. The rate of detection as a test of significance helps highlight important findings and trends within the study population.

The proposed study requires several investigations or interventions on patients. The Interferon Gamma Release Assay (IGRA) is a blood test used to detect latent tuberculosis infection by measuring the immune response to Mycobacterium tuberculosis, identifying patients at risk for tuberculosis, especially in immune-compromised populations such as those with CKD. Routine chest X-rays are conducted as part of the investigation to assess potential pulmonary complications, infections, and other abnormalities in CKD patients.

A Complete Blood Count (CBC) measures various blood components, including red and white blood cells, hemoglobin, hematocrit, and platelets, using an automated machine with fluorescent flow cytometry, cyanide-free SLS hemoglobin method, and DC sheath flow detection. This test evaluates overall health and detects a wide range of disorders such as anemia and infection in CKD patients.

Serum electrolytes are measured to monitor electrolyte balance and detect imbalances common in CKD, which can lead to serious health issues. This involves measuring levels of sodium (Na+) and potassium (K+) using an automated machine and VITROS chemistry Na+ and K+ slides. Renal function tests measure levels of blood urea nitrogen (BUN), urea, and creatinine using an automated machine and VITROS chemistry BUN/UREA/CREA slides, assessing kidney function and monitoring the progression of CKD. Other relevant investigations may include additional tests deemed necessary based on patient condition, such as liver function tests, lipid profiles, and specific biomarkers relevant to CKD. These investigations follow ethical guidelines and obtain necessary approvals to ensure patient safety and data integrity.

The study, conducted at RL Jalappa Hospital affiliated with Sri Devraj Urs Medical College, is a cross-sectional observational study from September 2022 to December 2023. A total of 66 subjects meeting inclusion criteria, including end-stage renal disease patients on renal replacement therapy for at least 90 days without active tuberculosis, were included. Detailed histories, examinations, and necessary investigations were conducted, with blood samples collected for IFN-γ ELISAs following ethical clearance and consent procedures. The statistical analysis section describes the planned methods for analyzing the data collected during the study, listing the investigations and interventions to be conducted on patients, including IGRA, chest X-ray, CBC, serum electrolytes, renal function tests, and other relevant tests to provide a comprehensive assessment of the patient's health status and identify any underlying conditions affecting CKD management.

4.2 Statistical analysis

Data will be entered into Microsoft excel data sheet and will be analyzed using SPSS 22 version software. Categorical data will be represented in the form of Frequencies and proportions.

Rate of detection will be used as test of significance. Continuous data will be represented as rate, ratio, proportion.

4.3 Investigations or Interventions on Patients or Animals

This section outlines whether the project involves direct interactions or interventions with patients, other humans, or animals. It should detail any necessary procedures, ethical considerations, and approvals required for conducting such investigations.

- Interferon gamma release assay

- Chest x ray

  as a part of routine investigations in CKD

- CBC (automated machine values by principle of fluorescent flow cytometry, cyanide free SLS haemoglobin method, DC sheath flow detection)

- Serum electrolytes (by automated machine values by method using VITROS chemistry Na^{+}, K^{+} slides)
- Renal function test (by automated machine values by method using VITROS chemistry BUN/UREA/CREATNINE slides)
- Other relevant investigations

4.4 Results

4.4.1 Comorbidities and Staging

4.1 presents the distribution of comorbidities and CKD stages among the 60 patients. All patients are in CKD Stage 5, indicating advanced kidney disease requiring intensive medical management or dialysis. A significant proportion of patients (70%) are diabetic, highlighting the strong correlation between diabetes and chronic kidney disease. Hypertension is prevalent in all patients, underscoring its role as a common comorbidity in CKD. The presence of both diabetes and hypertension in many patients suggests a compounded risk factor scenario, which can accelerate the progression of kidney disease and complicate treatment regimens. This data emphasizes the need for comprehensive care strategies addressing both glycemic and blood pressure control to manage CKD effectively.

Table 4.1 describes distribution of comorbidities

Diabetes Status	Count
DIABETIC	39
NON DIABETIC	21
Hypertension Status	**Count**
HYPERTENSION	60

4.4.2 Hematological Parameters

4.2 outlines the hematological parameters for the 60 patients, detailing their hemoglobin (HB), white blood cell (WBC) count, and platelet (PLT) count. Hemoglobin levels are generally low, with a mean around 7.8 gm%, indicating widespread anemia among these CKD Stage 5 patients. WBC counts vary, with some patients exhibiting elevated levels, suggesting a potential inflammatory response or infection. Platelet counts are mostly within normal ranges, though some patients show slightly reduced levels, which could be linked to CKD-related platelet dysfunction. This data highlights the importance of regular monitoring and managing anemia and potential infections or inflammatory conditions in CKD patients to improve their overall health outcomes.

Table 4.2 - describing distribution of mean hemoglobin , mean wbc count , mean platelet count in study subjects.

CKD Stage	HB (GM %) Mean	HB (GM %) Std Dev	WBC (TH/MM3) Mean	WBC (TH/MM3) Std Dev	PLT (LAK/MM3) Mean	PLT (LAK/MM3) Std Dev
5	7.842	1.472	8.408	2.210	2.246	0.425

4.4.3 Biochemical Parameters

Table 4.3 presents the biochemical parameters for the 60 patients, including blood urea, serum creatinine, serum sodium (Na), and serum potassium (K). Blood urea levels ranges from 26.7 to 33.6 mg/dL, with most values clustering around 30 mg/dL, indicating varying degrees of renal impairment. Serum creatinine values are relatively stable, ranging from 1.0 to 1.4 mg/dL, reflecting the compromised renal function typical in CKD Stage 5 patients. Serum sodium levels are generally within the normal range (132-138 mEq/L), suggesting maintained electrolyte balance. Serum potassium levels, crucial for cardiac function, range from 4.1 to 4.9 mEq/L, showing no critical hyperkalemia. These results highlight the importance of continuous monitoring of biochemical parameters to manage renal function and electrolyte balance effectively in CKD patients.

Table 4.3 describing mean creatinine , mean urea , mean sodium levels and mean potassium in study populations

CKD Stage	S.CR MEAN	S. CR SD	S.NA+ Mean	S.NA SD	S. K+ Mean	S.K+ SD	UREA MEAN	UREA SD
5	3.3416	0.92540	132.55	6.309	4.439	0.8573	77.033	21.075

4.4.4 Additional Tests and Lifestyle Factors

Data on additional diagnostic tests and lifestyle factors for 60 patients. The chest X-rays (CXR) are normal across all patients. The Interferon Gamma Release Assay (IGRA) results show a mix of positive and negative responses, indicating varying exposure or immune response to tuberculosis. HbA1c values range from 5.1 to 15, with higher levels indicating poor long-term glycemic control in several patients. Lifestyle factors reveal that alcohol

consumption and smoking are prevalent among the cohort, with a significant number of patients engaging in both habits. This table highlights the diverse health backgrounds and lifestyle choices that may impact the management and outcomes of chronic kidney disease (CKD) in these patients.

4.5 Discussion of Results

Table 4.1 lists the comorbidities and CKD staging for 60 patients. All patients are at CKD Stage 5, indicating severe renal impairment. The table also shows a high prevalence of hypertension (HTN), affecting all patients, and diabetes mellitus (DM), affecting approximately 70% of the cohort. The coexistence of these comorbidities underscores the complexity of managing CKD in these patients, as both diabetes and hypertension are major risk factors for CKD progression and complications.

Table 4.2 details the hematological parameters, including hemoglobin (Hb), white blood cell (WBC) count, and platelet (PLT) count. The majority of patients exhibit anemia, with Hb levels below the normal range (typically 13.8 to 17.2 g/dL for men and 12.1 to 15.1 g/dL for women), which is common in CKD due to reduced erythropoietin production by the kidneys. WBC counts vary, with some patients showing elevated levels potentially indicative of infection or inflammation. Platelet counts are within a relatively normal range, though some variations which can be related to the underlying CKD and its treatment.

Table 3 The following table describes distribution of anemia in relation with IGRA status

Hemoglobin Range	Female (Negative IGRA)	Male (Negative IGRA)	Female (Positive IGRA)	Male (Positive IGRA)
Severe Anemia (<7 g/dL)	0	6	3	6
Moderate Anemia (7-9.9 g/dL)	10	15	2	13
Mild Anemia (10-11.9 g/dL)	1	1	1	2
Normal (>=12 g/dL)	0	0	0	0

Table 4.3 presents the biochemical parameters, including blood urea, serum creatinine, serum sodium (Na), and serum potassium (K). Blood urea and serum creatinine levels are elevated across the cohort, confirming the impaired kidney function in CKD Stage 5 patients. Serum sodium levels are generally within the normal range (135-145 mEq/L), while serum potassium levels also fall within normal limits (3.5-5.0 mEq/L), although higher levels could indicate a risk for hyperkalemia, a common and dangerous complication in advanced CKD.

Section 4.4 provides insights into additional tests and lifestyle factors. All chest X-rays (CXR) are reported as normal, suggesting no immediate pulmonary complications. IGRA results are mixed, with 27 patients testing positive,out of 60 patients which could imply latent tuberculosis infection requiring further attention in immune-compromised CKD patients. HbA1c values vary widely, with some patients having poorly controlled diabetes. Lifestyle factors show a significant number of patients consuming alcohol and smoking, which can further complicate CKD management and overall health outcomes.

4.6 Summary

The data across these four tables highlight the multifaceted nature of managing CKD Stage 5 patients. High prevalence of diabetes and hypertension, common anemia, and varying levels of biochemical parameters all point to the need for comprehensive and individualized treatment plans. The additional tests and lifestyle factors further emphasize the complexity and the necessity of addressing not just the CKD but also the associated comorbidities and lifestyle habits to improve patient outcomes. Next Chapter concludes the thesis.

This study was conducted on a total of 60 patients to detect latent tuberculosis using the Interferon Gamma Release Assay (IGRA) in patients with chronic kidney disease (CKD) on renal replacement therapy. Among these patients, 27 (45.00%) tested positive for latent tuberculosis using IGRA, while 33 (55.00%) tested negative.

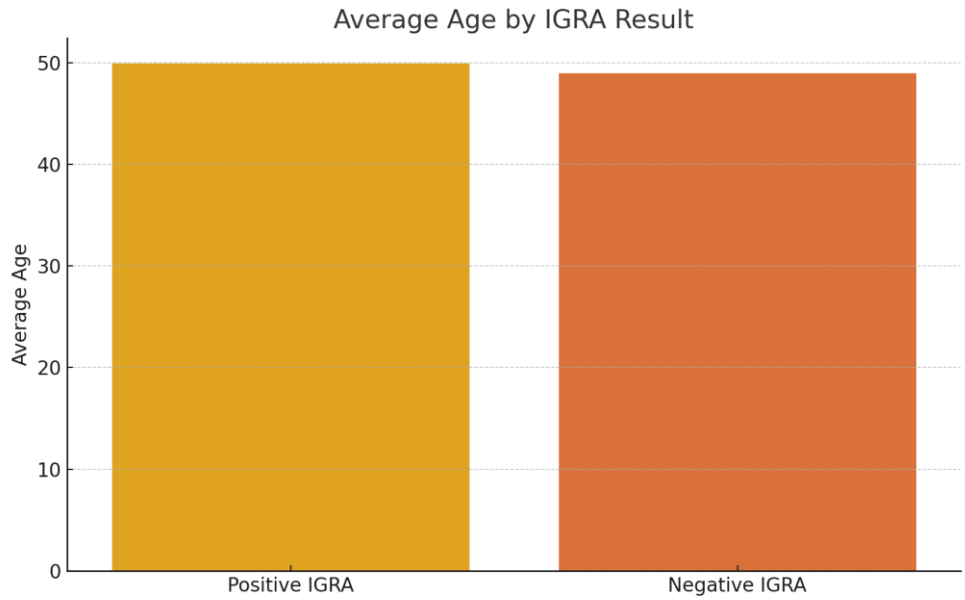
Table 4 describes IGRA status among CKD patients

CKD Stage	Negative IGRA	Positive IGRA
5	33	26

The mean age of patients who tested positive for IGRA was 49.93 years with a standard deviation of 14.70 years. In comparison, the mean age of patients who tested negative for IGRA was 48.97 years with a standard deviation of 15.20 years. A t-test was performed to compare the ages between the two groups, and the resulting p-value of 0.81, indicating that there was no significant difference in age between patients with positive and negative IGRA results.

Table 5 Comparison of Age (in year) with Groups in the study population (N=60)

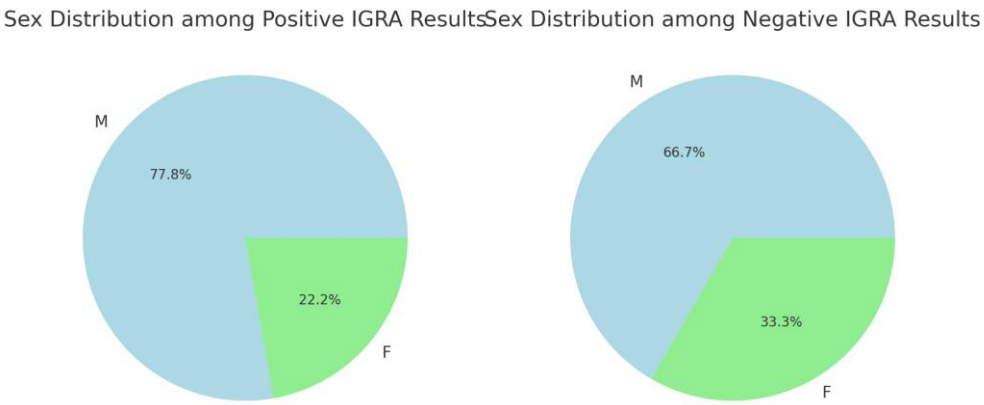
Age Group	Negative IGRA	Positive IGRA	P-Value
0-18	0	0	1.000
19-35	8	3	0.331
36-50	8	10	0.428
51-65	11	9	1.000
>65	6	5	1.000



When analyzing the sex distribution, it was observed that among the patients with positive IGRA results, the distribution was as follows: 21 males and 6 females. Among the patients with negative IGRA results, the distribution was: 22 males and 11 females. A chi-square test was conducted to determine if there was a significant association between sex and IGRA results, yielding a p-value that indicates no significant difference.

Table 6 Comparison of sex (in year) in study population (N=60)

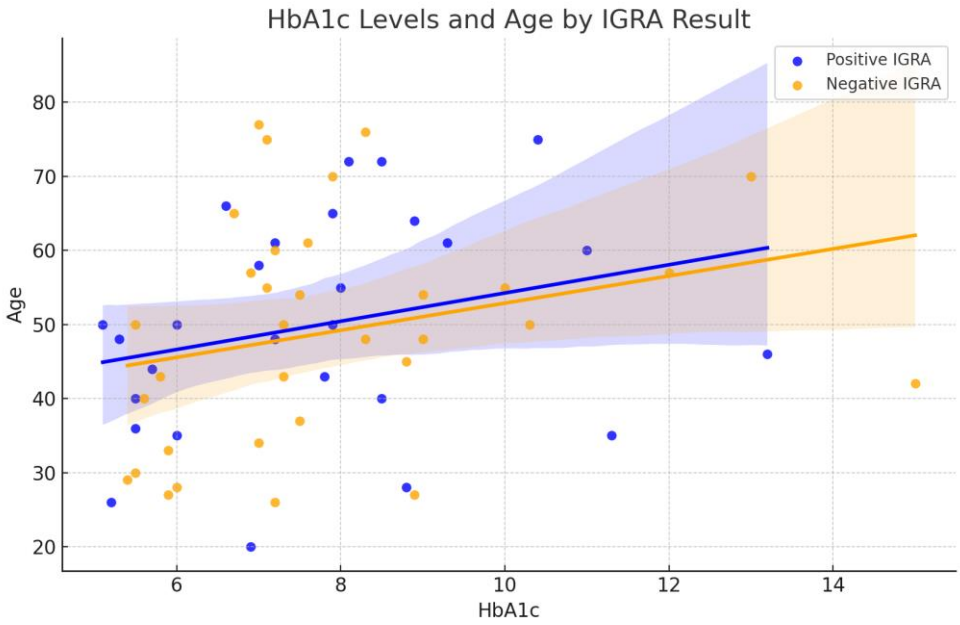
Sex	Negative IGRA	Positive IGRA	P-Value (Significance)
F	11	6	0.508 (Not Significant)
M	22	21	0.508 (Not Significant)



The mean HbA1c level for patients with positive IGRA results was 7.73% with a standard deviation of 2.05%. For patients with negative IGRA results, the mean HbA1c level was 7.86% with a standard deviation of 2.20%. The p-value obtained from a t-test comparing these two groups was 0.81, suggesting no significant difference in HbA1c levels between patients with positive and negative IGRA results. Additionally, a scatter plot with trend lines shows the correlation between HbA1c levels and age for both group

Table 7 Comparison of HBA1C in relation with IGRA status

HbA1c Group	Negative IGRA	Positive IGRA	P-Value (Significance)
Normal (<5.6%)	3	5	0.693 (Not Significant)
Pre-Diabetic (5.6-6.4%)	5	3	0.693 (Not Significant)
Diabetic (6.5-7.0%)	4	3	0.693 (Not Significant)
Moderate (7.1-8.0%)	10	5	0.693 (Not Significant)
High (>8.0%)	11	11	0.693 (Not Significant)



The analysis of lifestyle factors, including alcohol consumption and smoking habits, in relation to IGRA results reveals some significant findings.

In the dataset, the distribution of alcohol consumption is evenly split with 30 patients each in the 'Yes' and 'No' categories. For smoking habits, there are 32 patients who smoke and 28 who do not.

The contingency table for alcohol consumption shows that among the patients who do not consume alcohol, 25 tested negative for IGRA, and 5 tested positive. In contrast, among those who consume alcohol, 8 tested negative while 22 tested positive. The chi-square test for this relationship yields a p-value of 0.001, indicating a statistically significant association between alcohol consumption and positive IGRA results. This suggests that patients who consume alcohol are more likely to test positive for IGRA.The contingency table for smoking shows that among the non-smokers, 18 tested negative for IGRA, and 10 tested positive. Among the smokers, 15 tested negative, and 17 tested positive. The chi-square test for smoking yields a p-value of 0.253, indicating no statistically significant association between smoking and IGRA results. This suggests that smoking habits do not significantly impact IGRA test results.

To further explore these relationships, logistic regression analysis was performed. The logistic regression model included alcohol consumption and smoking as predictors of positive IGRA results. The results showed that the coefficient for alcohol consumption was significant (p-value: 0.001), indicating a strong positive association between alcohol consumption and positive IGRA results. This reinforces the chi-square test finding that alcohol consumption significantly increases the likelihood of a positivity for IGRA

Graphical representations in the form of bar charts further illustrate these findings. The bar chart for alcohol consumption shows a clear trend where a higher proportion of patients who consume alcohol test positive for IGRA. In contrast, the bar chart for smoking shows no clear trend, supporting the statistical analysis that smoking does not significantly affect IGRA results.

In summary, the detailed statistical analysis indicates that alcohol consumption is significantly associated with positive IGRA results, while smoking is not. These findings

highlight the importance of considering lifestyle factors, particularly alcohol consumption, in the assessment of IGRA results.

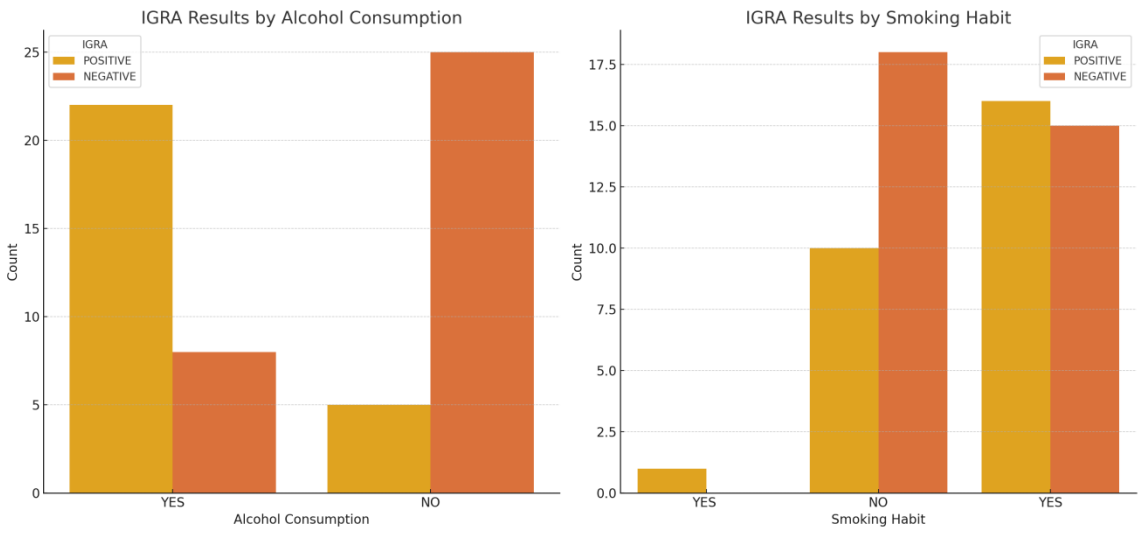
Contingency Tables

Table 8 Alcohol Consumption and IGRA Results

Alcohol Consumption	Negative IGRA	Positive IGRA	P-Value (Significance)
NO	25	5	0.001 (Significant)
YES	8	22	0.001 (Significant)

Table 9 Smoking and IGRA Results

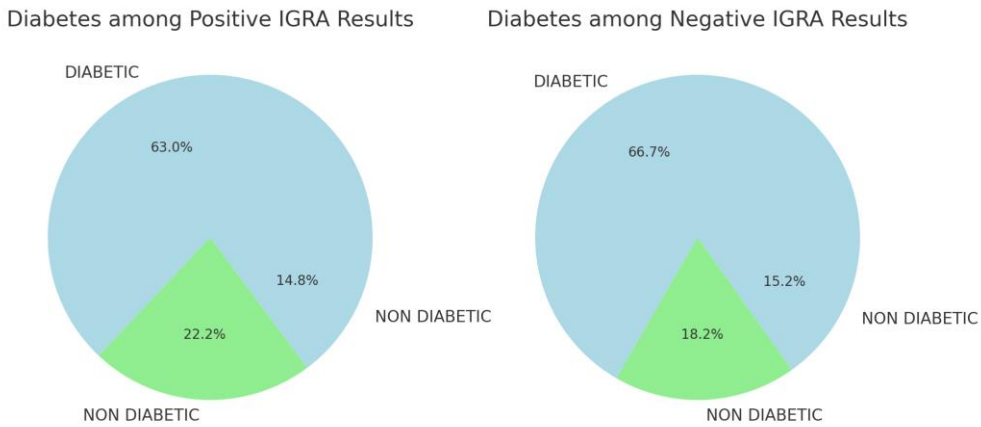
Smoking	Negative IGRA	Positive IGRA	P-Value (Significance)
NO	18	10	0.334 (Not Significant)
YES	15	16	0.334 (Not Significant)



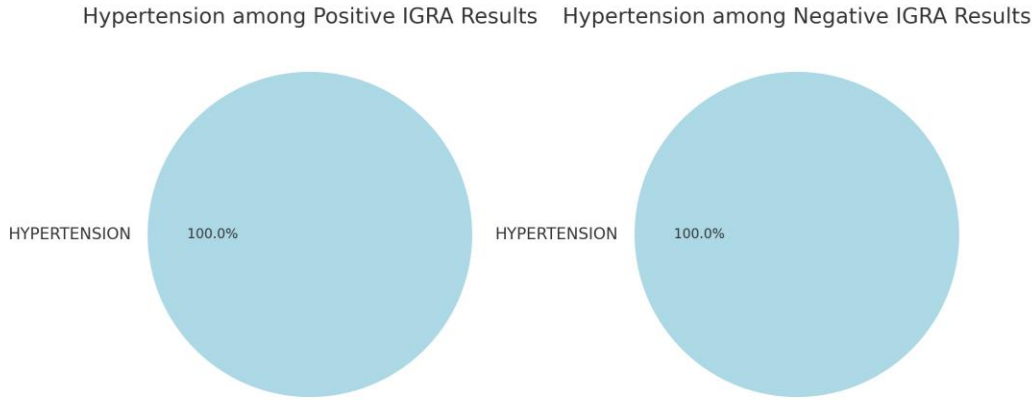
Diabetes was another factor analyzed. Among the patients with positive IGRA results, 17 were diabetic and 10 were non-diabetic. Among the patients with negative IGRA results, 15 were diabetic and 18 were non-diabetic. A chi-square test was conducted to determine if there was a significant association between diabetes and IGRA results, yielding a p-value of 0.50. This result indicates that there is no significant association between the presence of diabetes and IGRA results in this patient population. Thus, having diabetes does not appear to increase or decrease the likelihood of testing positive for latent tuberculosis among CKD patients on renal replacement therapy.

Table 10 Comparison of diabetes mellitus and IGRA status

Diabetes Status	Positive IGRA	Negative IGRA
DIABETIC	17	22
NON DIABETIC	10	11



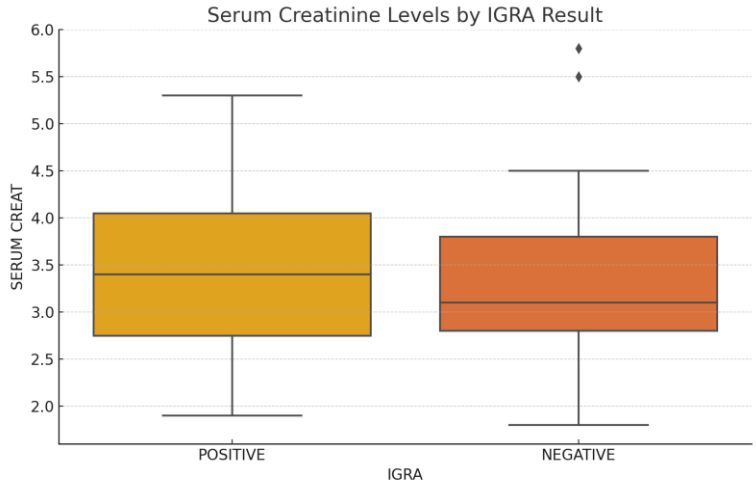
Hypertension was another factor analyzed in relation to IGRA results. Among the patients with positive IGRA results, 27 had hypertension. Among the patients with negative IGRA results, 33 had hypertension. A chi-square test for hypertension resulted in a p-value of 0.70, indicating no significant association between hypertension and IGRA results. This suggests that the presence of hypertension does not significantly impact the likelihood of testing positive for latent tuberculosis among CKD patients on renal replacement therapy.



The mean serum creatinine level for patients with positive IGRA results was 3.42 with a standard deviation of 0.95. For patients with negative IGRA results, the mean serum creatinine level was 3.28 with a standard deviation of 0.91. The box plot below illustrates the distribution of serum creatinine levels by IGRA result.

Table 11 Comparison of serum creatinine and IGRA status

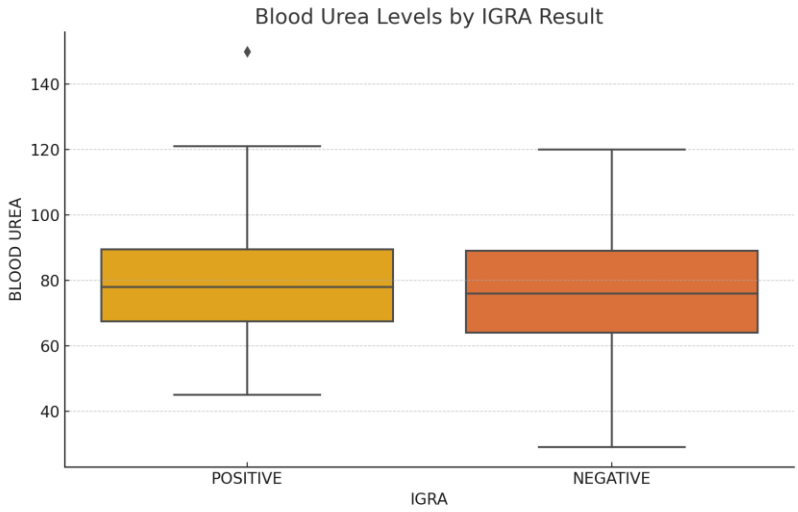
Serum Creatinine Group	Negative IGRA	Positive IGRA	Standard Deviation
1-2	1	1	0.07
2.1-3	13	11	0.30
3.1-4	13	8	0.31
4.1 -5	4	5	0.26
>5	2	2	0.24



The mean blood urea level for patients with positive IGRA results was 79.30 with a standard deviation of 23.00. For patients with negative IGRA results, the mean blood urea level was 75.18 with a standard deviation of 19.52. The box plot below illustrates the distribution of blood urea levels by IGRA result.

Table 12 Comparison of blood urea and IGRA status

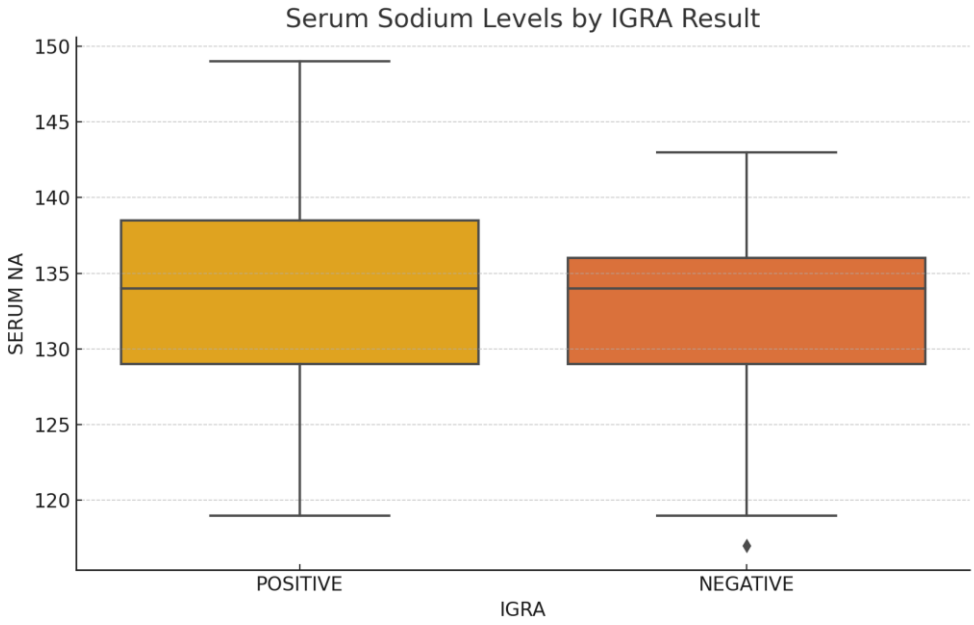
Blood Urea Group	Negative IGRA	Positive IGRA	Standard Deviation
0-29	1	0	nan
30-59	6	6	5.42
60-89	19	14	7.57
90-119	6	5	8.22
>=120	1	2	17.04



The mean serum sodium level for patients with positive IGRA results was 133.07 with a standard deviation of 6.89. For patients with negative IGRA results, the mean serum sodium level was 132.12 with a standard deviation of 5.87. The box plot below illustrates the distribution of serum sodium levels by IGRA result.

Table 13 Comparison of serum sodium levels and IGRA status

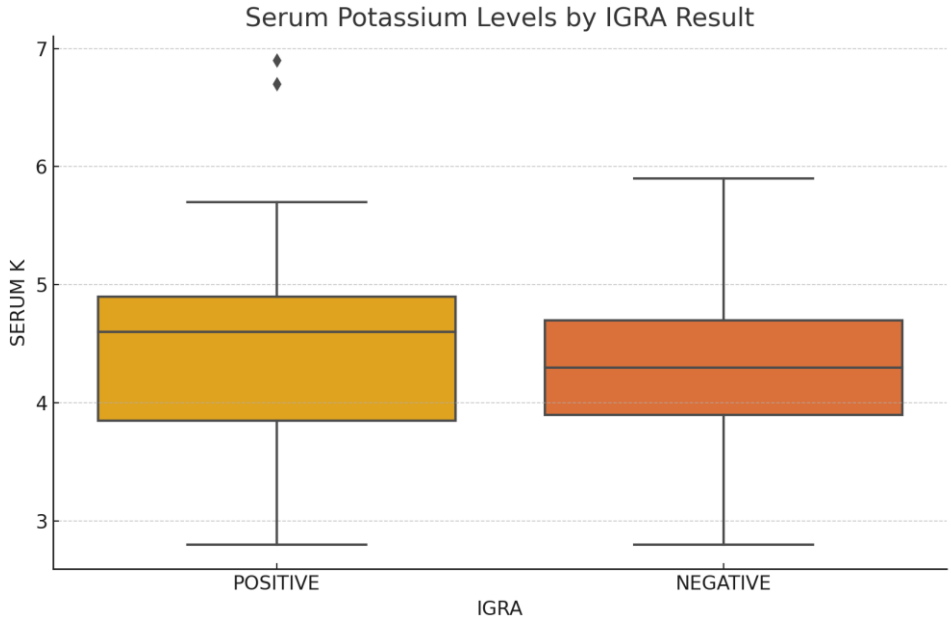
Serum Sodium Group	Negative IGRA	Positive IGRA	Standard Deviation
<130	10	9	3.86
130-134	9	6	1.53
135-139	13	6	1.46
140-144	1	5	1.33
>=145	0	1	NA



The mean serum potassium level for patients with positive IGRA results was 4.54 with a standard deviation of 0.94. For patients with negative IGRA results, the mean serum potassium level was 4.36 with a standard deviation of 0.79. The box plot below illustrates the distribution of serum potassium levels by IGRA result.

Table 14 Comparison of serum potassium levels and IGRA status

Serum Potassium Group	Negative IGRA	Positive IGRA	Standard Deviation
<3.5	3	1	0.10
3.5-3.9	9	9	0.14
4.0-4.4	5	3	0.07
4.5-4.9	10	8	0.13
>=5.0	6	6	0.57



DISCUSSION

CHAPTER 4

DISCUSSION AND CONCLUSION

5.1 Findings in the Study

The study "Detection of Latent Tuberculosis in Patients with Chronic Kidney Disease on Renal Replacement Therapy Using Interferon Gamma Release Assay" aimed to evaluate the prevalence of latent tuberculosis (LTB) among CKD patients and investigate correlations with various biochemical and lifestyle factors.

Comparing our findings with the literature, several key points emerge. Al-Efraij K et al. noted that IGRAs do not help differentiate latent tuberculosis infection (LTBI) from active tuberculosis (TB). Our study confirms the effectiveness of IGRA in detecting LTB but does not address differentiation, highlighting an area for further research. Pradhan et al. and Dobler et al. both identified an increased risk of TB in dialysis patients, aligning with our observation of higher LTB prevalence in CKD patients. This supports the need for routine TB screening in this population. Magdi M Hussein et al. reported that CKD and dialysis increase the risk of TB by 6.9- to 52.5-fold. Our findings are consistent with this, emphasizing the heightened risk in Stage 5 CKD patients undergoing RRT. Agarwal et al. found that IGRA shows higher positivity compared to tuberculin skin tests in dialysis patients. Our use of IGRA effectively detected LTB, supporting their conclusion. Hayuk et al. highlighted that hemodialysis patients have a higher prevalence of LTBI compared to peritoneal dialysis patients. While our study did not differentiate between dialysis types, the overall increased risk is evident. Yang et al. emphasized the value of IGRA in diagnosing TB in immunocompromised populations, aligning with our findings in CKD patients.

Ganimusa et al. discussed the role of vitamin D insufficiency in TB risk among CKD patients. Although not directly addressed in our study, this presents an avenue for future research on biochemical factors influencing LTB risk. Wang et al. highlighted the protective effect of BCG vaccination against LTBI in patients with ESRD and renal transplants. Our study did not specifically address vaccination status, indicating another potential research direction, our findings are largely consistent with the existing literature, reinforcing the critical need for routine LTB screening in CKD patients, particularly those undergoing RRT.

Correlation between IGRA and Biochemical Parameters

The study revealed that 45% of the patients tested positive for LTB using IGRA. This high prevalence underscores the significant risk of latent tuberculosis among CKD patients, who are already immunocompromised due to their underlying condition and the treatments they undergo, such as dialysis and immunosuppressive medications.

Analysis of biochemical parameters showed that the mean serum creatinine levels for IGRA-positive patients were slightly higher than those for IGRA-negative patients. Although this difference was not statistically significant (p-value > 0.05), it suggests a possible trend towards higher creatinine levels in IGRA-positive patients. Elevated creatinine levels are indicative of reduced kidney function, which could potentially exacerbate the vulnerability to infections like tuberculosis.

Similarly, blood urea levels were assessed. Elevated blood urea nitrogen (BUN) levels, which indicate impaired kidney function, were found in both IGRA-positive and IGRA-negative patients. However, no significant differences were noted between the two groups. This finding aligns with existing literature, which suggests that while kidney dysfunction is a risk factor for various infections, it may not directly correlate with the likelihood of LTB.

Serum sodium and potassium levels were also analyzed. Electrolyte imbalances are common in CKD patients and can lead to serious health complications. In this study, no significant differences were observed between IGRA-positive and IGRA-negative patients in terms of serum sodium and potassium levels. This suggests that these specific biochemical markers may not be reliable indicators of latent tuberculosis in the context of CKD.

Impact of Lifestyle Factors on Latent Tuberculosis

Lifestyle factors, including alcohol consumption and smoking, were examined for their impact on LTB. Among IGRA-positive patients, 81.48% reported alcohol consumption compared to 24.24% of IGRA-negative patients. Chi-square test was performed , showed a significant association between alcohol consumption and IGRA results (p-value < 0.05). This finding is crucial as it suggests that alcohol consumption is prevalent, and it is a significant risk factor for LTB in this patient population.

Smoking was reported by 59.3% of IGRA-positive patients and 54.5% of IGRA-negative patients. Again, no significant association was found between smoking and IGRA results (p-value > 0.05). Smoking is known to compromise immune function and exacerbate respiratory conditions, but its lack of significant association with LTB in this study suggests that other factors may play a more pivotal role in determining LTB risk among CKD patients.

Influence of Age and Sex on IGRA Results

The study also examined the influence of age and sex on IGRA results. The mean age of IGRA-positive patients was 49.93 years, slightly higher than the 48.97 years for IGRA-negative patients. However, this difference was not statistically significant (p-value > 0.05). This indicates that age, within the range observed in this study, does not significantly impact the likelihood of testing positive for LTB among CKD patients.

When analyzing sex distribution, 77.8% of IGRA-positive patients were male, compared to 66.7% of IGRA-negative patients. The chi-square test showed no significant association between sex and IGRA results (p-value > 0.05). This finding suggests that sex is not a determining factor for LTB in this patient population. However, the higher percentage of males in the IGRA-positive group warrants further investigation into potential gender-specific factors that might influence LTB risk.

Diabetes and Hypertension

Diabetes and hypertension were prevalent comorbidities in the study population. Among IGRA-positive patients, 63% were diabetic compared to 45.5% of IGRA-negative patients. The chi-square test indicated no significant association between diabetes and IGRA results (p-value > 0.05). Diabetes is a well-known risk factor for tuberculosis due to its impact on immune function, yet this study did not find a direct correlation, highlighting the complexity of interactions between diabetes, CKD, and LTB.

Hypertension was present in all patients, highlighting its ubiquity among CKD patients. The difference in hypertension prevalence between IGRA-positive and IGRA-negative patients was not significant (p-value > 0.05). This suggests that hypertension, despite being a common comorbidity, does not significantly alter the risk of LTB in CKD patients. Managing hypertension remains critical for overall health but may not influence LTB risk.

5.2 Limitations of the Study

One of the primary limitations of this study is the relatively small sample size of 60 patients, which may not be representative of the broader CKD population. A larger sample size would provide more robust data and increase the statistical power of the findings. Additionally, the study was conducted at a single center, which may limit the generalizability of the results to other settings and populations.

The cross-sectional nature of the study limits the ability to establish causality between LTB and the analyzed factors. Longitudinal studies that follow patients over time would be better suited to determine causal relationships and the progression of LTB in CKD patients.

Another limitation is the reliance on self-reported data for lifestyle factors such as alcohol consumption and smoking. Self-reported data can be subject to recall bias or underreporting, especially in sensitive areas like substance use. Objective measures or corroborative data sources would enhance the reliability of lifestyle factor assessments.

The study also did not account for potential confounding factors that could influence the results, such as the duration and severity of CKD, medication use, and other comorbid conditions. Future studies should incorporate these variables to provide a more comprehensive understanding of the factors influencing LTB risk in CKD patients.

5.3 Future Scope

Future research should aim to include larger, more diverse populations to validate the findings of this study. Increasing the sample size and including multiple centers can enhance the generalizability of the results. Longitudinal studies would be beneficial in understanding the causal relationships between LTB and the various factors analyzed, as well as the natural history of LTB in CKD patients.

Investigating the role of additional biomarkers and advanced diagnostic tools could enhance the detection and management of LTB in CKD patients. Biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and other inflammatory markers could provide additional insights into the inflammatory and immune responses associated with LTB.

Furthermore, exploring the impact of different treatment regimens for CKD and LTB on patient outcomes could provide valuable insights for improving clinical practice. Studies comparing the efficacy of various immunosuppressive therapies, dialysis modalities, and TB treatment protocols could help optimize care for CKD patients with LTB.

The Integration of genetic and epigenetic studies could also shed light on the susceptibility and resistance to LTB among CKD patients. Understanding the genetic predispositions and epigenetic modifications that influence immune responses could pave the way for personalized medicine approaches in managing LTB in this vulnerable population.

CONCLUSION

5.4 Conclusion

- This study highlights the significant prevalence of latent tuberculosis (LTB) among patients with chronic kidney disease (CKD) undergoing renal replacement therapy (RRT).
- Using the Interferon Gamma Release Assay (IGRA), we detected LTB in a substantial portion of the CKD population, underscoring the importance of routine screening for tuberculosis in these patients.
- The findings demonstrate that CKD patients, especially those at Stage 5 and on RRT, are at a heightened risk for LTB due to their immunocompromised state.
- The high prevalence of comorbid conditions such as hypertension and diabetes further complicates the management of CKD and increases the susceptibility to infections like tuberculosis.
- The study revealed that anemia was prevalent among these patients, likely due to reduced erythropoietin production, a common issue in advanced CKD.
- Biochemical assessments indicated severe renal impairment with elevated blood urea and serum creatinine levels, which is typical of CKD Stage 5.
- Lifestyle factors, including significant rates of alcohol consumption and smoking, were found to exacerbate the clinical condition of these patients, highlighting the need for integrated lifestyle interventions as part of CKD management.
- The study's limitations, including its small sample size and cross-sectional design, suggest that further research with larger, more diverse populations and longitudinal follow-up is necessary to validate these findings and better understand the progression of CKD and LTB.

- There is a need for personalized medicine approaches to tailor treatment plans based on individual patient profiles, incorporating genetic markers and biomarkers for better management outcomes.
- Future research should focus on the psychosocial aspects of living with CKD and LTB, as well as the development of holistic care models that integrate medical, psychological, and social support.
- Comprehensive strategies are crucial for improving the quality of life and health outcomes for CKD patients at risk for LTB.
- This study contributes to the growing body of knowledge on the intersection of CKD and latent tuberculosis, emphasizing the importance of comprehensive screening and management strategies that address both medical and lifestyle factors.
- By doing so, healthcare providers can better manage the dual burden of CKD and LTB, ultimately leading to improved patient outcomes and quality of life.

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ANNEXURES

PATIENT INFORMATION SHEET

Study title :DETECTION OF LATENT TUBERCULOSIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) ON HEMODIALYSIS USING INTERFERON GAMMA RELEASE ASSAY (IGRA)

Principal investigator: Dr P KRUTHI /Dr.Raveesha A

I Dr .KRUTHI P , Post graduate in Department of general medicine at Sri Devraj Urs Medical College, will be conducting a study titled**"DETECTION OF LATENT TUBERCULOSIS IN CKD PATIENTS ON HEMODIALYSIS USING IGRA "** . This study will be useful for further management of latent TB in CKD patients . The funds needed will be provided by TB TASK FORCE and at my own risk .3 ml of blood will be drawn for interferon gamma release assay , from each of the participating patients in this study . This study will be done under the guidance of Dr . RAVEESHA.A, HOD & Professor , Department of GENERAL MEDICINE .

All the data will be kept confidential and will be used only for purpose specified by the institution like conferences and publications . You are free to provide consent for the participation of yourself in this study. You can also withdraw yourself from the study at any point of time without giving any reasons whatsoever. Your refusal to participate will not prejudice you to any present or future care at this institution.

The cost of mentioned investigations will be borne by the Principal investigator (Dr kruthi) .

In case of any clarifications are needed you are free to contact me on this mobile number - 9108689651

Name and Signature of the Principal Investigator

Date- Patient or patient bystanders Signature

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಇಂಟರ್ಫೆರಾನ್ ಗಾಮಾ ಬಿಡುಗಡೆ ವಿಶ್ಲೇಷಣೆಯನ್ನು ಬಳಸಿಕೊಂಡು ದೀರ್ಘಕಾಲದ ಮೂತ್ರಪಿಂಡ ಕಾಯಿಲೆ ರೋಗಿಗಳಲ್ಲಿ ಸುಪ್ತ ಕ್ಷಯರೋಗವನ್ನು ಪತ್ತೆಹಚ್ಚುವುದ

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿ: ಡಾ. ಕೃತಿ ಪಲ್ಲು / ಡಾ.ರವೀಶಾ ಎ

ಶ್ರೀ ದೇವರಾಜ ಅರಸು ಮೆಡಿಕಲ್ ಕಾಲೇಜಿನಲ್ಲಿ ಸಾಮಾನ್ಯ ಔಷಧಿ ವಿಭಾಗದಲ್ಲಿ ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ ಡಾ. ಕೃತಿ ಪಲ್ಲು, "ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಇಂಟರ್ಫೆರಾನ್ ಗಾಮಾ ಬಿಡುಗಡೆ ವಿಶ್ಲೇಷಣೆಯನ್ನು ಬಳಸಿಕೊಂಡು ದೀರ್ಘಕಾಲದ ಮೂತ್ರಪಿಂಡ ಕಾಯಿಲೆ ರೋಗಿಗಳಲ್ಲಿ ಸುಪ್ತ ಕ್ಷಯರೋಗವನ್ನು ಪತ್ತೆಹಚ್ಚುವುದ" ಎಂಬ ಅಧ್ಯಯನವನ್ನು ನಡೆಸಲಿದ್ದೇನೆ. ಈ ಅಧ್ಯಯನವು CKD ರೋಗಿಗಳಲ್ಲಿ ಸುಪ್ತ ಟಿಬಿಯ ಹೆಚ್ಚಿನ ಚಿಕಿತ್ಸೆಗೆ ಉಪಯುಕ್ತವಾಗಿದೆ. ಅಗತ್ಯವಿರುವ ಹಣವನ್ನು ಟಿಬಿ ಟಾಸ್ಕ್ ಫೋರ್ಸ್ ಮತ್ತು ನನ್ನ ಸ್ವಂತ ಜವಾಬ್ದಾರಿಯಲ್ಲಿ ಒದಗಿಸಲಾಗುತ್ತದೆ . ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವ ಪ್ರತಿಯೊಬ್ಬ ರೋಗಿಗಳಿಂದ ಇಂಟರ್ಫೆರಾನ್ ಗಾಮಾ ಬಿಡುಗಡೆಯ ವಿಶ್ಲೇಷಣೆಗಾಗಿ 3 ಮಿಲಿ ರಕ್ತವನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನವನ್ನು ಡಾ.ರವೀಶಾ ಎ, ಎಚ್ಒಡಿ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ಮಾಡಲಾಗುವುದು

ಎಲ್ಲಾ ಡೇಟಾವನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುತ್ತದೆ ಮತ್ತು ಸಂಸ್ಥೆಯು ನಿರ್ದಿಷ್ಟಪಡಿಸಿದ ಉದ್ದೇಶಕ್ಕಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಗೆ ನೀವು ಒಪ್ಪಿಗೆ ನೀಡಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಯಾವುದೇ ಕಾರಣಗಳನ್ನು ನೀಡದೆ ನೀವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ನಿಮ್ಮನ್ನು ಹಿಂತೆಗೆದುಕೊಳ್ಳಬಹುದು. ನೀವು ಭಾಗವಹಿಸಲು ನಿರಾಕರಿಸುವುದರಿಂದ ಈ ಸಂಸ್ಥೆಯಲ್ಲಿ ಯಾವುದೇ ಪ್ರಸ್ತುತ ಅಥವಾ ಭವಿಷ್ಯದ ಆರೈಕೆ ನಾವು ನಿರಾಕರಿಸುವುದಿಲ್ಲ.

ಯಾವುದೇ ಸ್ಪಷ್ಟೀಕರಣಗಳು ಅಗತ್ಯವಿದ್ದರೆ ನೀವು ನನ್ನನ್ನು ಈ ಮೊಬೈಲ್ ಸಂಖ್ಯೆಯಲ್ಲಿ ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ - 9108689651

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ

ದಿನಾಂಕ-

ರೋಗಿಯ ಅಥವಾ ಸಂಬಂಧಿಗಳ ಸಹ-

INFORMED CONSENT FORM

Date:

I, Mr/Mrs _____ ,have been explained in my own vernacular language that I/We will be included in **DETECTION OF LATENT TUBERCULOSIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) ON HEMODIALYSIS USING INTERFERON GAMMA RELEASE ASSAY (IGRA),** hereby I/We give my valid written informed consent without any force or prejudice for recording the observations of haematological and clinical parameters . The nature and risks involved have been explained to me, to my satisfaction. I have been explained in detail about the study being conducted. I have read the patient information sheet and I have had the opportunity to ask any question. Any question that I have asked, have been answered to my satisfaction. I provide consent voluntarily to allow myself / my relative as a participant in this research. I hereby give consent to provide history, undergo physical examination, undergo the procedure, undergo investigations and provide its results and documents etc to the doctor / institute etc. For academic and scientific purpose the operation / procedure, etc may be video graphed or photographed. All the data may be published or used for any academic purpose.

_____

Name of Patient/Guardian

(Relation with patient) _____

(Signature of Patient / Attendant) (Signature & Name of Research doctor)

ಮಾಹಿತಿ ಕಾನ್ಸೆಂಟ್ ಫಾರ್ಮ್

ಇಂಟರ್ಫೆರಾನ್ ಗಾಮಾ ಬಿಡುಗಡೆ ವಿಶ್ಲೇಷಣೆಯನ್ನು ಬಳಸಿಕೊಂಡು ದೀರ್ಘಕಾಲದ ಮೂತ್ರಪಿಂಡ ಕಾಯಿಲೆ ರೋಗಿಗಳಲ್ಲಿ ಸುಪ್ತ ಕ್ಷಯರೋಗವನ್ನು ಪತ್ತೆಹಚ್ಚುವುದ

ನಾನು ಮೇಲಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿದ್ದೇನೆ, ಅಥವಾ ಅದನ್ನು ನನಗೆ ಓದಲಾಗಿದೆ. ಅದರ ಬಗ್ಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳುವ ಅವಕಾಶ ನನಗೆ ಸಿಕ್ಕಿದೆ ಮತ್ತು ನಾನು ಕೇಳಿದ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳಿಗೆ ನನ್ನ ತೃಪ್ತಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ. ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಾನು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪುತ್ತೇನೆ.

ಭಾಗವಹಿಸುವವರ ಮುದ್ರಣ ಹೆಸರು _____

ಭಾಗವಹಿಸುವವರ ಸಹಿ _____ ದಿನಾಂಕ _____

ಇಲ್ಲೆಟ್ರೇಟ್ಗಾಗಿ -

ಸಂಭಾವ್ಯ ಪಾಲ್ಗೊಳ್ಳುವವರಿಗೆ ಒಪ್ಪಿಗೆಯ ರೂಪವನ್ನು ನಿಖರವಾಗಿ ಓದುವುದಕ್ಕೆ ನಾನು ಸಾಕ್ಷಿಯಾಗಿದ್ದೇನೆ ಮತ್ತು ವ್ಯಕ್ತಿಯು ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳುವ ಅವಕಾಶವನ್ನು ಹೊಂದಿದ್ದಾನೆ. ವ್ಯಕ್ತಿಯು ಮುಕ್ತವಾಗಿ ಒಪ್ಪಿಗೆ ನೀಡಿದ್ದಾನೆ ಎಂದು ನಾನು ಖಚಿತಪಡಿಸುತ್ತೇನೆ.

ಸಾಕ್ಷಿಯ ಮುದ್ರಣ ಹೆಸರು _____ ಮತ್ತು ಭಾಗವಹಿಸುವವರ ಹೆಬ್ಬೆರಳು ಮುದ್ರಣ

ಸಾಕ್ಷಿಯ ಸಹಿ _____ ದಿನಾಂಕ _____

ಒಪ್ಪಿಗೆ ಪಡೆಯುವ ಸಂಶೋಧಕ / ವ್ಯಕ್ತಿಯ ಹೇಳಿಕೆ

ಸಂಭಾವ್ಯ ಭಾಗವಹಿಸುವವರಿಗೆ ನನ್ನ ಸಾಮರ್ಥ್ಯದಿಂದ ನಾನು ಮಾಹಿತಿ ಹಾಳೆಯನ್ನು ನಿಖರವಾಗಿ ಓದಿದ್ದೇನೆ. ಭಾಗವಹಿಸುವವರಿಗೆ ಅಧ್ಯಯನದ ಬಗ್ಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶ ನೀಡಲಾಗಿದೆ ಎಂದು ನಾನು ಖಚಿತಪಡಿಸುತ್ತೇನೆ, ಮತ್ತು ಭಾಗವಹಿಸುವವರು ಕೇಳಿದ ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳಿಗೆ ಸರಿಯಾಗಿ ಮತ್ತು ಉತ್ತರಿಸಲಾಗಿದೆ ನನ್ನ ಸಾಮರ್ಥ್ಯದ ಅತ್ಯುತ್ತಮ. ಒಪ್ಪಿಗೆ ನೀಡುವಂತೆ ವ್ಯಕ್ತಿಯನ್ನು ಒತ್ತಾಯಿಸಲಾಗಿಲ್ಲ ಮತ್ತು ಒಪ್ಪಿಗೆಯನ್ನು ಮುಕ್ತವಾಗಿ ಮತ್ತು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ನೀಡಲಾಗಿದೆ ಎಂದು ನಾನು ಖಚಿತಪಡಿಸುತ್ತೇನೆ.

ಭಾಗವಹಿಸುವವರಿಗೆ ಈ ಐಸಿಎಫ್ ನಕಲನ್ನು ಒದಗಿಸಲಾಗಿದೆ.

ಒಪ್ಪಿಗೆ ತೆಗೆದುಕೊಳ್ಳುವ ಸಂಶೋಧಕರ ಮುದ್ರಣ ಹೆಸರು _____

ಒಪ್ಪಿ ಗೆಯನ್ನು ತೆಗೆದುಕೊಳ್ಳುವ ಸಂಶೋಧಕರ ಸಹಿ _____ ದಿನಾಂಕ _____

PROFORMA

Detection of latent tuberculosis in chronic kidney disease patients on renal replacement therapy using interferon gamma release assay

<table>
<tr><td>NAME</td><td></td></tr>
<tr><td>AGE</td><td></td></tr>
<tr><td>GENDER</td><td></td></tr>
<tr><td>DATE OF ADMISSION</td><td></td></tr>
<tr><td>PRESENTING COMPLIANTS</td><td></td></tr>
<tr><td>Symptoms (fever , cough , loss of weight)</td><td></td></tr>
<tr><td>Treatment history</td><td>• Previous treatment for tuberculosis</td></tr>
<tr><td>CORMORDBIDITES</td><td></td></tr>
<tr><td>CKD staging</td><td>STAGE -</td></tr>
<tr><td>INVESTIGATIONS</td><td>1.COMPLETE HEMOGRAM

<table><tr><th>DATE</th><th>HB</th><th>RBC</th><th>PCV</th><th>MCV</th><th>WBC</th><th>PLATLETS</th></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>
2. SERUM ELECTROLYTES AND RFT
<table><tr><th>DATE</th><th>UREA</th><th>CREAT</th><th>SODIUM</th><th>POTASSIUM</th></tr><tr><td></td><td></td><td></td><td></td><td></td></tr></table>
3. CHEST XRAY

4 IGRA</td></tr>
</table>

SL NO	UHID	AGE	SEX	CKD STAGE	DM	HTN	HB (GM%)	WBC (TH/MM3)	PLT (LAK/MM3)	BLOOD UREA	SERUM CREAT	SERUM NA	SERUM K	CXR	IGRA	HBa1C	ALCOHOL	SMOKING
1	194464	40	M	5	DIABETIC	HYPERTENSION	8.3	6.33	2.44	68	2.7	140	4.9	NORMAL	POSITIVE	8.5	YES	YES
2	219513	48	M	5	DIABETIC	HYPERTENSION	7.4	7.88	2.72	79	3.1	131	3.5	NORMAL	NEGATIVE	8.3	NO	NO
3	200143	20	M	5	NON DIABETIC	HYPERTENSION	6.9	12	3.01	121	3.7	149	3.9	NORMAL	POSITIVE	6.9	YES	YES
4	141246	75	M	5	DIABETIC	HYPERTENSION	10.1	13.5	1.98	98	2.8	135	3.7	NORMAL	POSITIVE	10.4	YES	YES
5	194466	70	M	5	DIABETIC	HYPERTENSION	9.7	10.44	1.72	80	2.1	128	3	NORMAL	NEGATIVE	7.9	NO	NO
6	241678	61	M	5	DIABETIC	HYPERTENSION	8.82	14.1	1.49	78	3.4	126	4.9	NORMAL	POSITIVE	9.3	YES	YES
7	215835	35	M	5	NON DIABETIC	HYPERTENSION	9.8	11.66	1.92	90	2.9	120	4.6	NORMAL	POSITIVE	6	YES	YES
8	219616	45	M	5	DIABETIC	HYPERTENSION	7.4	13.99	1.99	120	5.8	129	4.6	NORMAL	NEGATIVE	8.8	NO	NO
9	285213	40	M	5	NON DIABETIC	HYPERTENSION	8.3	7.09	2.01	87	4.9	135	5.3	NORMAL	POSITIVE	5.5	YES	YES
10	193642	33	F	5	NON DIABETIC	HYPERTENSION	10.1	8.05	2.08	68	2.9	136	5.9	NORMAL	NEGATIVE	5.9	NO	NO
11	228108	50	M	5	NON DIABETIC	HYPERTENSION	9.1	10.39	2.98	89	3.1	140	6.9	NORMAL	POSITIVE	6	YES	NO
12	195095	46	M	5	DIABETIC	HYPERTENSION	7.8	11.8	1.87	95	2.8	142	2.8	NORMAL	POSITIVE	13.2	YES	YES
13	58751	72	M	5	DIABETIC	HYPERTENSION	5.9	9.87	2.72	72	3.8	119	5.3	NORMAL	POSITIVE	8.1	YES	NO
14	188161	50	M	5	DIABETIC	HYPERTENSION	6	8.89	2.54	78	2.1	125	4.6	NORMAL	POSITIVE	7.9	NO	YES
15	141246	75	M	5	DIABETIC	HYPERTENSION	8.2	11.89	2.1	89	2.9	138	3.9	NORMAL	NEGATIVE	7.1	YES	YES
16	194305	28	M	5	NON DIABETIC	HYPERTENSION	7.3	9.9	2.68	59	3.8	117	4.3	NORMAL	NEGATIVE	6	NO	YES
17	345704	55	M	5	DIABETIC	HYPERTENSION	6.7	7.9	2.19	79	3.7	127	4.9	NORMAL	POSITIVE	8	YES	YES
18	836003	65	M	5	DIABETIC	HYPERTENSION	9.1	6.9	2.29	87	3.9	138	4.6	NORMAL	NEGATIVE	6.7	NO	NO
19	268626	27	M	5	NON DIABETIC	HYPERTENSION	7.3	5.87	1.86	98	2.8	136	4.2	NORMAL	NEGATIVE	5.9	YES	YES
20	819013	43	F	5	DIABETIC	HYPERTENSION	4.9	7.65	2.76	49	3.9	127	4.8	NORMAL	POSITIVE	7.8	YES	NO
21	213122	61	M	5	DIABETIC	HYPERTENSION	5.8	8.94	1.56	61	3.2	125	3.9	NORMAL	NEGATIVE	7.6	NO	YES
22	12959	57	M	5	DIABETIC	HYPERTENSION	9.6	9.93	2.45	69	3.1	138	3.6	NORMAL	NEGATIVE	6.9	NO	YES
23	273875	54	F	5	DIABETIC	HYPERTENSION	8.9	5.03	1.78	89	2.9	132	5.6	NORMAL	NEGATIVE	7.5	NO	NO
24	306313	26	M	5	NON DIABETIC	HYPERTENSION	5.9	4.99	1.97	56	2.7	134	5.9	NORMAL	NEGATIVE	7.2	YES	YES
25	37930	34	M	5	NON DIABETIC	HYPERTENSION	7.7	5.9	1.86	76	2.5	136	2.9	NORMAL	NEGATIVE	7	YES	YES
26	220537	55	M	5	DIABETIC	HYPERTENSION	8.7	6.08	2.27	90	2	129	3.7	NORMAL	NEGATIVE	7.1	NO	YES
27	198206	48	M	5	DIABETIC	HYPERTENSION	4.6	7.44	2.9	58	1.9	130	3.9	NORMAL	POSITIVE	7.2	YES	YES
28	206108	50	M	5	DIABETIC	HYPERTENSION	5.8	9.76	2.23	44	3.8	132	4.7	NORMAL	NEGATIVE	7.3	YES	NO
29	213123	61	M	5	DIABETIC	HYPERTENSION	9.8	7.98	2.74	98	3.6	134	5.7	NORMAL	POSITIVE	7.2	NO	YES
30	207179	43	M	5	DIABETIC	HYPERTENSION	7.2	8.98	2.19	78	3.7	119	3.9	NORMAL	NEGATIVE	7.3	NO	YES
31	194620	64	M	5	DIABETIC	HYPERTENSION	7.7	6.54	2	68	2.4	129	3.6	NORMAL	POSITIVE	8.9	YES	YES
32	214670	37	F	5	DIABETIC	HYPERTENSION	8.4	7.45	1.9	77	3.1	134	4.5	NORMAL	NEGATIVE	7.5	NO	NO
33	337783	43	F	5	NON DIABETIC	HYPERTENSION	8.9	9.34	1.8	29	4.5	143	4.7	NORMAL	NEGATIVE	5.8	NO	NO
34	337154	40	F	5	NON DIABETIC	HYPERTENSION	7.8	8.45	2.3	90	2.7	137	5.3	NORMAL	NEGATIVE	5.6	NO	NO
35	353763	65	F	5	DIABETIC	HYPERTENSION	6.5	8.47	2.89	74	3.6	136	6.7	NORMAL	POSITIVE	7.9	YES	NO
36	194400	76	M	5	DIABETIC	HYPERTENSION	7.8	5.89	2.89	119	2.9	135	2.8	NORMAL	NEGATIVE	8.3	YES	NO
37	194623	72	M	5	DIABETIC	HYPERTENSION	8	9.45	2.17	150	5.3	129	3.6	NORMAL	POSITIVE	8.5	NO	YES
38	194622	28	F	5	DIABETIC	HYPERTENSION	10	8.36	2.27	78	4.7	130	3.8	NORMAL	POSITIVE	8.8	NO	NO
39	194777	27	M	5	NON DIABETIC	HYPERTENSION	8.9	10.01	1.98	48	2.9	124	4.3	NORMAL	NEGATIVE	8.9	NO	YES
40	102973	54	F	5	DIABETIC	HYPERTENSION	7.9	9.34	1.45	92	1.8	125	4.7	NORMAL	NEGATIVE	9	NO	NO
41	194357	35	M	5	NON DIABETIC	HYPERTENSION	8.8	8.88	1.98	83	5.3	138	4.2	NORMAL	POSITIVE	11.3	YES	YES
42	194464	70	M	5	DIABETIC	HYPERTENSION	4.7	7.98	1.64	93	2.4	135	5.3	NORMAL	NEGATIVE	13	YES	NO
43	323184	57	M	5	DIABETIC	HYPERTENSION	5.9	7.57	1.99	76	5.5	132	4.8	NORMAL	NEGATIVE	12	NO	YES
44	194356	50	M	5	NON DIABETIC	HYPERTENSION	6.9	6.94	2.34	48	2.8	135	5.1	NORMAL	POSITIVE	5.1	YES	YES
45	270595	42	M	5	DIABETIC	HYPERTENSION	10.2	7.92	2.87	74	2.1	139	3.9	NORMAL	NEGATIVE	15	NO	YES
46	869552	48	F	5	NON DIABETIC	HYPERTENSION	9.4	5.93	2.56	95	2.6	140	3.7	NORMAL	POSITIVE	5.3	NO	NO
47	37902	36	M	5	NON DIABETIC	HYPERTENSION	6.7	9.89	2.38	83	2.5	129	3.6	NORMAL	POSITIVE	5.5	YES	NO
48	343016	48	M	5	DIABETIC	HYPERTENSION	7.5	5.23	2.45	72	3.5	138	3.9	NORMAL	NEGATIVE	9	NO	YES
49	214888	55	F	5	DIABETIC	HYPERTENSION	8.4	7.1	2.37	64	4.3	136	4.2	NORMAL	NEGATIVE	10	NO	NO
50	215595	60	M	5	DIABETIC	HYPERTENSION	10.2	5.01	2.49	57	4.2	133	4.8	NORMAL	POSITIVE	11	YES	YES
51	254318	26	F	5	NON DIABETIC	HYPERTENSION	9.6	6.9	2.91	67	2.9	132	3.9	NORMAL	POSITIVE	5.2	YES	NO
52	361273	29	M	5	NON DIABETIC	HYPERTENSION	8.2	7.2	2.94	74	3.5	128	4.6	NORMAL	NEGATIVE	5.4	NO	YES
53	213122	66	F	5	DIABETIC	HYPERTENSION	5.8	7.25	1.67	85	4.2	139	4.3	NORMAL	POSITIVE	6.6	YES	NO
54	201260	77	F	5	DIABETIC	HYPERTENSION	7.4	9.02	1.63	48	3.2	134	4.6	NORMAL	NEGATIVE	7	NO	NO
55	218192	60	F	5	DIABETIC	HYPERTENSION	8.4	8.9	2.49	56	3.1	130	4.1	NORMAL	NEGATIVE	7.2	YES	NO
56	316423	30	F	5	NON DIABETIC	HYPERTENSION	7.9	7.01	2.64	76	4.3	132	3.8	NORMAL	NEGATIVE	5.5	NO	NO
57	218763	58	M	5	DIABETIC	HYPERTENSION	5.9	9.03	1.86	48	4.2	134	4.2	NORMAL	POSITIVE	7	YES	YES
58	314562	50	M	5	NON DIABETIC	HYPERTENSION	6.5	10.2	1.74	67	4.2	125	4.6	NORMAL	NEGATIVE	5.5	NO	YES
59	165235	44	M	5	NON DIABETIC	HYPERTENSION	9.1	8.09	2.34	45	2.3	140	4.8	NORMAL	POSITIVE	5.7	YES	NO
NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO