Burden of Tuberculosis in stage 5 chronic kidney disease patients undergoing maintenance haemodialysis therapy in governmental and non-governmental dialysis centers in Addis Ababa, Ethiopia: A cross-sectional study

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APPROVAL SHEET

ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE, POSTGRADUATE PROGRAM

I, Dr. Eyob Beyene, hereby declare that this thesis entitled "Burden of Tuberculosis in stage 5 chronic kidney disease patients undergoing maintenance haemodialysis therapy in all governmental and non-governmental dialysis centers in Addis Ababa, Ethiopia: A cross-sectional study" in line with the requirement of graduate studies was fully undertaken by me under the guidance of my advisors and that I have, to the best of my knowledge and effort, avoided plagiarism or duplication of materials unless and otherwise cited and/or acknowledged and that it has not been so far submitted for any form of publication or consideration before the final approval.

Principal investigator	Signature	Date

We hereby certify that we have read and evaluated this research thesis relating to "Burden of Tuberculosis in stage 5 chronic kidney disease patients undergoing maintenance haemodialysis therapy in all governmental and non-governmental dialysis centers in Addis Ababa, Ethiopia: A cross-sectional study" under our guidance from its inception up to in its current format and that it can be submitted for final approval in partial fulfillment to the Certificate of subspecialty in infectious disease.

Advisor	Signature	Date

As a member of the research open defence examination, I certify that I have read and evaluated the thesis prepared by Dr. Eyob Beyene (MD), and examined the candidate. I recommend that the thesis be accepted as fulfilling the thesis requirements for the Certificate of subspecialty in infectious disease.

Examiner	Signature	Date

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Abbreviations / Acronyms

AAU- Addis Ababa University

BP- Blood Pressure

CHS- College of Health Sciences

CKD- chronic kidney disease

CVD- cardiovascular disease

DM- Diabetes Mellitus

EPTB- Extrapulmonary Tuberculosis

ESRD- End Stage Renal Disease

HD- Hemodialysis

HF- Heart Failure

MDRD- Modification of Diet in Renal Diseases

NCD- Non-Communicable Diseases

NGOs- Non-Governmental Organizations

PTB- Pulmonary Tuberculosis

RCTs- Randomized controlled Trials

SOM- School of Medicine

TASH- Tikur Anbessa Specialized Hospital

TB- Tuberculosis

WHO- World Health Organization

ABSTRACT

Background
Patients with End stage renal disease appear to be at a higher risk of TB due to immunosuppression along with socioeconomic, demographic, and comorbidities. Despite high burden of Tuberculosis in developing countries, there is a scarcity of data regarding burden of TB in ESRD in Ethiopia.

Objective
The objective of this study is to assess the burden of TB in End stage renal patients receiving haemodialysis in Addis Ababa, Ethiopia.

Method
A cross-sectional study was conducted on Burden of Tuberculosis in stage 5 chronic kidney disease patients undergoing maintenance hemodialysis therapy in governmental and non-governmental dialysis centers in Addis Ababa, Ethiopia from August 2022 to October 2022 G.C. Patients with a baseline diagnosis of ESRD on HD and age 18 years and above were included in the study. Patients were recruited during their dialysis visit using convenient sampling method and consent was obtained from all participants. A total of 263 participants were included in this study. The diagnosis of ESRD and TB was defined using KDGIO and WHO guidelines. Data were collected through patients interview and reviewing the patient's electronic medical records. The Collected Data was analyzed using SPSS version 26.0.

Results
Our study found a diagnosis of tuberculosis in 71 (27%) of study participants. Among the study participants who was diagnosed with TB, 64 (24.3%) had a previous diagnosis of TB and 12 had active TB.Pulmonary tuberculosis was diagnosed in two-third of TB patients and about third had EPTB, TB lymphadenitis was the commonest followed by pleural TB. Imaging evidence was used to make a diagnosis of TB in one-third patients followed by FNAC (26.6%) and Pleural fluid analysis (26.6%). More than half (54.7%) of TB diagnosis was made after initiation of haemodialysis. More than half (54.7%) of TB diagnosis was made after initiation of haemodialysis. Having a contact history with a known TB patient, presence of HIV infection and duration on dialysis for more than 1 year were associated with increased prevalence of TB among CKD patients.

Conclusions
Because of its atypical presentation and since it is a mimicker of uremic symptoms, physicians should maintain a high degree of suspicion to consider TB among CKD patients. Early identification and treatment of TB among CKD patients is important in decreasing morbidity and mortality among these patients and in decreasing the transmission of TB among patients who undergo dialysis in the same center. TB preventive therapy should also be considered for this group of patients

Keywords: Tuberculosis, End stage renal disease, chronic kidney disease, dialysis, Addis Ababa

Contents

1. Introduction

1.1 Background

Tuberculosis (TB) is a communicable disease which was the leading cause of death from a single infectious agent until the corona virus (COVID 19) pandemic. TB is caused by the bacillus mycobacterium tuberculosis. These bacteria are spread by droplets which are expelled from people sick with TB (e.g., while coughing.). TB is curable and preventable. About 85% of people who develop TB disease can be successfully treated with six months drug regimen [1, 2].

In 2014 and 2015, all member states of the WHO and the United Nations (UN) committed to ending TB epidemic through their adoption of WHO's End TB strategy and the UN Sustainable Development Goals (SDGs). The End TB strategy milestone for reducing TB disease burden in 2020 were a 35% reduction in the number of TB deaths and a 20% reduction in TB incidence rate, compared to 2015. But the COVID 19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. Global TB targets are mostly off-track, although there are some country and regional success stories. Six high TB burden countries (Ethiopia, Kenya, Namibia, South Africa and the United Republic of Tanzania) are among the countries which achieved the 20% reduction in TB incidence rate milestone between 2015 and 2020 [1].

TB can affect anyone anywhere. It is believed that a quarter of the world's population is infected with M. Tuberculosis. Once an aerosol droplet containing M. Tuberculosis is inhaled and deposited in the lungs, one of the four outcomes are possible.

- Immediate clearance of the organism
- Primary disease: immediate onset of active disease
- Latent infection
- Reactivation disease: onset of active disease many years following a period of latent infection.

A relatively small proportion of (5-10%) will develop TB disease during their lifetime. However, the probability of developing TB disease is much higher among people living with HIV and among people affected by risk factors such as undernutrition, diabetes, smoking, alcohol consumption and poverty. In addition, chronic and end stage kidney disease, malignancies, corticosteroid use, usage of TNF-alpha inhibitors and age are mentioned as immunosuppressive stated which are associated with TB reactivation [1,3, 4].

1.2 Statement of the problem

The global incidence of TB peaked around 2003 and appears to be declining slowly. According to WHO, in 2020, 9.9 million individuals became ill with TB and 1.5 million died.

Highest rates of TB incidence are noted in sub-Saharan Africa, India and the islands of Southeast Asia and Micronesia. Poverty, HIV and drug resistance are major contributors of resurging global TB epidemic. Approximately 95% of TB cases occur in resource limited countries. In addition, immunosuppressive states are proven to be associated with development of active TB and reactivation. One of these immunosuppressive states is chronic kidney disease [1,2, 4].

Chronic Kidney disease (CKD) is a worldwide public health problem. The number of patients enrolled in the end-stage renal disease (ESRD) care is increasing every year. Globally, the estimated overall prevalence of CKD is 8% to 16%, and this nearly corresponds to more than 500 million individuals, of whom 78% reside in low to middle income countries. In sub-Saharan Africa, CKD more commonly affects individuals between the age of 20 – 50, and the age of onset for ESRD is 20 years earlier in population of African descent compared with other ethnic groups. Globally the leading causes of CKD and ESRD are diabetes (30 – 50%) and hypertension [20, 21].

Both early stages of CKD and ESRD are associated with high morbidity, mortality and increased health care utilization. Infections are major contributors to the morbidity and mortality. They are among the leading cause of hospitalizations and the third most common cause of mortality just after cardiovascular diseases and treatment withdrawal. Tuberculosis is one of the serious bacterial infections in CKD [6,7,20, 21].

The link between chronic kidney disease (CKD) and tuberculosis (TB) has been known for more than 40 years, but the interaction between these two diseases is still poorly understood. Dialysis and renal transplant patients appear to be at a higher risk of TB, in part related to immunosuppression along with socioeconomic, demographic, and comorbidities [6,7, 8].

Individuals with CKD especially those with ESRD on haemodialysis are at increased risk of progression to active disease once infected by Mycobacterium Tuberculosis. It is reported that there is a 6.9- to 52.5-fold increase in the incidence of TB in dialysis patients compared to the general population, which results from uremic immunodeficiency [7]. Additionally, a higher rate of primary infection due to regular visits to dialysis units, advanced age, and immunosuppressive medication may further increase the risk of infectious complications in these particular immunocompromised patients [6, 8].

TB diagnosis is more complex and difficult in haemodialysis patients because of an increased frequency of extrapulmonary TB, atypical clinical presentation, and non-specific symptoms and findings. Extrapulmonary TB has been reported in as many as 60% to 80% of cases, either alone or associated with pulmonary TB. The most common forms of presentation are lymphadenitis, gastrointestinal, bone, genitourinary, peritonitis, pleural effusion, pericardial effusion, miliary TB, and fever of unknown origin [6,7,16, 17]. On the other hand, uraemia is commonly associated with fatigue, malnutrition, and other nonspecific complaints, possibly

concealing the course of an underlying TB disease. This atypical presentation may often lead to a delay in accurate diagnosis and therapy, sometimes resulting in patients' death. Therefore, high degree of suspicion with consideration of possibility of TB whenever confronted with an ESRD patient presenting with general symptoms such as fever, weight loss, and/or lymphadenopathy is needed [10,11, 12].

The prevalence of latent TB infection (LTBI) in CKD is patients is also high, ranging between 20% and 70%, and those who become infected are at high risk of developing active disease. Therefore, screening for LTBI in this population is recommended, aiming to prevent progression to active TB and secondary contamination of other patients and healthcare workers. It has been shown that preventive treatment of latently infected people diminishes the risk of subsequent development of active TB by approximately 90% in different population groups [4, 10].

Ethiopia is one of the countries hardly hit by TB. The 2021 Global TB report puts Ethiopia as one of the countries with high TB and HIV associated TB burden countries in the period 2021 – 2025. (1) Though there are no population-based studies done on prevalence, causes and outcomes of CKD, population-based surveys on non-communicable diseases (NCDs) indicates that major risk factors of CKD are growing in the country. There are around 800 patients on maintenance hemodialysis, spread across 25 small centers in the country. Both number of patients requiring maintenance hemodialysis and the number of dialysis center are increasing by the day. Despite the growing burden of TB and CKD, Data about their effects on morbidity and the mortality in Ethiopian patients is lacking [9].

1.3 Justification of the study

The link between active TB and chronic kidney disease CKD was first reported in a 1974 case series involving dialysis patients.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.This association is thought to be driven by the immunosuppressed state of the dialysis population.Socioeconomic, demographic, and comorbidities also play significant additional roles in increasing the morbidity [5, 6].

There are also many additional factors that can be mentioned for high TB burden in CKD. One is high prevalence of latent TB infection (LTBI) in CKD patients [6]. These patients are at high risk of developing active disease. Other factor is TB diagnosis being more complex and difficult in CKD patients. This is mostly because of an increased frequency of extrapulmonary TB, atypical clinical presentation, and non-specific symptoms and findings. TB screening and diagnostic test performance is suboptimal in the CKD population, and there is limited evidence to guide protocols [6,10,16].

With the reported 6.9- to 52.5-fold increase in the incidence of TB in dialysis patients compared to the general population, the mortality rate is also high, ranging from 17% to 75% [7, 22]. In the US Renal Data System analysis, TB was independently associated with a 42% increased mortality [5, 7].

Given the increasing prevalence of CKD in TB endemic areas, a merging of CKD and TB epidemics could have significant public health implications, especially in low- to middle-income countries. Being one of the high burden countries for TB and HIV associated TB, Ethiopia's case is no different. Estimated incidence of drug sensitive TB is around 164 per 100,000 population and the mortality was 22 per 100,000 population; which is one of the highest in the world. With the increasing prevalence of NCDs, both CKD and tuberculosis incidence is expected to go higher [1, 9].

There are many measures put to use for prevention of tuberculosis. One of these methods is TB preventive therapy (TPT). TPT is given to people at highest risk of progressing from TB infection to disease. People living with HIV, household contacts patient with active TB, people receiving anti-TNF treatment, receiving dialysis, preparing for organ transplantation and those with silicosis are group of individuals recommended to undergo Latent TB infection testing and TPT by the WHO [2]. Ethiopia has ample experience in TPT in people living with HIV and is proven to effective. There are no data showing the experience of TPT in other group on individuals including patients with ESRD in Ethiopia.

The aim of this study is to assess the burden of TB in End stage renal patients receiving hemodialysis in Addis Ababa, Ethiopia.

1.4 Significance of the study

Despite the commitments of the WHO, regional and national health organizations, both TB and CKD remain to be major public health problems of our planet. TB is implicated in increasing morbidity and mortality in patients with CKD. Atypical presentation of TB and poor performance of screening and diagnostic modalities in CKD patients adds more to the problem at hand. TPT is one of the promising TB preventive tools in patients receiving dialysis. We believe that this study will provide us with a data on TB burden in ESRD patients receiving dialysis patients in Ethiopia and serves as a base for further preventive, diagnostic or therapeutic recommendations.

2. Literature review

Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. Most people (about 90%) who develop the disease are adults, with more cases among men than women. About a quarter of the world's population is infected with M. tuberculosis. TB is curable and preventable. About 85% of people who develop TB disease can be successfully treated with a 6-month drug regimen and regimens of 1–6 months can be used to treat TB infection [1].

Patients with ESRD are much more prone to develop TB than the general population. Studies reported a 6 – 25 times increased risk as compared to the general population mainly because of impaired cellular immunity in ESRD. Other factors mentioned are nosocomial transmission, high latent TB prevalence in ESRD, age groups affected, racial factors, smoking, low body mass index, low serum albumin, ischemic heart disease and anemia [5, 7]

A retrospective study conducted in 2006 on 272,024 patients from the US renal data system analysed 21 risk factors contributing for morbidity and mortality of TB in dialysis patients. Though the cumulative incidence of TB disease found was 1.2 – 1.6%, which was far lower than the world-wide rates, TB was found to be independently associated with increasing mortality, adjusted hazard ratio 1.42 (95% CI 1.18 – 1.70, $P < 0.001$). Other studies also reported a mortality rate of 17 – 75% for TB in dialysis patients [5].

Symptomatology of TB in dialysis patients has always been hinderance to early diagnosis and treatment. Late diagnosis in TB is directly related to increased mortality. Symptoms are mostly insidious, non-specific and mimicking uremic symptoms whereas localization are often extrapulmonary (60 – 80%). It is highly recommended that physicians be aware of the unusual presentations and have a high index of suspicion especially in countries with high TB prevalence. (17) Tuberculosis peritonitis makes up more that 50% of total number of TB cases in continuous ambulatory peritoneal dialysis (CAPD) patients while TB lymphadenitis, gastrointestinal and bone TB dominates in overall dialysis patients [7,12, 22].

A retrospective study done in Saudi Arabia in 2006 assessed 256 patients and found 18 patients diagnosed and managed for TB over a period of 10 years. In this study extrapulmonary TB was more common (77.8%) than pulmonary TB (22.2%). From the extrapulmonary ones lymphadenitis, gastrointestinal and genitourinary were the leading forms. Fever of unknown origin was also reported in 5.6% of the patients as a presentation of TB [12].

Another study from Turkey evaluated the frequency and clinical progression of TB in 18 of 343 dialysis patients diagnosed with TB over a period of five years in a university hospital.

This study also noted that extrapulmonary TB (> 75 %) predominates in dialysis patients [18]. High prevalence of TB in CKD is not only reported in countries.
United Kingdom bases study reported a 100-fold greater incidence of TB in dialysis patients as compared to the general population of England and Wales. Part of the explanation given was the impact of international migration. But symptomatology of TB and late diagnosis has also contributed for the morbidity and transmission rate [14].

A study which included stage 3 -5 CKD patients in UK found out that incidence of TB was higher amongst patients with CKD compared to those without CKD: 14.63 and 9.89 cases per 100,000 person-years. After adjusting for age, gender, ethnicity, socio-economic status, diabetes and COPD, the association between CKD and TB remained adjusted rate ratio [RR] 1.42 (95% confidence interval 1.01–1.85) [11].

In Asian countries like Nepal, a 2020 study in a university hospital in Kathmandu also revealed the association between TB and CKD. The study included patients starting from stage 3. The prevalence of TB was found to be 13.7% out of which 89% were diagnosed new cases. Mortality was 28.6% at two months. Out of the patients diagnosed with TB 63% were patients on dialysis [15].

A Single center retrospective cohort study conducted in one of the high TB burden countries in Africa, South Africa studied 111 patient receiving dialysis. Of these patients nineteen patients were diagnosed with 20 episodes of TB. This center had an incidence rate 4.1 times that of the local population and >5 times that of the general South African population [13].

Country of birth appears to be a particularly important TB risk factor in dialysis populations. In a recent national registry study from Australia, TB incidence was estimated at 18 per 100,000 per year in dialysis patients born in low TB incidence countries and 698 per 100,000 per year in those born in the highest TB incidence countries. This is consistent with the notion that active TB results from reactivation of LTBI acquired before dialysis initiation rather than from recent exposure and infection. That said, hemodialysis patients with active TB do pose a substantial risk to other patients and health care workers in hemodialysis units, particularly given the frequency and proximity of shared air space. Without effective screening and active TB case detection, dialysis and renal units can serve as means of ongoing TB transmission [6,24, 25].

In Ethiopia, both number of dialysis patients and center are steadily rising [9]. But lack of national kidney care data registry has made it difficult to track the exact number. According to WHO's report, the incidence of drug sensitive TB in Ethiopia is 164 per 100000 population. Though the number is steadily decreasing from the previous reports, it is still one of the highest in the world [1]. Published studies of TB in CKD patients in Ethiopia were not

available but indirect evidences and different centres' experiences imply high prevalence of TB in the CKD patients in the Ethiopian population.
Another factor contributing to high TB incidence in dialysis patients is high prevalence of latent TB infection (LTBI). In 1999 WHO estimated that one-third of world's population had LTBI. However, this was based on a controversial assumption in combination with Tuberculin Skin Tests (TST) surveys. Interferon-ɣ release assays (IGRA), which do have higher specificity than TST, has never been used to estimate global LTBI prevalence [7,12].

A systematic review and meta-analysis of LTBI estimates based on both TST and IGRA results published between 2005 & 2018, showed a global prevalence of 24.8% and 21.2% based on IGRA and 10 mm TST cut off respectively. This prevalence correlates well to WHO's reported incidence rate. In some areas prevalence of LTBI reaches to more than 70 % and those who are infected are at high risk of developing active TB [23].

In the US, CDC reported a maximum of 5% prevalence of LTBI in the US population [28]. In the Middle East&North Africa, a recent systematic review reported 41.78% prevalence of LTBI [26]. In Sub-Saharan Africa, though cumulative prevalence of LTBI is still under study, Studies done in South Africa reported 34.3% prevalence in the urban population and 89% prevalence among gold miners, which are one of the vulnerable groups [27, 30].

Latent TB prevalence rate were also reported to be high (48% - 84%) in health care workers in South Africa [29]. In Ethiopia, studies done in Southern pastoral communities & prisoners in Eastern Wollega reported a 50.5% & 51.2 % prevalence of LTBI respectively [31, 32].

Screening for LTBI in the population is important in preventing progression to active TB and secondary transmission to others. Tuberculin Skin Test (TST), which is a classic diagnostic tool for LTBI, has several drawbacks especially in dialysis patients. The main drawbacks are related with poor sensitivity and specificity. Poor sensitivity is related with high prevalence of anergy in dialysis patients. Studies reported as high as 50% anergy in dialysis patients. Poor specificity of TST is related to false positivity due to BCG vaccination. The new immunological testes use Interferon-ɣ release assays (IGRA). These tests are available and have shown better sensitivity and specificity for the diagnosis of TB as compared to TST in dialysis patients [6, 10, 19]. Currently IGRAs in combination with medical assessment are recommended for LTBI screening in dialysis patients than TST [10].

It has been shown that preventive therapy of lately infected people diminishes the risk of subsequent development of active TB by approximately 90%. Prevention of active TB disease by TB preventive therapy (TPT) is a critical component of WHO End TB Strategy and efforts to eliminate TB. The efficacy of currently available TPT reaches 90%. Most experiences of TPT are from people living with HIV/AIDS. The 2020 WHO consolidated guideline of

Tuberculosis has included peoples receiving dialysis as one of the groups who benefits from LTBI testing and TPT [2].

3. Objective

General

To determine the burden of Tuberculosis in ESRD patients receiving hemodialysis in Addis Ababa, Ethiopia from August 2022 to October 2022 G.C

Specific

- ✓ To measure the incidence of Tuberculosis in ESRD patients receiving hemodialysis in Addis Ababa, Ethiopia.
- ✓ Assess the current prevalence of Tuberculosis in ESRD patients receiving hemodialysis in Addis Ababa, Ethiopia.
- ✓ Identify risk factors associated with TB infection in ESRD patients receiving hemodialysis in Addis Ababa, Ethiopia.
- ✓ Characterize the type of Tuberculosis infection in ESRD patients receiving hemodialysis in Addis Ababa, Ethiopia.

4. Methods and Materials

4.1 Study location and Period

Until September 2021, there were 35 haemodialysis centers in Ethiopia. Out of these, 11 were governmental while the rest were private owned. 23 out of these 35 centers are located in Addis Ababa, the capital city. The study was conducted indialysis centers (both governmental and non-governmental) located in Addis Ababa, Ethiopia.

4.2 Study Period

The study was conducted from August 2022 to October 2022 G.C.

4.3 Research design

Cross-sectional Study

4.4 Study population

All Stage 5 CKD patients on haemodialysis ingovernmental and non-governmental haemodialysis centers in Addis Ababa were used as a source and study population.

4.5 Inclusion criteria

- Stage 5 CKD on maintenance hemodialysis
- Age >/= 18

4.6 Exclusion criteria

- Diagnosis of tuberculosis before the diagnosis of CKD
- Patients with incomplete medical records and those who are unable to provide the appropriate information
- Patients with mental health problems
- Critically ill patients
- Those who cannot provide consent

4.7 Sample size estimation

The sample size was calculated by single population proportion formula based on the results of a study conducted at inner-city biomedical research laboratory in Berlin with a biosafety level 3 facility showed a 20% prevalence of tuberculosis among CKD patients.[33]

The sample size (n) is calculated according to the following formula:

$$n = \frac{z^2_{1-\alpha/2}}{d^2} p(1-p)$$

z = 1.96 for a confidence level (α) of 95%,

P = proportion

d = margin of error

z = 1.96, p = 0.2, d= 0.05

n = 246

Considering a 10 % non-response rate, the final sample size will be 273.

4.8 Sampling method and procedure

The study participants were selected using convenient sampling method. All patients on dialysis at government and non-government setups was included during the study period.

4.9Variables

Dependent Variables

- ✓ Current or Past diagnosis of tuberculosis

Independent Variables

- ✓ Socio-demographic characteristics: Age, Sex, Residence, Religion, Occupation, Monthly income, Marital Status, Educational Status
- ✓ Clinical characteristics:Cause of ESRD, Duration of ESRD,contact history with known TB patient, Presence of HIV infection, Comorbidities, Smoking history
- ✓ Treatment related characteristics: Duration on dialysis, Frequency of dialysis per week, Use of TB prophylaxis, Use of immunosuppressive therapy

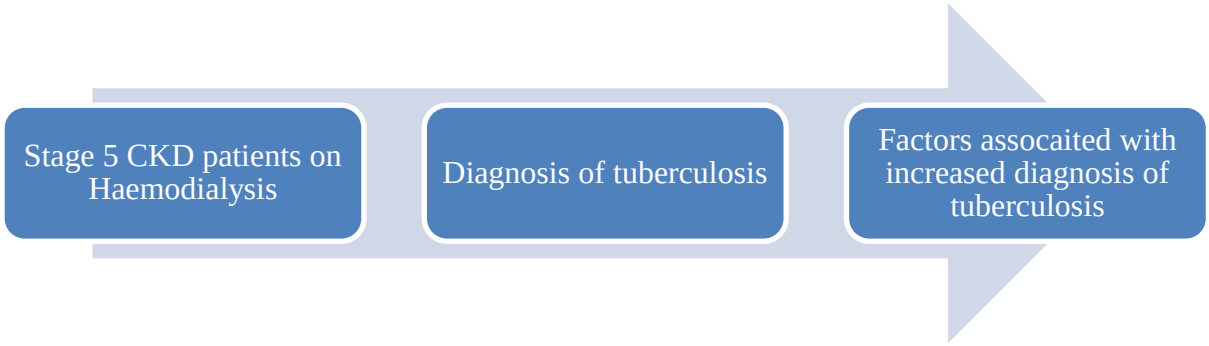
4.10 Operational definitions

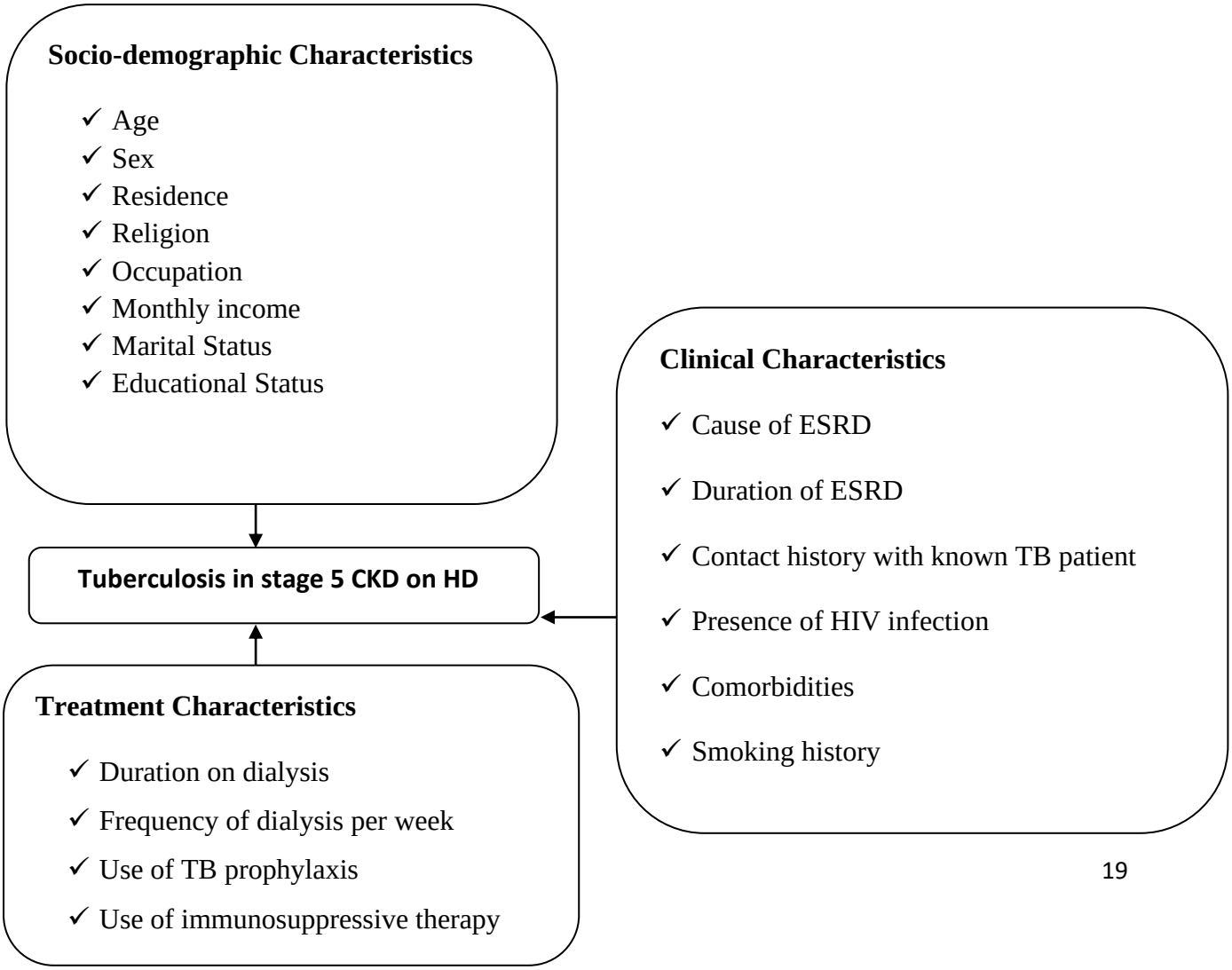
Chronic Kidney Disease is defined as abnormalities of kidney structure or function, present for >3 months, with implications forhealth (KDIGO 2012 CKD guideline)

End Stage Renal Diseaseis defined as glomerular filtration rate<15 mL/min per 1.73 m2 or treatment by dialysis ((KDIGO 2012 CKD guideline)

Diagnosis of Tuberculosis is established by signs and symptoms of TB (cough with/without hemoptysis, night sweat, fever, and weight loss), Imaging evidences (X-ray, CT-scan), Molecular tests (Xpert MTB/RIF Ultra and Truenat assays), Urine LAM in HIV patients, AFB and culture from different specimens.

4.11. Conceptual framework





4.12.Data collection method

After explaining the purpose of the study, informed written consent was obtained from all participants. Data were collected through patient interviews and a review of patient's medical records.

4.13.Data analysis procedures

The collected data was verified, cleaned, and checked for quality before the analysis. The IBM SPSS Statistics software package version 26 was used for the entry of statistical data and analysis. Descriptive statistics was used as a statistical data analysis method and was expressed as frequencies and numbers (percentages %) for categorical variables. The results were summarized by using tables, and figures. Continuous variables were represented as means, standard deviations, and minimum and maximum values, and categorical variables as frequencies. Multicollinearity was assessed among independent variables using the variance inflation factor (VIF) and none was collinear. Univariable logistic regression analysis was performed to determine the association of each independent variable with the increased diagnosis of tuberculosis. Furthermore, a multivariable binary logistic regression model was done to identify predictors of Tuberculosis diagnosis. P-values less than 0.05 are considered to determine the statistical significance of the association and an odds ratio with a 95% confidence interval is used to determine the presence, strength, and direction of association between covariates and the outcome variable.

4.14. Ethical Clearance

The study was conducted after approval of proposal by ethical review committee of Internal Medicine Department, and then approved ethical institutional review board of Addis Ababa University, College of health sciences. An informed consent was obtained from each respondent to participate in the study. Detail explanation about objectives, purposes and benefit of the study was given to the respondents. Confidentiality was assured before conducting data collection and data collectors was trained and oriented.

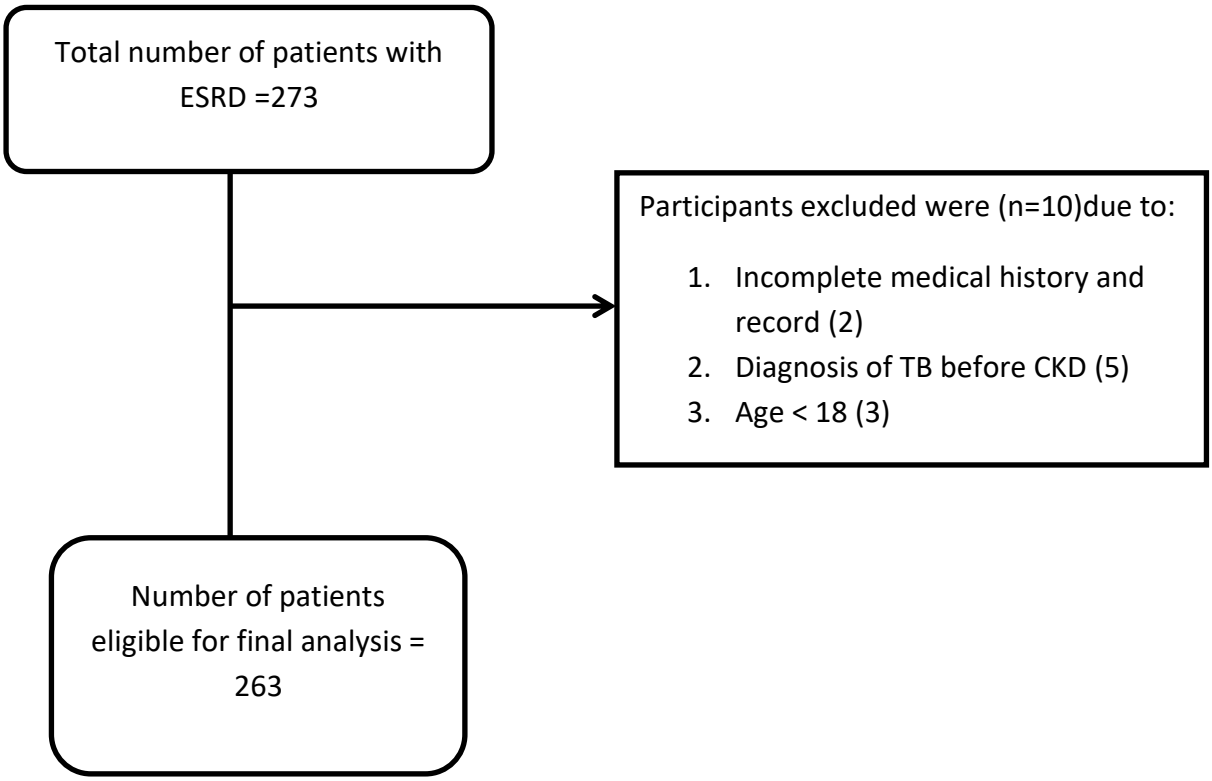
4.15. Dissemination of the results

Finally copy of the result will be disseminated to relevant authorities and to whom that needs the information as base line for further study. The result will be presented in meeting to concerned government & non-Government organizations. It will be Published in Local and International Journals. Also copy will be placed in the library as references.

5. Results

5.1 Statistical Analysis

During the study period, a total 273 patients with ESRD were approached during their visit to the dialysis center. Among them, 263 (97.4%) met the inclusion criteria and were included in the final analysis making a response rate of 100%.



5.2. Sociodemographic profiles

The mean [± standard deviation] age of the participants was 43.8 ± (15.96) with minimum and maximum ages of 18 and 88 respectively. Two-thirds participants were male. Themajority (87%) of the participants resided in Addis Ababa. About two-third of the participants were married and more than half were Orthodox Christian.

The Sociodemographic data are shown in Table 1 below.

Table 1: Sociodemographic characteristics of study participants at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n= 263)

Characteristics		Number (n)	Percentage (%)
Sex	Male	166	63.1
	Female	97	36.9
Residence	Addis Ababa	228	86.7
	Out of Addis Ababa	35	13.3
Religion	Orthodox	143	54.4
	Muslim	78	29.7
	Protestant	36	13.7
	Catholic	6	2.3
Marital Status	Single	78	29.7
	Married	160	60.8
	Divorced	14	5.3
	Widow	11	4.2
Educational Status	Ilitrate	7	2.7
	Read and write only	15	5.7
	Primary School	34	12.9
	Secondary School	65	24.7
	College or University	142	54
Occupation	None	4	1.5
	Student	34	12.9
	Housewife	42	16
	Farmer	6	2.3

	Self-Buisness	42	16
	Government employee	75	28.5
	Retired	41	15.6
	Other	19	7.2
Monthly Income	None	20	7.6
	< 1000	26	9.9
	1000-3000	27	10.3
	3000-5000	80	30.4
	5000-10,000	76	28.9
	> 10,000	34	12.9

5.3.Clinical and treatment related characteristics

The mean [± standard deviation] duration of follow up for ESRD of the participants was 3.77 ± (3.03) with minimum and maximum duration of 01 month and 17 years respectively. More than two-third of the participants were on follow-up for more than a year. About third of patients did not have identified documented cause of ESRD. Diabetes was responsible for one-third of ESRD cases and the other third was due to hypertension. About two-third of the participants were on dialysis for more than a year. The mean [± standard deviation] duration on dialysis was 3.23 ± (2.59) with minimum and maximum duration of 01 month and 11 years respectively and more than half of the participants undergo dialysis three times a week.

About 78% of participants had comorbidities and one-quarter of participants had more than one comorbidity. Hypertension was the commonest comorbidity identified in 166 (63.1 %) patients followed by diabetes in 86 (32.7 %). 53 (20.2 %) patients had both diabetes and hypertension. HIV and CLD were found in 18 and 3 participants, respectively.

The mean [± standard deviation] follow-up for treatment of HIV among HIV positive patients was 8.83 ± (4.7) with minimum and maximum duration of 2 and 17 years respectively. The mean [± standard deviation] CD4 count among HIV positive patients was 209 ± (135) with minimum and maximum CD4 of 86 and 500 years respectively. ABC + 3-TC + EFV was the most commonly used regimen. Among HIV patients 50% had history of Tuberculosis prophylaxis use.

23 participants had history of smoking and 4 were on immunosuppressive therapy. One-third of the participants were underweight and more than two-third had a normal BMI.

The Clinical and Treatment Related Characteristics are shown in Table 2 and Figure 1 and 2 below.

Table 2: The Clinical and Treatment Related Characteristics of study participants at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n= 263)

Characteristics		**Number (n)**	**Percentage (%)**
Mean duration of follow up for ESRD in Year (+/- SD)		3.77 ± 3.03	
Documented Cause of ESRD	Unknown	78	29.7
	Diabetes	79	30
	Hypertension	77	29.3
	CGN	16	6.1
	Obstructive Uropathy	6	2.3
	HIV	3	1.1
	CIN	2	0.8
	PCKD	2	0.8
Mean duration on hemodialysis (+/- SD)		3.23 ± (2.59)	
	Twice	115	43.7
	Thrice	148	56.3
Comorbidities	Hypertension	166	63.1
	Diabetes	86	32.7
	HIV	18	6.8
	Heart Failure	4	1.5
	CLD	3	1.1
History of Smoking		23	8.7
BMI	Underweight	80	30.4

	Normal Range	158	60.1
	Overweight	22	8.4
	Obese	3	1.1
On Immunosuppressive Therapy		4	1.5
TB prophylaxis Use		9	3.4
Contact History		34	12.9

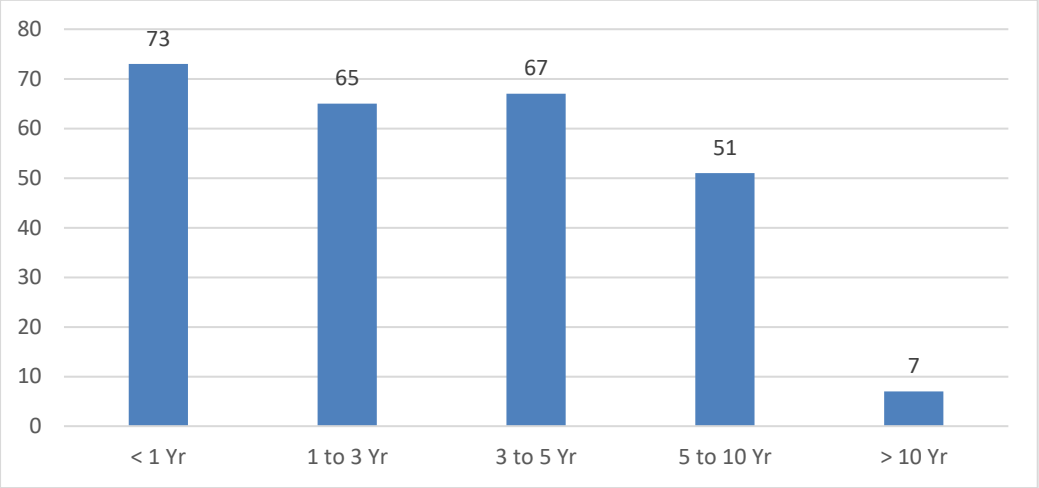


Figure 1: Distribution of duration of follow up in year among patients with ESRD at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=263)

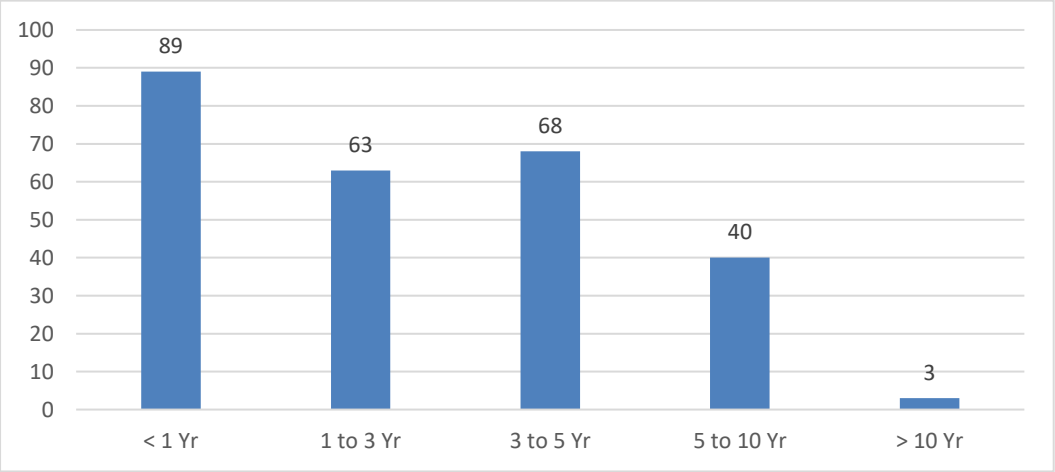


Figure 2: Distribution of duration on dialysis in year among patients with ESRD at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=263)

5.4. Tuberculosis diagnosis and treatment related characteristics

Among 263 participants 71 (27 %) had diagnosis of tuberculosis. 64 (24.3 %) had pervious history of tuberculosis. Pulmonary tuberculosis was diagnosed in two-third of TB patients and about third had EPTB, TB lymphadenitis was the commonest followed by pleural TB. Imaging evidence was used to make a diagnosis of TB in one-third patients followed by FNAC (26.6%) and Pleural fluid analysis (26.6%). Clinical diagnosis of TB was made only in two patients. More than half (54.7%) of TB diagnosis was made after initiation of haemodialysis. All participants with diagnosis of TB were received first-line anti-TB and only one had treatment failure.

Active TB was found in 12 patients and among them 5 had previous history of TB. Pulmonary TB accounted for 66 % of participants. Again, imaging evidence was the commonest modality to make a diagnosis of TB followed by sputum and cytology evidences. All patients with active TB were receiving first-line anti-TB.

TB diagnosis and treatment related characteristics are shown in Table 3 and 4 and Figure 3 and 4 below.

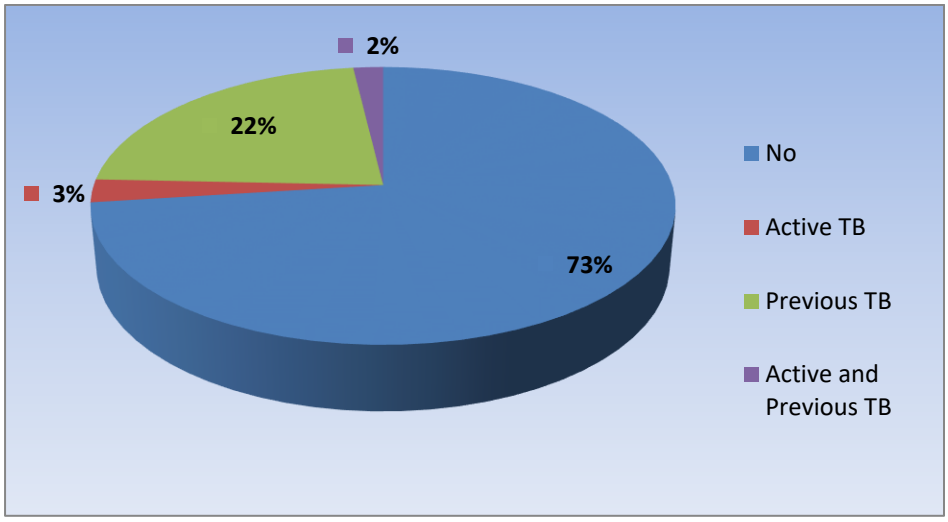


Figure 3: TB diagnosis in Patients with ESRD at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=263)

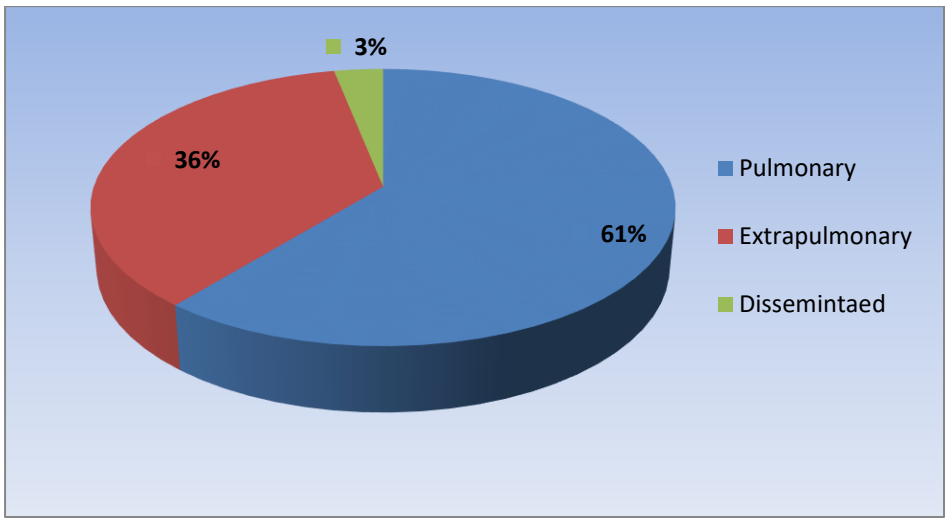


Figure 4: Types of TB in Previously Diagnosed Patients at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=64)

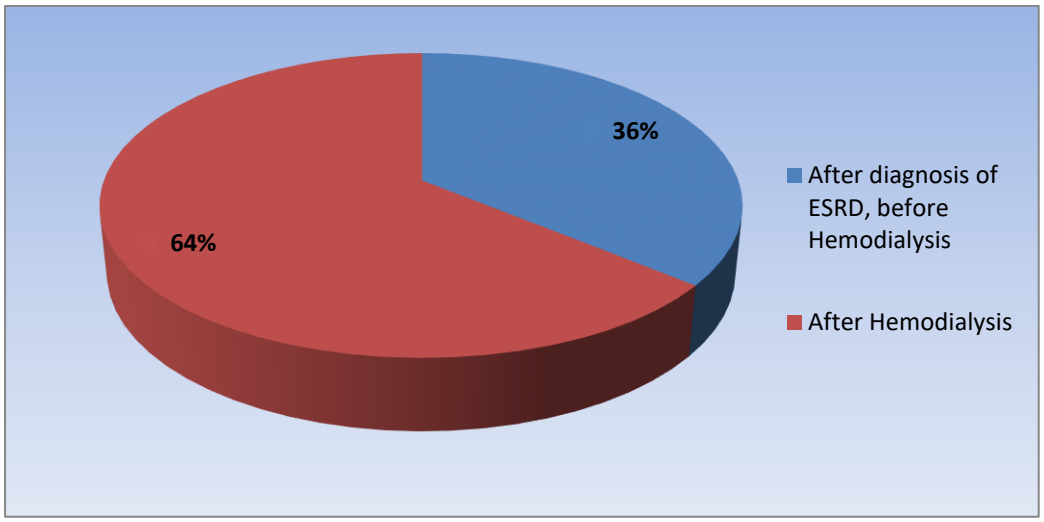


Figure 5: Timing of TB diagnosis in Patients with ESRD at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=71)

Table 3: Previous TB diagnosis, type, and treatment related Characteristics of study participants at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=64)

Previous TB Characterstics		**Number**	**Percentage**
Type of TB	Pulmonary	39	61
	EPTB	23	35.9
	Disseminated	2	3.1
Diagnostic Modality	Imaging	19	29.7
	FNAC	17	26.6
	Pleural Fluid Analysis	17	26.6
	Cytology	5	7.8
	Sputum Exam	4	6.2
	Clinical Judgment	2	3.1
Timing of diagnosis	After CKD, before HD	23	32.4
	After HD initiation	48	67.6
Treatment Outcome	Improved	63	98.4
	Failed	1	1.6

Table 4: Current TB diagnosis, type, and treatment related Characteristics of study participants at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=12)

Current TB Characterstics		**Number**	**Percentage**
Type of TB	Pulmonary	8	66.7
	EPTB	2	16.7
	Disseminated	2	16.6

Diagnostic Modality	Imaging	4	33.3
	FNAC	1	8.3
	Pleural Fluid Analysis	1	8.3
	Cytology	2	16.7
	Sputum Exam	3	25
	Clinical Judgment	1	8.3
Anti-TB Regmen	1st line	12	100

5.5. Factors associated with TB occurrence

Table5 showed the logistic regression analysis of factors associated with increased tuberculosis diagnosis and odd ratio and a 95% confidence interval was used to measure the degree of association between the independent variables and increased tuberculosis diagnosis. Multicollinearity was assessed among independent variables using the variance inflation factor (VIF) and none was collinear. Initially, bivariate binary logistic regression was performed on selected sociodemographic, clinical, and treatment-related characteristics to identify variables candidate for multivariate binary logistic regression and a total of 5 variables were found to be candidates at a *P*-value of ≤0.2.

These include contact history with a known TB patient (Crude odd ratio (COR) 3.241, 95% confidence interval (CI) 1.549-6.781), presence of HIV infection (COR 8.383, 95% CI: 2.868-24.504), presence of comorbidities (COR 1.670, 95% CI: 0.809-3.448), duration on dialysis for more than 1 year (COR 2.341, 95% CI: 1.235-4.439), and dialysis sessions 3 times per week (COR 1.920, 95% CI: 1.084-3.402). However, in the final multivariate regression model, only 3 variables were found to have a statistically significant association with increased tuberculosis diagnosis at a *P*-value of ≤0.05. These included having a contact history with a known TB patient, presence of HIV infection, and duration on dialysis for more than 1 year.

The diagnosis of tuberculosis among participants who had a contact history with a known TB patient was 2.5 times as compared to patients who had not a contact history (Adjusted odd ratio (AOR 2.581, 95% CI: 1.152-5.781, p=0.021).

The study also found a significant association between the presence of HIV infection and diagnosis of tuberculosis, which was 15 times as compared to HIV negative patients (AOR 15.047, 95% CI: 2.841-79.697, p=0.001).

Participants who were on dialysis for more than 01 year had 2.5 times increased TB diagnosis as compared to participants on dialysis for 01 and less year (AOR 2.510, 95% CI: 1.219-5.171, *P*=0.013).

Table 5: Factors associated with TB occurrence among the study participants at haemodialysis centres, Addis Ababa, Ethiopia, August 2022 – October 2022 (n=263)

Variables	Diagnosis of TB		COR (95% CI)	*P value*	AOR (95% CI)	*P value*
	Yes	No				
Contact history with a known TB patient						
Yes	17	17	3.241(1.549-6.781)	0.002	**2.581 (1.152-5.781)**	**0.021**
No	54	175	1	1		
Presence of HIV infection						
Yes	13	5	8.383(2.868-24.504)	0.0001	**15.047 (2.841-79.697)**	**0.001**
No	58	187	1	1		
Presence of comorbidities						
Yes	60	147	1.670 (0.809-3.448)	0.165	1.155 (0.525-2.543)	0.720
No	11	45	1	1		
Duration on dialysis for more than 1 year						
</=1 Year	15	74	1	1		
>1 Year	56	118	2.341(1.235-4.439)	0.009	**2.510 (1.219-5.171)**	**0.013**
Dialysis sessions 3 times per week						
Twice	23	92	1	1		
Thrice	48	100	1.920 (1.084-3.402)	0.025	1.656 (0.888-3.089)	0.113

6. Discussion

Tuberculosis is preventable and curable communicable disease, which is caused by mycobacterium tuberculosis. Ethiopia is one of the high TB burden countries [1, 2]. Infections are one of the major causes of morbidity and mortality in CKD patients. Although TB affects anyone anywhere, patients with CKD are at increased risk of acquiring tuberculous infection and severe disease. Patients with ESRD on HD are at an increased risk of active tuberculosis by 6.9 to 52.5 fold compared to the general population. The clinical presentation and diagnosis of TB is complex and difficult in dialysis patients [6, 7, 8, 21].

Our study found a diagnosis of tuberculosis in 71 (27%) of study participants. This result is higher as compared to previous studies done, 13% in Nepal, 5.2% in Turkey, and 2.4 to 14.5% in Saud Arabia [15, 18, 34]. Among the study participants who was diagnosed with TB, 64 (24.3%) had a previous diagnosis of TB and 12 had active TB. The variation in the rate of TB diagnosis among CKD patients could be due to difference in the setting of study and sample characteristics. The higher prevalence of TB in our study could be due to the delay in the initiation of dialysis which results in prolonged immunosuppression from uremia, higher TB burden among the general population, the overcrowding of dialysis centers and the higher clinical suspicion by treating physicians.

In this study, only one-third of patients were diagnosed with EPTB and TB lymphadenitis was the commonest type followed by pleural TB. This figure shows a lower prevalence of EPTB in our setting as compared to studies. Study done in Nepal showed a diagnosis of EPTB in 69% and pleural effusion was the commonest form of EPTB [15]. Study done in Saud Arabia showed a diagnosis of EPTB in 55.3% and TB lymphadenitis was the commonest type [34]. Another study done in the Saud Arabia showed a 77.8% EPTB diagnosis and lymphadenitis followed by gastrointestinal and genitourinary type was the common forms [12]. The lower rate of EPTB diagnosis in our study could be due to atypical presentation of TB among CKD patients, scarcity of advanced diagnostic tools, and the lower sensitivity of available diagnostic tools for specimens from extrapulmonary site.

The diagnosis of TB among CKD patients is difficult because of atypical presentation of the disease and insidious and non-specific symptoms mimicking uremia [17]. The diagnosis of TB was made by imaging (X-ray or CT-scan) evidence in about third of patients followed by FNA and pleural fluid aspiration. This is comparable with study from Saud Arabia in which the diagnosis of TB was made by X-ray in 55.3% followed by lymph node biopsy in 22% of study participants [34]. Microbiologic evidence from sputum was found only in 4.1% of participants in the Nepal study [15].

In this study, three variables were found to be associated with the higher prevalence of TB among CKD patients. Having a contact history with a known TB patient, presence of HIV

infection and duration on dialysis for more than 1 year were associated with increased prevalence of TB among CKD patients.

The diagnosis of TB among participants who had a contact history with a known TB patient was 2.5 times higher as compared patients who had no a contact history. A possible justification might be, a contact history in a patient living in higher TB burden are with underlying immunosuppression from CKD and other related and concomitant comorbidities increase predisposition of these patients.

The diagnosis of TB is 15 times higher in the presence of concomitant HIV infection. This could be due to the higher burden of LTBI and its reactivation among HIV and CKD patients. Higher immunosuppression rate from a combined effect of CKD and IV also contributes for predisposition of TB among these patients.

Patients on dialysis for more than 01 year had 2.5 times increased risk of TB diagnosis as compared to participants on dialysis for less than one year. The possible justification might be a frequent and prolonged visit of these patients to the dialysis centres,predispose patients for increased risk of repeated exposure with active TB patients in overcrowded dialysis centers.

7. Conclusion

The association of TB and CKD is well known for more than four decades. Our study found a higher prevalence of TB among CKD/ESRD patients on HD. Having a contact history with a known TB patient, presence of HIV infection and duration on dialysis for more than 1 year were associated with increased prevalence of TB among CKD patients. A significant association was not found for socio-demographic characteristics, underlying etiology, and comorbidities. Because of its atypical presentation and mimicker of uremic symptoms, physicians should maintain a high degree of suspicion to consider TB among CKD patients. Early identification and treatment of TB among CKD patients is important in decreasing morbidity and mortality among these patients and in decreasing the transmission of TB among patients who undergo dialysis in the same center.

8. Strengths and limitations ofthe study

The strength of this study is as it is a cross-sectional study, and data were collected over specified time duration and which enabled us to execute an accurate assessment of the descriptive and analytic analysis. To our best knowledge, this is the first study of its kind in Ethiopia in assessing the burden of TB and associated factors in CKD patients on HD. Since it is done in as many dialysis centers, the results speak the actual burden of the disease in our country.We believe this study will give a baseline figure regarding the burden of TB among CKD patients and the result will alert the dialysis centers and researchers to assess factors associated with the higher prevalence of TB among CKD patients and remedy the gap.

Although the burden of TB among CKD patients on HD and associated factors are assessed, this study did not assess treatment outcome of patients, drug adherence, and dialysis setups

(Spacing between beds, number of patients per room, and staff number).Even though the finding of this study is similar to many studies, it cannot be generalized to the general population because this is a study done in a single city and multicenter study is required.

9. Recommendation

This is a dialysis centers-based study with small sample size, thus a large-scale prospective study with a longer duration of follow-up is needed for the determination of prevalence of TB, associated factors, and treatment outcomes among CKD/ESRD patients on maintenance HD. A different study should be done to assess the infrastructure of dialysis centers. Physicians should practice the use of TB prophylaxis among high-risk patients including ESRD patients on HD. Policy and implementing strategy should be facilitated by higher authorities including federal ministry of health.

10. References

1. Global Tuberculosis Report 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO

2. WHO consolidated guidelines on Tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO

3. Centers for Disease Control and Prevention. Tuberculosis: Basic TB Facts. https://www.cdc.gov/tb/topic/basics/risk.htm

4. Horsburgh CR Jr, Rubin EJ. Clinical Practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364(15):1441.

5. Klote M, Agodoa L, Abbott C. Risk factors for Mycobacterium tuberculosis in US chronic dialysis Patients. Nephrol Dial Transplant (2006) 21: 3287–3292. doi:10.1093/ndt/gfl488

6. Romanowski K, Clark E, Levin A, et al. Tuberculosis and chronic kidney disease: an emerging global syndemic. Kidney International (2016) 90, 34–40; http://dx.doi.org/10.1016/j.kint.2016.01.034

7. Segall L, Covic A. Diagnosis of Tuberculosis in Dialysis Patients: Current Strategy. Clin J Am Soc Nephrol 5: 1114–1122, 2010. doi: 10.2215/CJN.09231209

8. Chia S, Karim M, Elwood RK, et al. Risk of tuberculosis in dialysis patients: a population-based study. INT J TUBERC LUNG DIS 2(12):989–991, 1998.

9. Ejigu AM, Ahmed MM., Mengistu YT (2021) Nephrology in Ethiopia. In:Moura-Neto J.A., Divino-Filho J.C., Ronco C. (eds) Nephrology Worldwide. Springer, Cham. http://doi.org/10.1007/978-3-030-56980-0_4

10. Passalent L, Khan K, Richardson R, et al. Detecting Latent Tuberculosis Infection in Hemodialysis Patients: A Head-to-Head Comparison of the T-SPOT.TB Test, Tuberculin Skin Test, and an Expert Physician Panel. Clin J Am Soc Nephrol 2: 68–73, 2007. doi: 10.2215/CJN.01280406

11. Ruzangi J, Iwagami M, Smeeth L, et al. The association between chronic kidney disease and tuberculosis; a comparative cohort study in England. BMC Nephrology (2020) 21:420 https://doi.org/10.1186/s12882-020-02065-4

12. Abdelrahman M, Sinha A, Karkar A. Tuberculosis in end-stage renal disease patients on hemodialysis. Hemodialysis International 2006; 10:360–364.

13. Ndamase S, Okpechi I, Carrara H, et al. Tuberculosis burden in stage 5 chronic kidney disease patients undergoing dialysis therapy at Livingstone Hospital, Port Elizabeth, South Africa. S Afr Med J 2020;110(5):422-426. https://doi.org/10.7196/SAMJ.2020.v110i5.14035

14. Moore D, Lightstone L, Javid B, et al. High Rates of Tuberculosis in End-Stage Renal Failure: The Impact of International Migration. EmergInf Dis (2002) ;8(1).

15. Pradhan R, Sigdel M. Prevalence, Clinical Presentation, and Outcome of Tuberculosis in Patients with Chronic Kidney Disease at a Tertiary Care Hospital in Nepal. Hindawi Intl J Nephrol 2020; 7401541. https://doi.org/10.1155/2020/7401541

16. Ates G, Yildiz T, Danis R, et al. Incidence of Tuberculosis Disease and Latent Tuberculosis Infection in Patients with End Stage Renal Disease in an Endemic Region. Renal Failure 2010, 32:91–95.

17. Dervisglu E, Yilmaz A, Senglu E. The spectrum of tuberculosis in dialysis patients. Scand J Inf Dis, 2006; 38: 1040-1044.

18. Sen N, Turunc T, Karatasli M, et al. Tuberculosis in patients with end-stage renal disease undergoing dialysis in an endemic region of Turkey. Transplant Proc. 2008 Jan-Feb;40(1):81-4. doi: 10.1016/j.transproceed.2007.12.003. PMID: 18261551.

19. Shankar MS, Aravindan AN, Sohal PM, et al. The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis, Nephrology Dialysis Transplantation, Volume 20, Issue 12, December 2005, Pages 2720–2724. https://doi.org/10.1093/ndt/gfi141

20. Carney E.F. The Impact of Chronic Kidney Disease on Global Health. Nat Rev Nephrol 16, 251(2020). https://doi.org/10.1038/s41581-020-0268-7

21. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. Adv Exp Med Biol. 2019; 1165:3-15. Doi:10.1007/978-981-13-8871-2_1.

22. Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. Semin Dial 16: 38–44, 2003.

23. Cohen A, Mathiasen VD, Schon T, et al. The global prevalence of Latent Tuberculosis: a systematic review and metanalysis. European Respiratory Journal 2019: 54: 1900655; DOI: 10.1183/13993003.00655-2019.

24. Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. PloS One. 2011;6:e29563

25. Linquist JA, Rosaia CM, Riemer B, et al. Tuberculosis exposure of patients and staff in an outpatient hemodialysis unit. Am J Infect Control. 2002;30: 307–310.

26. Barry M. Prevalence of Latent Tuberculosis Infection in the Middle East and North Africa: A systematic Review. Pulmonary Medicine, vol 2021, 6680651. https://doi.org/10.1155/2021/6680651.

27. Ncayiyana JR, Basset J, West N, et al. Prevalence of latent Tuberculosis Infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: A cross-sectional study. BMC Infect Dis 16, 661 (2016). https://doi.org/10.1186/s12879-016-1989-x

28. Wilson JW, Kissner DG, Escalante. (2021) Cascade of care in the Management of Latent Tuberculosis in the United States: A lot to improve and to scale up. Annals of the American Thoracic society. 18:10, 1620-1621.

29. Grobler L, Mehtar S, Dheda K, et al. The Epidemiology of tuberculosis in health care workers in South Africa: A systematic review. BMC Health services research (2016) 16:416.

30. Hanifa Y, Grant AD, Lewis J, et al. Prevalence of Latent Tuberculosis infection among gold miners in South Africa. Int J Tuberc Lung Dis (2009) 13(1):39-46.

31. Chekesa B, Gumi B, Chanyalew M, et al. (2020) Prevalence of latent tuberculosis infection and associated risk factors in prison in East Wollega Zone of western Ethiopia. PLoS ONE 15(5): e0233314. https://doi.org/10.1371/journal.pone.0233314

32. Teklu, T., Legesse, M., Medhin, G. et al. Latent tuberculosis infection and associated risk indicators in pastoral communities in southern Ethiopia: a community based cross-sectional study. BMC Public Health 18, 266 (2018). https://doi.org/10.1186/s12889-018-5149-7

33. F. H. Pilsczek, S. H. E. Kaufmann, and S. H. E. Kaufmann, "Prevalence and predictors of positive tuberculin skin test results in a research laboratory," *Revista da SociedadeBrasileira de Medicina Tropical*, vol. 41, no. 4, pp. 416–418, 2008.

34. Malik GH, Al-Mohaya SA, Al-Harbi AS, et al. Spectrum of tuberculosis in dialysis patients in saudiarabia. Saudi J Kidney Dis Transpl. 2003;14(2):145-152.

11. Annex

1. English Version Questionnaire

CODE - _____

1. Sex

1) Male 2) Female

2. Age in years ……

3. Religion

1) Orthodox 2) Muslim

3) Catholic 4) Protestant

5) Others specify----------

4. Marital statues

1) Single 2) Married

3) Divorced 4) Widowed

5. Occupation

1) Farmer 2) Student

3) House wife 4) Gov't employee

5) Merchant 8) Retired

7) Others specify----------

6. Address ……

7. Education

1) Illiterate 2) Read and write only

3) Primary education (1-8) 4) Secondary educations (8-12)

5) Above grade 12 6) college or university

8. Estimated monthly income (ETB)

1) <1000 2) 1000-3000

3) 3000 -5000 4) 5000-10000

5) Above 10000

9. Smoking history

1) Current smoker

2) Ex-smoker

3) Non-smoker pack years …….

10. HIV status

a) Positive
b) Negative
c) Unknown status

10.1. if positive, years after the diagnosis……..

10.2 Current CD4……

Current viral load……

Current HAART regimen……

Years on HAART_____

10.3 TB Prophylaxis use Yes____ No_____

11. Body builds (habitus)

1) Weight (Kg) ------- 2) Height(cm) ----------3, BMI_____ 4, MUAC…….

12. Cause of ESRD…… Time since ESRD ……

13. Any other comorbidities? Yes_____ No_____

If yes, please specify_____

14. Hemodialysis Profile Dialysis

a. Frequency of Dialysis/week……
b. Years on dialysis…….

15. Use of Immunosuppressive drugs A. yes B. No

a) If yes which Drugs ……
……
b) Indication of Immunosuppressives drugs ……

16. History of Contact with TB patient A. yes B. No

17. Previous Diagnosis and treatment of TB A. yes____ B. No____

If Yes,

a) Diagnosis done by……
b) Treatment outcome ……
c) Type of TB A, Pulmonary_____ B, Extrapulmonary_____
d) Timing
   A, After CKD Diagnosis but before HD initiation _____
   B, After HD initiation _____

18, Current Diagnosis and Treatment of TB A. yes ____ B. No____

If Yes,

a) Type of TB……Diagnosis confirmed by…….
b) Treatment regimen……..
c) Drug susceptibility ……

19. Vit D status ……

Eligibility criteria

Inclusion Criteria	
- Is the patient aged 18 or above	Yes□ No□
- Does the patient have a diagnosis of stage 5 CKD and on maintenance haemodialysis?	Yes□ No□
Exclusion Criteria	
- Does the patient have any of the following precaution or contraindications to the use of beta blockers? • Diagnosis of tuberculosis before the diagnosis of CKD • Patients with incomplete medical records and those who are unable to provide the appropriate information • Patients with mental health problems • Critically ill patients • Those who cannot provide consent	Yes□ No□

‘

2. Information Sheet

Title of the project

The Burden of Tuberculosis in patients with stage 5 CKD following in Renal follow up clinics at Dialysis centers of Addis Ababa

Name of investigators: Dr Eyob Beyene

My name is Dr. Eyob Beyene. I am ID fellow in Addis Ababa University. Currently I am investigating Tuberculosis burden in Patients with ESRD at Addis Ababa. You are kindly invited to participate in this study. Before you decided to take part in the study, it is prudent for you to understand why this research is being done and what it involves. Please take time to listen or read to the following information carefully. Raise question if there is anything not clear. Thank you for your time.

Background of the study

We would like to see The Burden of Tuberculosis in patients with stage 5 CKD following in Renal follow up clinics at Dialysis centers of Addis Ababa.

Selection criteria

You are selected to participate in this research project randomly from patients whose follow-up is at this Dialysis center. You will be interviewed with questioners; your chart will be reviewed for relevant information.

Possible harm

There is no risk in participating in this study. You will be interviewed with questionnaires. Your chart will be reviewed for relevant information. the interview may take 5-10 minutes of your time.

Benefits

The outcome of the study will help health sector stakeholders to Give attention for prevention and appropriate management of tuberculosis in patients with ESRD

Confidentiality

During the data collection your name and personal identifications will not be asked. All information collected during the study about you will be coded and the data collection tools will be locked and will not be accessed by any individuals. all the data and the information's will be confidential.

Autonomy

All the information you give is highly valuable to the study. It is up to you to decide whether to take part or not. If you decided to participate, you will be given this information that to keep and be asked to sign a consent form. You have the right to withdraw at any time. Withdrawal from the study will not have an impact on your treatment

Who is organizing and funding the research?

Research grant will be from AAU post graduate office CHS. The research organized by researchers in Addis Ababa University, SOM, internal medicine department, ID Unit. The Research protocol has been reviewed by research committee of internal medicine Department and by institutional review board of AAU, CHS.

Institutional Review Board (IRB) address:

Collage of health sciences

Addis Ababa University

Addis Ababa, Ethiopia

Contact person

Dr. Eyob Beyene, Tel.0923952126

E-mail address: eyobebu@gmail.com

3. Investigators Signature Form

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission of Department of Internal Medicine, except when necessary to protect the safety, rights, or welfare of study participants. I agree to personally conduct or supervise this study. I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and are met. I agree to maintain adequate and accurate study records and to make those records available for inspection by the department or unit heads, hospital administrators, and/or other applicable regulatory entities. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Signature: _____ Date: _____