Original Article

Analysis of Latent Tuberculosis Risk Factors Detected by Tuberculin Skin Tests in Chronic Kidney Disease Patients Undergoing Routine Hemodialysis

Muhammad Andi Mardiansyah, Yunita Arliny, Nurrahmah Yusuf, Abdullah

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia

Abstract

Background: Due to changes in the immune system, chronic kidney disease (CKD) patients on routine hemodialysis (HD) are at increased risk for latent tuberculosis (LTB). Latent tuberculosis requires special attention to prevent its development into active form because infection increases mortality in CKD patients. This study aims to determine the prevalence and risk factors associated with LTB in CKD in routine HD patients.

Method: This research uses a cross-sectional design and is an analytical observational study. The study was conducted in the Hemodialysis Unit at dr. Zainoel Abidin Hospital between June and August 2023, using consecutive non-probability sampling.

Results: Of the 289 CKD patients undergoing routine hemodialysis, 54 met the inclusion criteria. The prevalence of latent tuberculosis among these patients was 27.8%, as determined by the Tuberculin Skin Test (TST). Statistical analysis revealed no significant association between LTB and risk factors such as age, gender, body mass index, smoking status, or CKD etiology (P>0.05). Due to the value of P>0.25, multivariate analysis could not be performed.

Conclusion: There is a high prevalence of latent tuberculosis among chronic kidney disease patients undergoing dialysis. The risk factors for LTB remain unclear. However, early diagnosis and treatment are recommended to prevent progression to active TB.

Keywords: chronic kidney disease, hemodialysis, latent tuberculosis, tuberculosis, tuberculin test

Corresponding Author:
Yunita Arliny | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia | nita.arliny@unsyiah.ac.id

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INTRODUCTION

Tuberculosis (TB) remains a major global health burden with high morbidity and mortality. The World Health Organization (WHO) estimates 10.4 million new cases worldwide resulting in 1.8 million deaths. The Global TB Report for 2022, globally estimates 1.6 million deaths from TB. The death rate increased between 2019 and 2021, whereas it had previously decreased between 2005 and 2019.[1,2]

The Global TB Report 2022 estimates that Indonesia has 969,000 pulmonary TB cases among a population of 273.8 million, with a high mortality rate of 144,000 deaths. Immunocompromised individuals, such as hemodialysis (HD) patients, face an increased TB activation risk—10 to 25 times higher than the general population—due to immunosuppression, diabetes (DM), and HIV.[2–4]

Latent Tuberculosis (LTB) at the global level in 2018 is estimated to be a quarter of the world's population or around 1.8 billion people, of which 35% are from the Southeast Asian region including Indonesia. The estimated LTB caseload in Indonesia is estimated to be around 2,795,994 people in contact with active TB cases.[5,6]

Chronic Kidney Disease has been observed to have a prevalence of 10%, indicating its escalating significance as a public health issue. Moreover, a multitude of research has provided evidence supporting the notion that those undergoing dialysis treatment are at heightened susceptibility to tuberculosis, with the risk ranging from 7 to 53.[1,7–10]

Based on the data provided by the Indonesian Renal Registry in 2018, it was observed that a total of 176 individuals, constituting 1% of patients diagnosed with stage 5 chronic kidney disease, presented tuberculosis as a concomitant condition. The meta-analysis study examined the incidence of tuberculosis disease in patients with chronic kidney disease using data from 104 studies conducted in 32

countries. The dataset included information from a total of 1,548,774 CKD patients. The findings revealed that the prevalence of TB disease among CKD patients was 3718 cases per 100,000 patients.[1,7–10]

The prevalence of Latent Tuberculosis in patients with chronic kidney disease is influenced by various factors. These include advanced age, a prior history of tuberculosis, smoking behavior (both current and former smokers), dietary factors such as carbohydrate, vitamin, and mineral intake, living in densely populated areas, and household contact with individuals affected by TB. Given these risk factors, WHO recommends LTB screening in high-risk patients such as those with CKD. Patients diagnosed with LTB should receive preventive TB therapy to reduce mortality, prevent active TB progression, and limit disease transmission.[1,9,11–14]

CKD patients are a high-risk population for ILTB. This is because CKD patients experience systemic inflammation and impaired immune response. The World Health Organization recommends CKD patients be screened for LTB, and patients proven to have LTB should be treated with TB preventive therapy to prevent the progression of LTB to active TB, which worsens prognosis and increases mortality to patients. Tuberculin skin test should be the mainstay due to its low cost, ease of application, no need for special skills, standardized laboratory with a sensitivity of 68–71.5% and specificity of 86–88.7%.

Until now, there is not much data and references regarding the use of the Tuberculin Skin Test (TST) in developing, low and middle-income countries in terms of diagnosing Latent Tuberculosis, especially in Indonesia itself, especially in Aceh Province and especially in the dr. Zainoel Abidin Banda Hospital Aceh where complete data is not yet available regarding the proportion and risk factors for latent TB infection, especially in CKD patients.

Researchers feel it is important to conduct a study to determine the proportion and analyze risk factors for LTB. in CKD patients undergoing routine hemodialysis at dr. Zainoel Abidin Hospital Banda Aceh uses TST examination to achieve early diagnosis of LTB and provide preventive therapy for tuberculosis so that it does not develop into active TB in CKD patients undergoing HD. So that it can reduce morbidity and mortality improve the quality of life of patients and reduce transmission rates, which is to WHO recommendations and National Guidelines for Medical Services for Tuberculosis Management in Indonesia to achieve the goal of Ending Tuberculosis by 2035.

METHODS

This analytical observational study employed a cross-sectional design to determine the prevalence and risk factors of LTB in CKD patients undergoing routine hemodialysis. The research was carried out in the Hemodialysis Installation room at dr. Zainoel Abidin Hospital Banda Aceh. The study population consisted of patients with CKD who underwent regular Hemodialysis in the aforementioned facility during the period of June to August 2023. The sample was obtained using a non-probability sampling methodology, specifically the sequential sampling method.

The inclusion criteria in this study were male and female CKD patients aged >17 years who had undergone routine hemodialysis 2 times a week for >3 months when the sample was taken and were willing to follow and undergo all research procedures while the exclusion criteria were CKD patients with malignant comorbidities, HIV and received immunosuppressant therapy, CKD patients who had a history of TB disease and received anti-tuberculosis drug therapy and had clinical symptoms suspicious of TB, CKD patients who had recently contracted viral diseases such as measles and smallpox within 4–6 weeks of sample collection, CKD patients who had received viral vaccinations within 4–6 weeks of sample collection, CKD patients who had a history of skin and drug allergies, CKD patients who did not have a skin reaction with a diameter of 6–10 mm after tuberculin injection, patients who had an allergic reaction after tuberculin injection and were not willing to participate and undergo all study procedures.

Chronic kidney disease patients undergoing hemodialysis who elect to participate in the study must sign a consent form. The collection of data is then initiated, encompassing the subjects' age, gender, BMI, history of close contact with TB patients, smoking habits, and the underlying cause of CKD.

After the data collection, a tuberculin injection is administered to the subjects on the first day following their hemodialysis treatment. The tuberculin test is performed using the Mantoux technique, in which 0.1 mL (five tuberculin units of PPD) is injected intradermally into the volar surface of the forearm, excluding patients with atriovenous fistulas. The interpretation of results occurs 48 to 72 hours after injection.

The measurement of indurations is conducted with a measuring tape, and patients are categorized into groups based on duration: those with indurations <10 mm and those with indurations ≥10 mm. A TST result was declared positive if the induration was ≥10 mm and latent TB was diagnosed. Conversely, a TST result ≤10 mm was declared negative.

The researchers used univariate analysis to explain the frequency distribution and proportions of the variables studied. Bivariate analysis was utilized to evaluate the relationship between risk factors impacting the occurrence of latent tuberculosis. Furthermore, multivariate analysis was employed to ascertain the risk factors that exerted the greatest influence on the occurrence of latent tuberculosis in chronic kidney disease patients undergoing routine hemodialysis.

The bivariate analysis employed the chi-square and Mann-Whitney tests, while the multivariate analysis utilized the logistic regression analysis test. The statistical significance level was set at α=0.05 and a 95% Confidence Interval (CI) was applied. The statistical analysis was conducted using SPSS Version 24.0. A significance level of $P \leq 0.05$ was used to determine the presence of a relationship between the two variables. If the value of $P \leq 0.05$, it indicates a significant link. Conversely, if the value of $P > 0.05$, it suggests no significant relationship between the variables.

RESULTS

Chronic Kidney Disease patients undergoing HD in the Hemodialysis Installation room at dr. Zainoel Abidin Hospital Banda Aceh numbered 289 patients, 63 patients were excluded as research subjects because they had not undergone routine hemodialysis 2 times a week for >3 months when the sample was taken, 148 patients were excluded because they were not willing to participate and undergo all research procedures, 23 patients had a history of TB disease and received anti-tuberculosis drug therapy and had clinical symptoms suspicious of TB and 1 patient had a history of skin and drug allergies.

Table 1. Characteristics of Samples (n=54)

Characteristics	n	%
Age		
Late adolescence	1	1.9
Early adulthood	5	9.3
Late adulthood	12	22.2
Early elderly	14	25.9
Late elderly	22	40.0
Seniors	0	0
Gender		
Men	36	66.7
Female	18	33.3
Body Mass Index		
Very thin	0	0.0
Thin	7	13.0
Normal	39	72.2
Fat	6	11.1
Obese	2	3.7
Contact with TB		
Available	0	0.0
Not present	54	100
Smoking Status		
Smokers	31	57.4
Non-smoker	23	42.6
Etiology of CKD		
Diabetes mellitus	4	7.4
Hypertension	50	92.5

A total of 54 patients became the study sample who met the inclusion and exclusion criteria from 289 CKD patients undergoing HD in the Hemodialysis Installation room at dr. Zainoel Abidin Hospital Banda Aceh from a target sample of 138 subjects. Table 1 presents the demographic and clinical characteristics of the study population, including age, gender, BMI, TB contact history, smoking status, and CKD

etiology. Of the 54 research subjects, the mean age of the patients was 51.5 years (24-68). A total of 36 subjects (66.7%) were male with a mean subject BMI of 22.45 (SD 3.60).

A total of 54 subjects (100%) did not have close contact, 30 subjects (55.6%) with ex-smoker status, while the most common etiology of CKD was Hypertension with a total of 50 subjects (92.6%), diabetes mellitus 4 subjects (7.45%) while other CKD etiologies did not exist. None of the participants had clinical manifestations of tuberculosis, such as persistent cough lasting two weeks or more (with or without phlegm, or phlegm mixed with blood), chest discomfort, dyspnea, malaise, weight loss, decreased appetite, chills, fever, or night sweats.

Table 2. Proportion of LTB and Non-LTB in CKD Patients with TST Examination (n=54)

CKD	n	%
Latent tuberculosis	15	27.8
Not latent tuberculosis	39	72.2

Table 2 shows that among the 54 subjects who underwent TST, 15 subjects (27.8%) had an induration ≥10 mm, indicating LTB, while 39 subjects (72.2%) were negative (32 subjects with no induration and 7 with <10 mm induration). Of the 32 subjects who had no induration, 30 subjects had hypertension and 2 subjects had DM. Meanwhile, 7 subjects with induration <10 mm, all of them were hypertensive.

Table 3 provides an overview of the assessed of the research subjects with LTB results from TST examination found 7 subjects (31.8%) aged late elderly, where the median age was 43.00 (24–65), while in research subjects with non-LTB results from TST examination, there were 15 subjects (68.2%) aged late elderly, with a median age of 50.00 (30–68). Based on gender, 12 subjects (33.3%) with LTB results were male, while 24 subjects (66.7%) with non-LTB results were male.

Body mass index in LTB patients was 9 subjects (23.1%) with normal BMI, where BMI ranged from 18.1-31.2 with a mean BMI of 23.02±3.77, while in non-LTB are 30 subjects (76.9%) with normal BMI, BMI ranged from 16–37.7 with a mean BMI of 22.2±3.56. Smoking variables in LTB patients found that 8 subjects (26.7%) were former smokers, while in non-LTB subjects, 22 subjects (73.3%) were former smokers. The etiology of CKD in LTB patients is hypertension in as many as 13 subjects (26%), while in non-LTB subjects 37 subjects (74%) with hypertensive CKD etiology.

Table 3. Relationship between Risk Factors and LTB in CKD Patients with TST Examination

Variable	LTB	Not LTB	Total	*P*
Age				
Late adolescence	1 (100.0%)	0 (0.0%)	1 (100.0%)	0.831
Early adulthood	2 (40.0%)	3 (60.0%)	5 (100.0%)	
Late adulthood	3 (25.0%)	9 (75.0%)	12 (100.0%)	
Early elderly	2 (14.3%)	12 (85.7%)	14 (100.0%)	
Late elderly	7 (31.8%)	15 (68.2%)	22 (100.0%)	
Gender				
Male	12 (33.3%)	24 (66.7%)	36 (100.0%)	0.197
Female	3 (16.7%)	15 (83.3%)	18 (100.0%)	
Body Mass Index				
Thin	2 (28.6%)	5 (71.4%)	7 (100.0%)	0.321
Normal	9 (23.1%)	30 (76.9%)	39 (100.0%)	
Fat	3 (50.0%)	3 (50.0%)	6 (100.0%)	
Obese	1 (50.0%)	1 (50.0%)	2 (100.0)%	
Contact with TB				
Available	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Not present	15 (27.8%)	39 (72.2%)	54 (100.0%)	
Smoking status				
Smokers	9 (29.0%)	22 (71.0%)	31 (100.0%)	0.811
Not smoker	6 (26.1%)	17 (73.9%)	23 (100.0%)	
Etiology of CKD				
Diabetes mellitus	2 (50.0%)	2 (50.0%)	4 (100.0%)	0.302
Hypertension	13 (26.0%)	37 (74.0%)	50 (100.0%)	

The results of bivariate analysis using chi-square and Mann-Whitney tests with a 95% CI and α=0.05 obtained age variables with a value of *P*=0.831, gender with a value of *P*=0.197, BMI with a value of *P*=0.321, smoking status with a value of *P*=0.632, and CKD etiology with a value of *P*=0.302. It can be concluded that all variables do not have a statistically significant relationship with the risk of LTB using TST examination, while the variables of close contact with TB patients cannot be carried out bivariate analysis because there is no comparison.

Multivariate analysis in this study cannot be done, because from the results of bivariate analysis only the gender variable with a value of *P*=0.197 or *P*<0.25, while for other variables with a value of *P*>0.25.

DISCUSSION

This study involved 54 subjects, from the study obtained 36 subjects (66.7%) were male and 18 subjects (33.3%) were female. This is similar to the characteristics of research subjects conducted by Hussein et al, Rao et al, Chagas et al, and Ismail et al with the proportion of subjects male gender more than female with a ratio of 60–70% male and 30–40%. This is because men suffer more from hypertension, which is the main cause of CKD. The etiology of CKD in this study was DM in 4 subjects (7.4%) and hypertension in 50 subjects (92.6%).[4,12,15,16]

This is similar to the characteristics of the research subjects conducted by Chagas et al, Ismail et al, and especially Bandiara et al with hypertensive CKD etiology when compared to diabetes mellitus.[12,13,15] The most common cause of CKD is hypertension, then DM.

Some of the above studies also showed similar results for other characteristics such as age with 45–65 years of age, normal BMI and smoker or ex-smoker status, while the history of close contact with TB patients tended to be different because the research subjects had close contact with TB patients, this may occur due to lack of knowledge about TB disease.

The prevalence of LTB in CKD patients undergoing hemodialysis, based on TST results, was 27%. This is slightly greater than several previous studies such as Chagas et al in Campo Grande Brazil, Wu et al in Taiwan, Ferreira et al in Brazil, and Ismail et al in Lebanon, where the prevalence of ILTB in CKD patients undergoing hemodialysis in the five studies ranged from 10–20%.[12,15,17,18]

When compared to a study by Bandiara et al at the Hemodialysis Unit of Hasan Sadikin Bandung Regional General Hospital, Indonesia, the prevalence of LTB in CKD patients undergoing hemodialysis in this study was lower, where the prevalence of ILTB in Bandiara et al's study was 39.2%. Latent TB screening in CKD patients undergoing hemodialysis showed a higher LTB positivity rate with the interferon-gamma release assay (IGRA) (35.1%) compared to using TST (13.5%).[13]

A study by Setyawati et al examined 30 CKD patients undergoing routine HD and found a 23.3% prevalence of TBL using TST and TB SPOT TB with positive results in 20% of patients with TST and only 16.7% of those with TB SPOT. This study revealed that CKD patients exhibited a higher prevalence of TBL than TB, estimated at approximately 25% of the global population.[19] This estimate exceeds the prevalence in the general population, where approximately one-quarter of the global population is infected with TB. Furthermore, this finding highlights a higher prevalence of latent TB infection (LTBI) in CKD patients.

The variability in study findings is attributable to differences in the number of study subjects and geographical variations in the country of origin, which exhibit different burdens of active TB patients and consequently affect the prevalence of latent TB. This study's sample size was comparatively small due to numerous patients refusing to undergo TST. Additionally, the diagnostic tools utilized differed across studies, with some employing TST alone, TST and IGRA, or TST and TB SPOT TB.

The findings of earlier studies, which documented fewer positive TST results than other diagnostic tools, were attributed to anergy in chronic

kidney disease patients undergoing hemodialysis, resulting in false negative outcomes in the TST examination. Anergy in these patients is characterized by impaired innate and adaptive immunity.

Conversely, studies that reported more positive TST results than other diagnostic tools were deemed to be influenced by subjective readings and false positives in the TST examination. While TST is considered a valuable test, the issue of false positivity remains a concern. In low-risk individuals, most positive reactions are, in fact, false positives due to the low specificity of the TST test. For induration to occur on the TST, T cell-antigen interaction is required which leads to activation and secretion of cytokines which in turn will lead to recruitment and activation of macrophages after exposure to a given soluble antigen.

The result is localized reactivity manifested as erythema and induration through local vasodilation, edema, fibrin deposition, and the appearance of other inflammatory cells in the area, so it can be concluded that in CKD patients who do not appear induration due to severe immunodeficiency disorders caused by other factors not examined in this study such as length of HD, serum albumin levels and other factors that conclude need further research.

Multiple studies, including systematic reviews, have compared TST and IGRA, consistently showing that IGRA has higher sensitivity and specificity for LTBI diagnosis in dialysis patients. However, IGRA is more costly and requires specialized laboratory equipment.

The present study found that dialysis patients, in general, and hemodialysis patients, in particular, had higher LTBI prevalence than pre-dialysis and post-renal transplanted patients. Dialysis patients, notably those undergoing hemodialysis, are susceptible to M.tb infection through person-to-person contact due to their frequent travel and prolonged stay in healthcare facilities. Hemodialysis patients exhibited a higher LTBI prevalence compared to pre-dialysis and post-renal transplanted CKD patients.[20]

The results of bivariate analysis for the variables of age, gender, CKD etiology and BMI are by several studies such as Chagas et al, Ferreira et al, Bandiara et al, Ismail et al, where the four variables mentioned above did not have a statistically significant relationship with LTB using TST examination with P>0.05.[12,13,15,17]

The smoking variable in this study also did not have a statistically significant relationship with LTB using a TST test with P>0.05, as evidenced by several studies above. [12,13,15,17] This does not follow the research of Bandiara et al, who concluded that smokers had a statistically significant relationship with LTB using the IGRA test.[13]

The close contact variable with TB patients in this study could not be analyzed because all subjects did not have a history of close contact with TB patients. This is a shortcoming in this study, although many studies have concluded that there is no statistically significant relationship with LTB. Research conducted by Chagas et al showed that TBL is associated with a history of contact with LTB; in that study, contact history was found in 80% of the study subjects. People newly infected with M.tb have a high risk of reactivation, and those in close contact with people with active TB have a 15 times greater chance of infection and reactivation of TB in the last 2 years.[12]

Body mass index is associated with a person's susceptibility to various infections and diseases. However, the relationship between BMI and the risk of TB infection has not been well-studied. Research by Goweda showed that an increase in LTB prevalence was associated with an increase in BMI (P=0.046).[21] The results of a systematic review by Saag et al found that underweight individuals were not at higher risk of developing LTBI.[22]

Another study from rural China found that BMI ≥28.0 kg/m2 was independently associated with individual susceptibility to TB infection. The relationship between BMI and TB infection is not well understood, although its association with active TB has been studied for years. Increased adipose tissue affects immune function negatively and lowers the body's defenses in obese individuals. In addition,

accumulated adiposity may reduce pulmonary defenses through metabolic dysfunction.[23]

The variables of close contact with TB patients cannot be analyzed because 54 subjects (100%) do not have a history of contact with TB patients so there is no comparison for the analysis of the relationship between the two variables with the SPSS program.

The smoking variable in this study also did not have a statistically significant relationship with LTB using a TST test with *P*>0.05, as evidenced by several studies above.[12,13,15,17] This does not follow the research of Bandiara et al, who concluded that smokers had a statistically significant relationship with LTB using the IGRA test.[13]

The above leads to the conclusion that for induration to occur on the TST, T cell-antigen interaction is required which leads to activation and secretion of cytokines which in turn will lead to recruitment and activation of macrophages after exposure to a given soluble antigen.

The result is localized reactivity manifested as erythema and induration through local vasodilation, edema, fibrin deposition, and the appearance of other inflammatory cells in the area, so it can be concluded that in CKD patients who do not appear induration due to severe immunodeficiency disorders caused by other factors not examined in this study such as length of HD, serum albumin levels and other factors that conclude need further research.

LIMITATION

This study is subject to several limitations. First, due to most risk factor variables having *P*>0.25, multivariate analysis could not be performed. This limitation affects the study's ability to identify complex associations between risk factors and LTB occurrence. Second, since none of the study participants reported close contact with TB patients, this variable could not be analyzed as a risk factor.

Other potential risk factors, such as hemodialysis duration, nutritional status, serum albumin levels, and immunologic conditions, were not assessed. As this study was conducted in a single tertiary referral hospital in Aceh province, its findings may not be generalizable to the broader CKD population at national or international levels. The study's reliance on the TST as the sole method for diagnosing LTBI without corroboration by additional methods, such as the IGRA, which is more sensitive in immunocompromised patients, is a limitation.

CONCLUSION

The prevalence of LTB in this study was relatively high, highlighting the need for routine LTB screening in CKD patients undergoing HD. Given the significant impact of TB on morbidity, mortality, and quality of life in CKD patients, preventive measures are crucial. No significant association was found between LTB incidence and risk factors such as age, gender, BMI, smoking, or CKD etiology. Further, longitudinal studies are needed to determine and evaluate risk factors associated with TBL in CKD patients undergoing hemodialysis.

Based on these findings, CKD patients can be categorized into three groups, there are 1) subjects exposed to MTB, but no T cell antigen interaction occurs, due to low T cell count or severe immunodeficiency disorders; 2) subjects who have not been exposed to MTB, so there is no T cell antigen interaction; and 3) subjects exposed or unexposed to MTB, no T cell antigen interaction occurred due to incorrect TST examination procedures.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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