The 4th International Agronursing Conference
"Optimizing The Role of Nursing and Health Professionals to Enhance Health Care Quality in The New Normal Era"
Faculty of Nursing, University of Jember, Ph (0331) 323450 Email: ianc@unej.ac.id

DETECTION OF LATENT TUBERCULOSIS INFECTION IN HAEMODIALYSIS PATIENTS: A SYSTEMATIC REVIEW

Hamidah Retno Wardani[1], Damon Wicaksi[1]

[1]Nursing Study Program, Universityof Bondowoso, Indonesia
Corresponding author: Hamidahretno77@gmail.com

ABSTRACT
Background: Patients with end-stage renal disease (ESRD) undergoing hemodialysis are at risk of developing active TB 6 to 25 times higher than the general population. The importance of screening tuberculosis infection using diagnostic tests such as the Tuberculin Skin Test (TST) and QuantiFeron TB-Gold (QFT-G) and proper treatment in hemodialysis patients can prevent the increase of LTBI to active TB. **Purpose:** To determine the prevalence of Latent Tuberculosis Infection (LTBI) cases in hemodialysis patients using the Tuberculin Skin Test (TST) and Quantiferon TB-Gold (QFT-G). **Methods:** A Systematic Review study to determine the prevalence of LTBI in hemodialysis patients using the Prefered Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocol. **Results:** Derived from 67 related articles and obtained 4 articles using the Randomized Control Trial (RCT) which met the criteria involving 516 ESRD patients undergoing hemodialysis. The study showed that the prevalence of LTBI using the diagnostic Tuberculin Skin Test (TST) (cut off ≥ 10 mm) and QuantiFERON-Tuberculosis Gold (QFT-G) showed TST + / QFT + 68 patients (18.47%), TST + / QFT- 22 patients (5.97 %), TST- / QFT + 77 patients (20.92%). **Conclusion:** This study shows a high prevalence of LTBI in hemodialysis patients. Screening and treatment of LTBI should be performed in hemodialysis patients to prevent the progression of LTBI to active TB.

Keyword*:* Latent tuberculosis infection, hemodialysis, TST, QFT-G, ESRD.

BACKGROUND

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. The leading cause of death worldwide is responsible for 1.5 million deaths each year (Houben & Dodd, 2016; Tang & Johnston, 2017). Globally, it is estimated that there are 10 million incidents of tuberculosis and 1.6 million cases of death due to Tuberculosis occurred in 2017. To end the global TB epidemic, the WHO End TB Strategy has established one of the main strategies for tuberculosis control is through individual identification of latent tuberculosis infection. Effective treatment for latent TB has been shown to reduce the risk of progression and increase. This can contribute to reducing the incidence of LTBI globally (WHO, 2019).

LTBI infection is a condition of dormant tuberculosis organisms. Often defined as an asymptomatic condition in which tuberculosis organisms present in the lung tissue without any clinical or radiological signs. LTBI can become active TB in hosts who experience immunosuppression caused by comorbid disease or medical therapy (Campbell, Krot & Mara, 2016). This condition also occurs in patients with end-stage renal disease (ESRD) who are receiving dialysis therapy. The incidence and mortality of TB infection are also higher in patients undergoing hemodialysis (HD) than in the general population (Chung, et al, 2009). Patients with end-stage renal disease (ESRD) develop immune dysfunction which increases the risk

of infection. At the stage of weak immunity, patients with latent tuberculosis infection (LTBI) will increase their reactivation and become active TB (Campbell, Krot & Mara, 2016). There is currently no gold standard for identifying LTBI in a population primarily of hemodialysis patients. Diagnostic tests such as the tuberculin skin test (TST) and interferon-gamma release assay (IGRA) are commonly used in combination in diagnosing LTBI. This study aims to detect the incidence of LTBI in patients undergoing hemodialysis with IGRA and TST examinations. This study is presented in the form of a systematic review to investigate the incidence of LTBI in hemodialysis patients.

METHODE

Search strategy

The study was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) which was carried out systematically by following the correct research stages or protocols. The procedure of this systematic review consists of several steps, namely 1) preparing the background and objectives; 2) Research question; 3) Searching for the literature; 4) Selection criteria; 5) Practical screen; 6) Quality checklist and procedures; 6) Data Extraction strategy. The researcher also scans the list of references to match the citations related to the research objectives. The database search was conducted from 12 to 17 August 2019. The keywords used were: 'Latent Tuberculosis infection', 'hemodialysis', 'TST', 'QFT-G', 'ESRD'.

Inclusion criteria and quality assessment

The inclusion criteria in this study were English articles, full text, prospective studies using TST and IGRA in hemodialysis patients who were then followed up. Interventions unrelated to the topic were included in the exclusion criteria section. The three main electronic databases used for the identification of relevant sources were PubMed, EMBASE, Google Scholar published from 1997-2018.

Data Extraction

Each journal is extracted separately. Parameters were extracted from each research journal including research information (author, year of publication), inclusion criteria, population demographics (gender, age, TB incidence, comorbidities), screening criteria, and results (TST / IGRA cut-off, positive and negative counts).

RESULTS

This study identified 67 journals. Journal identification was carried out by screening based on eligibility following the inclusion and exclusion criteria so that 4 articles were obtained for further review. The literature search strategy is shown in Figure 1. The population in this study were articles published in international journals with the topic of LTBI in hemodialysis patients. The sample in this study is an article published in an international journal with the topic of detection of LTBI in ESRD patients undergoing hemodialysis using TST and QFT-G. The sample inclusion criteria in this research article are as follows: 1) Full-text article; 2) Speak English; 3) Published in 2010-2019; 4) The type of research design in the article is a prospective study; 5) The topic of LTBI research in hemodialysis patients; 6) The LTBI examination uses the two-step TST and QFT-G. The number of sources obtained from the database includes PubMed 44, EMBASE 12, google scholar 11. Analysis of the 4 articles that have been identified shows that all journals use the prospective study method. Data extraction is done by analyzing data based on the author's name, title, research method, and results, namely the grouping of important data in articles. The results of data extraction are in table 2.

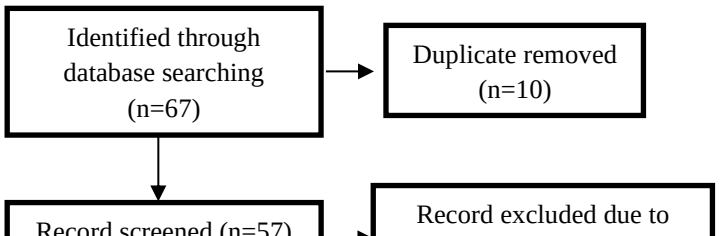

Figure 1. Journal identification flow

LTBI infection was evaluated in all four journals using TST and QFT-G. All studies reported positive TST results with a cutoff ≥ 10 mm and positive QFT results with IFN-gamma response to TB antigen ≥ 0.35 IU / ml. Based on table 1, the 4 articles that have been identified, data shows that in the first article there were 74 patients with ESRD who underwent hemodialysis and had 2-step TST and QFT-G examinations with results with 28 (37.8%) positive patients on QFT-G examination and TST, 26 (35.1%) patients were positive on QFT-G, and 10 (13.5) patients were positive on TST. The second article contained 200 patients with ESRD in the hemodialysis unit and 2-step TST, and QFT-G tests were carried out with positive results on TST and QFT-G as many as 21 (10.5%) patients, 44 (22%) patients were positive for QFT-G, and 5 (2.5%) patients were positive for TST. In the third article, there were 52 patients with ESRD in the hemodialysis unit and 2-step TST and QFT-G tests were carried out with positive results on both examiners, namely TST and QFT-G, 15 (28.8%) patients, 3 (5.8%) patients with positive results. in QFT-G and 5 (9.6%) patients with positive TST results. In the fourth article, there were 190 patients with ESRD in the hemodialysis unit, and 2-step TST and QFT-G examinations were carried out with 32 patients (34.4%) positive results on QFT-G and 42 (53.9%) patients.

Table 2. The results of extraction data

Tittle	Author and Year	Setting	Total Follow up Subject	Inclusion Criteria	Intervention	Result
Detection of latent tuberculosis infection in hemodialysis patients : comparison between the quantiferon-tuberculosis gold test	Hussein, Yousef & Ali, 2017	HD unit at the Sohag University Hospital, Sohag, Egypt	74	74 adults patients with ESRD on HD	2-step TST QFT-G	28 (37.8%) QFT-G/TST +, 26 (35.1%) QFT-G +, 10

and the tuberculin skin test						(13.5) TST +
Comparison of the tuberculin skin test and Quanti-FERON-TB Gold In-Tube (QFT-G) test for the diagnosis of latent tuberculosis infection in dialysis patients	Jahdali *et al*., 2013	Hemodialysis unit of King Abdul Aziz Medical City-National Guard Hospital-Riyadh (KAMC-R) Saudi Arabia	200	200 adults patients oh HD unit	2-step TST QFT-G	21 (10.5%) QFT-G/TST +, 44 (22%) QFT-G +, 5 (2.5%)
Value of the tuberculin skin testing and of an interferon-gamma release assay in haemodialysis patients after exposure to M. tuberculosis	Anibarro *et al*., 2012	Spanyol	52	52 patients with ESRD attending haemodialysis unit	2-step TST QFT-G	TST + 15 (28.8%) QFT-G +/TST +, 3 (5.8%) QFT-G +, 5 (9.6%)
High prevalence of latent tuberculosis infection in dialysis patients using the interferon-gamma release assay and tuberculin skin test	Leet et al., 2010	Taiwan	190	190 patient with ESRD	2-step TST and QFT-G	TST + QFT-G 32 (34.4%), TST 42 (53.9%)

HD Haemodialysis, TST Tuberculin skin test, QFT-G Quanti-FERON Tuberculosis-Gold, ESRD End-stage renal disease

DISCUSSION

Mycobacterium tuberculosis is present in airborne droplets from patients with active TB. Infected droplet droplets remain suspended in the air and can be transmitted when inhaled. About 90% of infected patients can usually respond to Mycobacterium tuberculosis infection with granuloma formation, without showing clinical symptoms of active TB disease, in a condition known as latent TB infection. 10% of patients infected with various immunological conditions, Mycobacterium tuberculosis began to grow and latent TB developing into active TB (Kim & Kim, 2018; Salgame, 2015).

One of the groups at risk that is easily infected with Mycobacterium tuberculosis in patients with end-stage renal disease (ESRD). Based on the analysis carried out on 4 selected articles, it was found that all studies used the same examination, namely TST with a cutoff ≥ of 10 mm and a positive QFT-G result with an IFN-gamma response to TB antigen ≥ 0.35 IU / ml. In our study, the total number of patients from the four studies was 516 hemodialysis patients. The data obtained is that there is a high prevalence of LTBI in ESRD patients undergoing hemodialysis. Patients with end-stage renal disease (ESRD) who undergo dialysis experience immune dysfunction which increases the risk of infection (Jha et al., 2013; Anand, Bitton & Gaziano, 2013; Anderson et al., 2009). In this group, tuberculosis develops and is at risk of reactivating from LTBI to active TB. Patients undergoing dialysis have 10-25 times increased risk of LTBI reactivation compared with the general population (http://www.respiratory guidelines.ca/tbstandards-2013).

Identification of LTBI in hemodialysis patients is an effort to provide treatment for infection and prevent morbidity and mortality

associated with TB reactivation (Campbell, Krot & Mara, 2016).

This systematic review identified the prevalence of LTBI incidence in patients with ESRD undergoing hemodialysis at the dialysis center unit which was obtained from 4 selected studies conducted in various countries such as Egypt, Saudi Arabia, Spain, and Taiwan using the same type of study, namely the prospective study. Each country has a different incidence of LTBI because it is also caused by differences in the incidence of tuberculosis in that country. In 2014, the global LTBI burden was 23%, or an estimated 1.7 billion individuals. According to WHO, Southeast Asia, West Pacific, and African regions are the regions with the highest prevalence and accounting for 80% of LTBI infection. The prevalence of new infections is 0.8% (95% UI: 0.7% ± 0.9%) of the global population, totaling 55.5 (95% UI: 48.2 ± 63.8) million people residing in the high risk of TB disease, in which 10.9% (95% UI: 10.2% ± 11.8%) were resistant to isoniazid. The current number of LTBI, assuming no additional infections from 2015 onwards, will cause new TB incidents in the region of 16.5 per 100,000 per year in 2035 and 8.3 per 100,000 per year in 2050 (Houben & Dodd, 2016). The South-East Asia Region bears more than 40% of the global burden of TB incidence including nearly 35% of LTBI burden worldwide. It is estimated that 43.3 million of the 587 million people living with LTBI include children under 15 years, namely 7% (WHO, 2019). The prevalence of LTBI in several countries in East Asia also shows a high number and shows the difference in the prevalence of several countries such as Malaysia and Japan which shows an average of 10.6% and 9.9%. However, it is still lower than Taiwan 14.5%, South Korea 17.2%, India 31%, and China 33.6% (Almufty, Abdulrahman & Merza, 2019).

Based on 4 identified articles, it is found that the study conducted by Hussein, Yousef & Ali reported a high prevalence of LTBI (37.8%) from a total of 74 patients with ESRD, and the study conducted by Jahdali et al., Reported the prevalence of LTBI (10.5%) which was lower compared to a later study of 200 patients with ESRD in the hemodialysis unit. The study, conducted in the third article by Anibaro et al, reported that there was a high prevalence of LTBI with positive QFT and two-step TST examination results (28.8%) in 52 hemodialysis patients with ESRD in the hemodialysis unit. Research conducted in the fourth article by Lee et al. reported that hemodialysis patients from countries with moderate TB burden also had a high prevalence of LTBI incidence using QFT (34.4%) and two-step TST with a cutoff ≥ 10 mm (53.9%) of a total of 190 patients. In this study, all hemodialysis patients were identified from a history of TB, history of BCG immunization, comorbid disease, chest x-rays, clinical examination for signs and symptoms, weight loss and none of them had active TB. Dialysis patients are not only at high risk for reactivation to active TB but also at risk of transmission from patient to patient in the dialysis center unit (Leet et al., 2010).

Based on the analysis of the systematic review conducted on 4 selected articles, it was found that all studies used the same examination, namely TST with a cutoff ≥ 10 mm and positive QFT-G results with IFN-gamma response to TB antigen ≥ 0.35 IU / ml. Two of these methods can be used to screen individuals exposed to Mtb with LTBI conditions, namely TST and QFT-G. TST was developed over a century ago at a lower cost and is more widely used. IGRA was applied to clinical practice more than a decade ago, but distribution and implementation cost a lot higher (Salgame et al. 2015). WHO (2018) recommends diagnosis using commercially available IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB). The diagnostic examination and clinical evaluation in LTBI are specifically for individuals who are at high risk of getting M. tuberculosis infection or at high risk of developing active TB followed by M. tuberculosis infection. The examination consists of a clinical evaluation and a radiological evaluation that can rule out active TB disease and determine the increased risk of

active TB. In conditions with active TB, and immunological examination of LTBI is needed (Salgame et al., 2015).

According to the 2019 CDC states that groups at risk who experience immunosuppression for other reasons (e.g., taking prednisone> 15 mg/day is equivalent to 1 month or more, using TNF-α antagonists) can be said to be LTBI positive with TST examination if the cutoff is> 5 mm. However, the TST test results can be false positive in conditions that cause anergy, such as in patients with end-stage renal disease. Then the Interferon-gamma Release Assay (IGRA) such as Quantiferon or T-Spot TB is more recommended than the tuberculin skin test (TST) because it has higher specificity and sensitivity than the tuberculin test. Interferon-gamma Release Assay (IGRA) is a diagnostic test that measures the release of IFN-gamma by T lymphocytes in response to a specific antigen M. tuberculosis (Druszcynska et al., 2012).

Based on a systematic review of data from 4 articles, it was identified that all respondents who were declared to have had LTBI were also given treatment according to the guidelines. All patients with LTBI should also undergo continued treatment until the results of the second test and other medical evaluations are known. In some high-risk contacts, treatment is recommended even in the absence of a positive TST or IGRA test result. This should be consulted with TB control programs for the management of people who have a history of close contact with TB. LTBI treatment that can be run according to the guidelines includes: 1) If a person is exposed to TB that is known to be sensitive to drugs or unknown drug sensitivity and the TST or IGRA results are positive then they are treated with the INH regimen and 12-dose RPT for individuals aged 2 years or more, or with INH or RIF regardless of age; 2) If a person is exposed to TB that is resistant to INH and the TST or IGRA result is positive then he / she is treated with RIF for 4 months; 3) If a person is exposed to TB that is resistant to RIF and the TST or IGRA result is positive then it is treated with INH alone; 4) If someone is exposed to TB with known MDR and positive TST or IGRA results, consult an expert in MDR TB treatment. Retreatment can be indicated for people who are at high risk of reinfection and developing TB disease (eg, young children and people who are immunocompromised) (CDC, 2019). The high prevalence of TST and QFT-G examination results can also be caused by several risk factors such as TB endemic areas, frequency of hospital contacts, elderly, and decreased immunity, especially in ESRD patients (Sayarlioglu et al, 2011).

CONCLUSSION

Based on tracing results from a systematic study by examining publications in the last 10 years, it was found that a high prevalence of LTBI in end-stage renal disease patients undergoing hemodialysis with a total sample of 516 patients through QFT-G and two-step TST examinations. This can be because patients with end-stage renal disease (ESRD) who undergo dialysis experience immune dysfunction which increases the risk of infection, one of which is an infection caused by Mycobacterium tuberculosis. Therefore, screening and treatment of LTBI in ESRD patients is needed to prevent LTBI reactivation from progressing to active TB and to prevent transmission from individual to individual.

REFERENCES

Almufty H B, Abdulrahman I S, Merza M A. 2019. Latent tuberculosis infection among healthcare workers in Duhok Province: from screening to prophylactic treatment. Tropical Medicine and Infectious Disease, 4:85; doi: 10.3390/tropicalmed4020085

Anand S, Bitton A, Gaziano T. 2013. The gap between estimated incidence of end-stage renal disease and use of therapy. PLOS ONE 2013; 8: e72860.

Anderson S, Halter J B, Hazzard W R, et al. Prediction, progression, and outcomes of chronic kidney disease in older

adults. J Am Soc Nephrol 2009; 20: 1199–1209.

Campbell J R, Krot J, & Marra F. 2016. Latent tuberculosis diagnostic tests to predict longitudinal tuberculosis during dialysis: a meta-analysis. International Journal Lung Disease, http://dx.doi.org/10.5588/ijtld.15.0825.

Canadian Thoracic Society and Public Health Agency of Canada.Canadian tuberculosis standards. 7th ed. Ottawa, ON, Canada: PHA. 2013. http://www.respiratoryguidelines.ca/tb standards-2013.Accessed Oktober 2020.

CDC, 2019, TB laten : a guide for primary health care providers. (Online) 1 Agustus 2019', Available from: https://www.cdc.gov/tb/publications/ltbi/treatment.htm#two.

Druszczynska M, Kulbat MK, Fol M, Wlodarczyk M, Rudnicka W. 2012. Latent M. tuberculosis Infection–pathogenesis, diagnosis, treatment and prevention strategies. Vol. 61, No 1,3-10, Polish Journal of Microbiology.

Hamdan Al Jahdali, Anwar E. Ahmed, Hanan H. Balkhy, Salim Baharoon, Fayez F. Al Hejaili Ali Hajeer, Ziad Memish, Salih Binsalih Abdullah A. Al Sayyari. 2013. Comparison of the tuberculin skin test and quanti-FERON-TB gold in tuber (QFT-G) test for the diagnosis of latent tuberculosis in dialysis patients. Journal of Infection and Public Health, http://dx.doi.org/10.1016/j.jiph.2013.02.002.

Houben R M G & Dodd P J. 2016.The global burden of TB laten : a re-estimation using mathematical modelling. PLOS ONE, 13(10): e1002152, doi:10.1371/journal. pmed.1002152.

Hussein MT, Yousef LM & Ali AT. 2017. Detection of latent tuberculosis infection in hemodialysis patients: Comparison between the quantiferon-tuberculosis gold test and the tuberculin skin test. Egyptian Journal of Bronchology. DOI: 10.4103/ejb.ejb_19_17

Jha V, Garcia-Garcia G, Iseki K, et al. 2013. Chronic kidney disease: global dimension and perspectives. Lancet Lond Engl, 382: 260–272.

Kim HW & Kim JS. 2018. Treatment of TB laten and its clinical efficacy.The Korean Academy of Tuberculosis and Respiratory Disease, Doi.org/10.4046/trd.2017.0052.

Lee SSJ, Chou KJ, Dou HY, Huang TS, Ni YY, Fang HC, Wu KS, Tsai HC, Wang YH, Len Sy C, Lin HH, Chen JK, Chen YS, 2010. High prevalence of latent tuberculosis infection in dialysis patients using the interferon-gamma release assay and tuberculin skin test. Clin J Am Soc Nephrol 5: 1451–1457.

Luis Anibarro, Matilde Trigo, Diana Feijoó, Mónica Ríos, Luisa Palomares, Alberto Pena Carlos Villaverde and África González-Fernández. 2012. Value of the tuberculin skin testing and of an interferon-gamma release assay in haemodialysis patients after exposure to M. tuberculosis. BMC Infectious Diseases, 12:195

Salgame P, Geadas C, Collins L, Lopez EJ, & Ellner JJ. 2015. TB laten revisiting and revising concepts. Tuberculosis Journal, http://dx.doi.org/10.1016/j.tube.2015.04.003

Tang P & Johnston J. 2017. Treatment of latent tuberculosis.Curr Treat Options Infect Dis. DOI 10.1007/s40506-017-0135-7.

Sayarlioglu H, Gul M, Dagli E, Dogan E, Sahin M, Ucar M. 2011. QuantiFERON-TB gold test for screening latent tuberculosis infection in haemodialysis patients. Tuberkuloz ve Toraks Dergizi; 59 (2) (2011) 105-110.

WHO, 2019, 'latent tuberculosis: Updated and consolidated guidelines for programmatic management. Background document on the 2019

revision'.Accesed July 17th2019, WHO Global TB Programme.

WHO, 2019, 'Programmatic management of latent tuberculosis, South-east Asia regional action plan', Accesed July 17th2019, WHO Global TB Programme.