Identification Latent Tuberculosis Infection In Hemodialysis Patients: A Systematic Review

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Abstract

Background and Aim: Tuberculosis is a chronic infectious disease that can spread through sputum droplets containing Mycobacterium tuberculosis (Mtb). Infection Mtb can give an asymptomatic condition that can persist for years in the host called latent tuberculosis infection (LTBI). LTBI is a dormant condition of the Mycobacterium tuberculosis. It is often defined as a condition without symptom with the tuberculosis organisms in the lung tissue, without clinical signs, or radiological signs. LTBI can become active tuberculosis (TB) in immunosuppressed hosts such as patients with end-stage renal disease (ESRD). Screening TB infection using examination tests such as the TST, QFT-G, and complete treatment in hemodialysis patients can avoid the progression of LTBI into active-TB. This study identified the incidence of LTBI in hemodialysis patients using the TST and QFT-G.
Methods: A Systematic Review study to identify LTBI in hemodialysis patients using the Prefered Reporting Items for Systematic Review and Meta-analysis protocol. The three main electronic databases used are PubMed, EMBASE, Google Scholar.
Results: Derived from 67 related articles and obtained 4 articles based on inclusion criteria. Totally 516 hemodialysis patients and the study showed that the incidence of LTBI using TST (cut off $\geq$ 10 mm) and QFT-G ($\geq$ 35 IU/ml) showed that TST /QFT-G positive 68 patients (18.47%), only positive TST 22 patients (5.97 %), only positive QFT-G 77 patients (20.92%).
Conclusion: This study showed that a high incidence of LTBI in hemodialysis patients. Early detection and complete treatment of LTBI should be performed in hemodialysis patients to avoid the reactivation of LTBI into active TB.

Keywords: ESRD; Hemodialysis patient; LTBI; TST; QFT-G

INTRODUCTION

Tuberculosis infection defined is an infectious disease caused by Mycobacterium tuberculosis, leading cause of morbidity and mortality in worldwide 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 infection and 1.6 million cases of death due to TB disease occurred in 2017. WHO End TB Strategy has conducted as one of the main strategies for tuberculosis control is through individual identification with latent tuberculosis infection. One of strategy to reduce TB is to give 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 Mycobacterium tuberculosis is present in the lungs tissue without any clinical or radiological signs. LTBI can become active-TB in hosts who experience immunosuppression due to comorbid disease or medical therapy (Campbell, Krot & Mara, 2016). This condition also occurs in patients with ESRD in hemodialysis center who are receiving hemodialysis therapy and undergoing immunosuppression. The incidence and mortality of Tuberculosis 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). Currently no gold standard for identifying LTBI in a population primarily of hemodialysis patients. The diagnostic tests such as the TST and QFT-G are commonly used in combination in diagnosing Latent Tuberculosis Infection. The purpose of this research to detect the incidence of LTBI in patients ESRD who undergoing hemodialysis in hemodialysis center with QFT-G and two step TST examinations. Using systematic review to investigate the incidence of LTBI in hemodialysis patients.

METHODS

This study uses PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) 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) identification of research question; 3) arrange of protocol; 4) Searching literature; 5) Selection criteria; 6) Practical screen; 7) Quality checklist and procedures; 8) 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: 'ESRD', 'Hemodialysis patients', Latent Tuberculosis infection', 'TST', 'QFT-G', (figure 1).

The inclusion criteria in this study were English articles, full text, prospective study, diagnostic test using two step-TST and QFT-G in hemodialysis patients who were then followed up. Interventions unrelated to the topic were excluded. The three main electronic databases used are

PubMed, EMBASE, Google Scholar published from 2010-2019.

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 (two step-TST / QFT-G cut-off, positive and negative counts).

RESULTS

This study identified from 4 journals. Journal identification was carried out by screening based on appropriateness following the inclusion criteria (Table 1).

The population in this study was published in the international journals with the topic of LTBI in hemodialysis patients. The sample in this study is published in an international journal with the topic of detection of LTBI in ESRD patients undergoing hemodialysis using two step-TST and QFT-G. The inclusion criteria in this study are: 1) English language; 2) Full text article; 3) Published in 2010-2019; 4) using prospective study; 5) The topic of LTBI research in hemodialysis patients; 6) The diagnostic of LTBI 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. The analyzed data based on the author's name, title, research method, diagnostic method, cut-off and results. The results of data extraction in the flow.
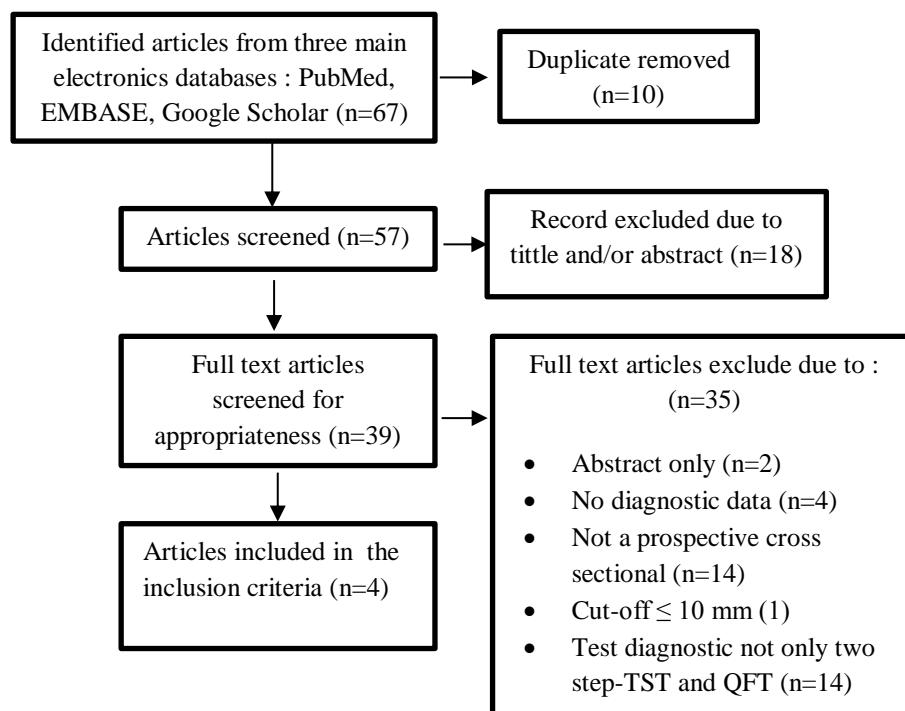

Figure 1. Article identification flow

LTBI infection was evaluated in four journals using two step-TST and QFT-G. All studies reported positive TST results with a cutoff $\geq$ 10 mm and

positive QFT results with IFN-gamma response to TB antigen ≥ 0.35 IU / ml. Based on table 1, totally 516 hemodialysis patients from this study. Data shows that there were 74 patients with ESRD who underwent hemodialysis and had two-step TST and QFT-G examinations result with 28 (37.8%) positive patients, QFT-G examinations result 26 (35.1%) positive patients and two-step TST examination 10 (13.5%) positive patients.

The second article contained 200 patients with ESRD in the hemodialysis unit and 2-step TST, and QFT-G tests with positive results as much 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. 2-step TST and QFT-G tests were carried out with positive results as much 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 1. The results of extraction data

Tittle	Author and Year	Setting	Total Follow up Subject	Inclusion Criteria	Intervention	Result
Detection of LTBI in hemodialysis patients : comparison between the QFT-G and the TST	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 (13.5) TST +
Comparison of the TST and QFT-G test for the diagnosis of latent tuberculosis infection in hemodialysis 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	two-step TST QFT-G	21 (10.5%) QFT-G/TST +, 44 (22%) QFT-G +, 5 (2.5%) TST +
Value of the TST and IGRA in hemodialysis patients after exposure to M. tuberculosis	Anibarro et al., 2012	Spanyol	52	52 patients with ESRD attending hemodialysis unit	two-step TST QFT-G	15 (28.8%) QFT-G +/TST +, 3 (5.8%) QFT-G +, 5 (9.6%) TST +
High prevalence of LTBI in hemodialysis patients using the IGRA and TST	Leet et al., 2010	Taiwan	190	190 patient with ESRD	two-step TST and QFT-G	QFT-G 32 (34.4%), TST 42 (53.9%)

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

DISCUSSION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, globally, affecting about 10 million people every year, and is one of the leading of mortality. Is present in airborne droplets from patients with active TB, so droplets remain suspended in the air and can be transmitted person to person when inhaled. About 90% individual who infected can respond to Mycobacterium tuberculosis infection with granuloma formation, without showing clinical symptoms of active-TB and cannot transmit the disease, this condition known as latent Tuberculosis infection or LTBI. LTBI is defined as a state of persistent immune response to Mycobacterium tuberculosis (Mtb) without clinical symptom of active-TB. End TB Strategy from WHO to reducing 90% of TB mortality and 80% of TB incidence in 2030. The best strategy to reduce the TB burden is to avoid further TB transmission through early diagnosis and complete treatment of LTBI in 10% of infected people and Mycobacterium tuberculosis can reactivation from LTBI into active-TB (Wu et, al., 2021; Kim & Kim, 2018; Salgame, 2015).

One of the risk groups that are easily infected with Mycobacterium tuberculosis are patients with ESRD. Based on the analysis carried out on 4 selected articles, it was found that all studies used the same examination, namely two-step Tuberculin Skin Test (cut-off ≥ of 10 mm) and QFT-G (IFN-gamma ≥ 0.35 IU/ml). In our study, the total number of patients from the four studies was 516 hemodialysis patients. The data obtained showed that there was a high incidence of LTBI in ESRD patients in hemodialysis center. Patients with ESRD who undergo hemodialysis experience immune dysfunction which increases the risk of infection (Jha et al., 2013; Anand, Bitton & Gaziano, 2013; Anderson et al. 2009). In hemodialysis patient, tuberculosis develops and more high risk to reactivating from LTBI to active TB. Patients who undergoing hemodialysis are ten to twenty-five times to have LTBI reactivation than the general population (http://www.respiratoryguidelines.ca/tb standards-2013). Identification of LTBI in hemodialysis patients is an effort to provide treatment for infection can prevent morbidity and mortality associated with TB reactivation (Campbell, Krot & Mara, 2016).

This systematic review identified the prevalence of LTBI in ESRD patients undergoing hemodialysis at the hemodialysis 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. 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 million people (95% UI: 48.2 ± 63.8) residing in the high risk of TB disease, 10.9% (95% UI: 10.2% ± 11.8%) were resistant to isoniazid. The South-East Asia Region contribute for more than 40% of the global burden, 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 show a high number and shows the difference in the prevalence of several countries such as Malaysia (10.6%), Japan (9.9%.), South-Korea (17.2%),Taiwan (14.5%), India (31%), and China (33.6%) (Almufty, Abdulrahman & Merza, 2019).

Based on 4 identified articles, it was 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 research by Jahdali et al. reported the incidence 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 Anibarro et al., reported that there was a high LTBI prevalence 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-G positive (34.4%) and two-step TST with a cutoff ≥ 10 mm (53.9%) from total 190 patients. According in this research, 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. Hemodialysis patients are not only more high risk for reactivation into TB but also more high risk to get transmission from other patient in the hemodialysis center unit (Lee 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 some years ago, but distribution, and implementation cost a lot higher (Salgame et al., 2015). WHO (2018) recommends diagnosis using QFT-G and T-SPOT-TB). The diagnostic examination, and clinical evaluation in LTBI are specifically for peoples who are at high risk of getting M. tuberculosis infection and developing into active TB. The examination consists of a clinical evaluation, and radiological evaluation that can rule out and determine the increased risk to active TB. In conditions with active TB, immunological examination is needed (Salgame et al., 2015).

According to the 2019 CDC states that groups at risk who experience immunosuppression (e.g., taking prednisone 15 mg/day is equivalent to one 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 ESRD. Then the IGRA such as Quanti-FERON or T-Spot TB are more recommended than TST because it has higher specificity and sensitivity than TST. IGRA is a diagnostic test which is used to

measure of IFN-gamma 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 second test and other medical evaluations. Treatment is recommended in some high-risk contacts, even the positive result TST or IGRA test. This should be consulted with TB control programs for the management of people who have 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 (CDC, 2019).

Re-treatment can be indicated for individuals at high risk of reinfection and developing TB disease (e.g., young children, and people who are immunocompromised persons) (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).

CONCLUSION

Based on tracing results from a systematic study by examining publications in the last 10 years, it was found that a high incidence of LTBI in patients with ESRD on hemodialysis center. Total sample of 516 patients through QFT-G and two-step TST examinations. This can be because patients with ESRD on hemodialysis center experience decreased immunity. Therefore, screening and complete treatment of LTBI in ESRD patients is needed to determine the incidence of LTBI in hemodialysis patients and prevent LTBI reactivation from progressing to active TB.

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