Association between Malnutrition Inflammation Score and Latent Tuberculosis among Chronic Hemodialysis Patients

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Abstract

Objective: To investigate the association of malnutrition with latent tuberculosis (TB) among chronic kidney disease (CKD) patients on hemodialysis (HD).

Methods: This was a cross-sectional study conducted at the Hemodiaylisis Unit of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Subjects were patients aged >18 years who had undergone HD twice a week for at least three months. Patients suspected of active tuberculosis (TB), malignancy, or immunocompromised were excluded. Latent TB was diagnosed using the interferon-gamma release assays (IGRA). Malnutrition was defined by a malnutrition inflammation score (MIS) of less than 5. All data including age, sex, CKD etiologies, and laboratory findings were obtained and recorded in a case report form.

Results: A total of 120 subjects were involved in this study. Subjects with positive, negative, and indeterminate IGRA results were 39.2%, 56.7%, and 4.2%, respectively. There was no significant differences in subjects characteristics between positive and negative IGRA subjects. The MIS>5 was shown to have no statistically significant association with positive IGRA subjects (OR=3.47, 95%CI 0.93–12.93).

Conclusion: Malnutrition based on an MIS score of less than 5 is not statically associated, but clinically associated, with latent TB. Further causal inference study to investigate these associations is needed.

Keywords: Chronic kidney disease, hemodialysis, latent tuberculosis, malnutrition

Introduction

Chronic kidney disease (CKD) patients have a greater risk of tuberculosis (TBC) compared to normal kidney function population. Suggestively, uremic retention in CKD patient alters immune response through various mechanisms. Declined phagocytosis function of granulocytes and monocytes/macrophages, suboptimal capacity of antigen presentation by antigen presenting cells (APCs), decreased B lymphocytes production ability, decreased CD4+ and CD8+ T lymphocytes due to increased T lymphocytes apoptosis, and disturbed cell-mediated immunity are the implication of chronic uremic retention.[1]

Protein energy wasting (PEW) and its consequences are commonly occurred among CKD patients, particularly in patients on chronic haemodialysis (HD). Malnutrition also contributes to declined various physiologic functions. Estimating prevalence of PEW in CKD on HD patients is 18–75%.[2] *Malnutrition inflammation score* (MIS) is one of the quantitative nutrition assessment tools. It consists of medical history, physical examination, anthropometry, and laboratory parameters such as albumin, transferrin, total iron binding capacity (TIBC). Previous studies

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proposed MIS as risk stratification among CKD on HD patients in Asia. Five-years study to 809 chronic HD outpatients in South California investigated the association between MIS and health-related quality of life (Hr-QoL). Increased MIS (>2) is associated with double risk of mortality. Another study investigated 155 CKD on HD patients, and concluded that MIS ≥5 is considered as malnutrition.[3,4]muscle wasting and cachexia are common and strongly associated with mortality in CKD, which is reviewed here. RECENT FINDINGS: The malnutrition-inflammation score (KALANTAR Score

Malnutrition has strength relationship with TBC infection. Malnutrition on TBC infection decreases immunity secondary to lymphocyte production and immune cells proliferation. As a consequence, it aggravates the growth of mycobacteria and increases dissemination risk. Reactivation of latent or previous subclinical TBC infection is associated with nutrition status worsening.[5,6]as defined by low body mass index (BMI Moreover, low protein intake is also observed in latent TBC on CKD patients.[7]

Latent TBC infection is frequently not proper documented in CKD on HD patients. Ironically, CKD on HD patient is the one of high-risk population to develop TBC infection. A reported TBC prevalence among CKD on HD patients is 10.6%.[8] In patient with chronic dialysis, the risk of TBC reactivation is increases 10–25 times. Based on interferon-gamma release assay (IGRA), latent TBC is occurred in 22,2% among CKD on HD patients.

Malnutrition status on CKD patient can affect the immune response. It can increase risk of the developing active TBC from the latent one. Furthermore, investigation about association between MIS and latent TBC is needed. By understanding its, progressivity latent-to-active TBC can be monitored. It makes the management of CKD on HD patient more comprehensive, and be able to decreases morbidity and mortality, as well as HrQoL. Our study is aimed to investigate the association of MIS with latent tuberculosis on chronic HD patients.

Methods

This was an analytic-observational study with cross-sectional approach. This study is conducted on routine HD patients in Hemodialysis Unit of Dr. Hasan Sadikin General Hospital Bandung, with the subjects recruitment period of March–May 2020. Subjects aged >18 years and at least three-months with twice a week of HD were included in this study. Patients with malignancy history, infected by human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), getting immunosuppressive therapy, have TB history, or receiving anti-tuberculosis drugs were excluded from this study.

MIS have ten components including change in end-dialysis dry weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, decreased fat stores or loss of subcutaneous fat, muscle wasting, body mass index (BMI), serum albumin, and total iron binding capacity (TIBC). Each component has 0–3 severity score, hence MIS have 0–30 score in range.[9]we matched 203 ND-CKD and 203 TX patients from two independently assembled cohorts of patients based on estimated glomerular filtration rate (eGFR Malnutrition was defined as MIS greater than 5.[4]73% of HD and 71% of PD patients exhibited moderate malnutrition, whilst using MIS, 88% and 90%, respectively were malnourished. DMS and MIS correlated significantly in HD ($r2=0.552$, $p<0.001$

Latent TB was diagnosed according to IGRA results (QUANTIFERON-TB IGRA). IGRA test has been done in 24–48 hours and can be interpreted based on interferon gamma qualitatively according to Table 1.[10]

Subjects that fulfil inclusion criteria and not meet the exclusion criteria was examined by the assessor including history taking, physical examination, and laboratory examination. TB symptoms and sign is consisted of fever, dyspnea, decreased body weight, chronic diarrhea, and lymph node enlargement. All patients were examined for thorax x-ray that expertized by independent radiologist. By certain indications, acid fast bacilli (AFB) staining, AFB culture, abdominal ultrasound, and histopathological examination for lymph node enlargement. All asymptomatic patients were examined for IGRA before HD procedure.

All data were analyzed using SPSS 25.0. Data were managed using REDCap electronical data recorder. Categorical descriptive such as prevalence was analyzed using binomial exact test to reveal its 95% confidence interval. Unpaired T-test with Mann-Whitney as alternative was used for numerical comparison for two-groups. Each p value <0.05 was considered as statistically significant.

This study was conducted and ethically approved by Health Research Ethics Committee of Medical Research, Dr.Hasan Sadikin General Hospital. This study is a part of study project of

Tuberculosis on Chronic Kidney Disease (CKD) on Routine Hemodialysis in Dr. Hasan Sadikin General Hospital Bandung and Habibie Kidney Hospital, Bandung with Ethical Clearance Number of LB.02.01/X6.5/302/2019.

Results

A total of 120 subjects were involved in this study. Subjects with positive, negative, and indeterminate IGRA results were 39.2%, 56.7%, and 4.2%, respectively. Due to small number indeterminate IGRA results (5 subjects), we did not perform further analysis for indeterminate IGRA subjects. Hypertension was predominant as cause of CKD. There was no significant difference in sex distribution, mean of age, hemodialysis duration, hemoglobin levels, serum iron, transferrin saturation, TIBC, and serum albumin between positive and negative IGRA subjects ($p>0.05$). Etiologies of CKD, such as hypertension, diabetes mellitus, etc, were also not significantly different between positive and negative IGRA subjects ($p>0.05$). Detailed baseline characteristics of the subjects was described in Table 2.

According to bivariate analysis in Table 3, malnutrition (MIS>5) was more prevalent in positive IGRA subjects compared to negative IGRA subjects (93.6% vs 80.9%), but not statistically significant ($p=0.052$). MIS>5 was not significantly associated with positive IGRA results (OR=3.47, 95%CI 0.93–12.93).

Discussion

According to our results, the prevalence of latent TB among routine HD patients was 40.9%. This results is higher than two studies reported prevalence in Taiwan, as high-prevalence CKD country.[11,12] Another study in Korea has similar prevalence of positive IGRA results. Forty-two percent of patients who underwent kidney transplantation has positive IGRA results.[13] A study in India also reported the prevalence of latent TB among CKD on HD patients was 36%.[14] These facts are the evidence of latent TB is common in CKD on HD patients.

In our study, among 5 indeterminate IGRA subjects, two subjects has nill value more than 8, meanwhile the others have low mitogen value. This pattern can be occurred due to inadequate lymphocyte amount, decreased lymphocytes activities, IFN-inability of lymphocytes to produce IFN-γ, as well as inappropriate specimen handling.[10] In our study, among 5 indeterminate IGRA subjects, two subjects has nill value more than 8, meanwhile the others have low mitogen value. This pattern can be occurred due to inadequate lymphocyte amount, decreased lymphocytes activities, IFN-inability of lymphocytes to produce IFN-γ, as well as inappropriate specimen handling. On the other hand, indeterminate IGRA results also can be occurred suboptimal immune response to mitogen control or excessive baseline immune activity of the subjects (high nill value). Sharninghausen *et al.*[15] reported the indeterminate results occurred in 3.8% of their subjects, and is associated with low mitogen levels and high nill. Furthermore, Asian ethic, anemia, and hypoalbuminemia are the independent risk factors. Genetic polymorphism on the T cells and natural killer (NK) cells are also related with mitogen control. Phytogemagglutinin is also associated with genetic loci that causing alteration of the lymphocytes activity.

On latent TB infection, host immunity and mycobacteria virulence reach equilibrium state. Hence, it does not yield inflammation state that have effects on symptoms, body composition and size alteration, fat stores, muscle mass, and laboratory findings that

Table 1 Interpretation of QuantiFERON-TB IGRA

Interpretation	Nill	TB response	Mitogen Response
Positive	≤8.0	≥0.35 IU/ml and ≥25% of nill	Any
Negative	≤8.0	<0.35 IU/ml and <25% of nill	≥0.5
Indeterminate	≤8.0	<0.35 IU/ml and <25% of nill	<0.5
	≥8.0	Any	Any

Table 2 Subjects Characteristics

Subjects Characteristics	Total n=115	IGRA (+) n=47	IGRA (-) n=68	P value
Age (years)				
Mean ± SD	47±13	48±12	47±14	0.669[a]
Sex				
Male	54 (47.0)	26 (55.3)	28 (41.2)	0.135[c]
Female	61 (53.0)	21 (44.7)	40 (58.8)	
Hemodialysis duration				
Median (IQR)	50 (27–83)	45 (26–80)	52 (28–87)	0.527[b]
Etiology of CKD				
Hypertensive kidney disease	60 (52.2)	26 (55.3)	34 (50.0)	0.619[c]
Diabetic nephropathy	18 (15.7)	9 (19.1)	9 (13.2)	
Uric acid nephropathy	4 (3.5)	2 (4.3)	2 (2.9)	
Lupus nephropathy	2 (1.7)	1 (2.1)	1 (1.5)	
Obstructive nephropathy	1 (0.9)	1 (2.1)	0 (0.0)	
Glomerulopathy	23 (20.0)	6 (12.8)	17 (25.0)	
Chronic pyelonephritis	6 (5.2)	2 (4.3)	4 (5.9)	
Polycystic kidney diseases	1 (1.5)	0 (0.0)	1 (1.5)	
Laboratory				
Hemoglobin (g/dL)				
Median (IQR)	9.3 (8.2–10.3)	9.4 (8.4 –9.7)	9.3 (8.2–10.3)	0.639[b]
Serum Iron (ug/dL)				
Median (IQR)	50 (41–72)	48 (41–72)	51 (41–72)	0.842[b]
Transferrin saturation (%)				
Median (IQR)	25.3 (19.9 – 37.8)	25.9 (20.4 – 37.3)	24.5 (19.3–37.3)	0.585[b]
Ferritin (ng/mL)				
Median (IQR)	412.6 (166.6–780.3)	397.8 (139.0–704.9)	427.9 (245.2–963.9)	0.270[b]
TIBC (mg/dL)				
Median (IQR)	201 (174–242)	190 (166–246)	204 (178–237)	0.400[b]
Albumin (g/dL)				
Median (IQR)	3.36 (3.17–3.54)	3.35 (3.20–3.46)	3.36 (3.17–3.57)	0.680[b]

Test used: [a]*Unpaired t-test* [b]*Mann Whitney,* [c]*Chi Square,* [d]*Fisher Exact*

Table 3 Association of Latent TB based on IGRA and Malnutrition based on MIS

MIS categories	IGRA (+) n=47	IGRA (-) n=68	P value	OR (95% CI)
>5	44 (93.6)	55 (80.9)	0.052	3.47(0.93 – 12.93)
≤5	3 (6.4)	13 (19.1)		

[a]Analyzed by *Chi Square;* IGRA: interferon-gamma release assay

associated with inflammation. Accordingly, in latent TB infection, mycobacteria proliferation is controlled. It is indicated by efficient cellular interaction and granuloma formation to prevent mycobacteria dissemination.[16] Latent phase of TB infection represents equilibrium state, when host immunity capable to control the infection, but not fully eradicate the pathogens. Granuloma represents immunological and physical barrier to suppress the infection and prevent the dissemination. They play dynamic and sustainable immune control to the mycobacteria replication. Latent TB patients are the highest reservoir for transmission potential. Although majority of patients are not death due to tuberculosis, the highest hazard are TB reactivation and close contact transmission. Estimated risk for TB reactivation is 10%. Disrupted immunity, such as HIV infection, increases the risk up to 10% per year.[6]

This study reveals no significant difference of MIS between positive and negative IGRA results. Suggestively, it is caused by subjective component in MIS assessment such as medical history. MIS have several subjective components such as daily nutritional intake and gastrointestinal symptoms. Depression, fatigue, and cognitive alteration are commonly occurred on CKD on HD patients. Hence, the assessment can be biased. However, MIS is still comparable with dialysis malnutrition score, and strongly correlated with other objective malnutrition parameters including BMI, triceps skin folds, mid-arm muscle area, mid-arm muscle circumference, and serum albumin.[17]one of the strongest predictors of morbidity and mortality in maintenance haemodialysis (HD Although, statistically no significant association of malnutrition (based on MIS>5) with latent TB, with odds ratio of 3.47 (95%CI 0.93–12.93), we consider it as clinically significant. Since no difference subjects' characteristics between positive and negative IGRA, we did not performed analysis for confounding in this study.

Variably results on the previous studies are existed about association between nutrition status and latent TB. Baek et al[7]whether hemodialysis adequacy is associated with LTBI in the ESRD population is unclear. In this study, we aimed to investigate the association between hemodialysis adequacy and LTBI in ESRD patients. METHODS: In the present cross-sectional study, we reviewed all outpatient-based ESRD patients in our artificial kidney room. Interferon gamma release assay (IGRA assessed nutrition status by normalized protein catabolic rate (nPCR) measurement and latent TB by IGRA. Nutrition inadequacy based on nPCR value less than 0.87 g/kg/day predicts latent TB among HD patients significantly. On the other hand, another study revealed no significant association between latent TB and malnutrition among CKD on HD patients.[18] Using simple assessment, such as BMI only, patient with malnutrition were similarly distributed in positive and negative tuberculin skin test subjects. [19]

This study used cut-off >5 of to determine malnutrition in this study. It refers to some previous studies. Another study revealed that MIS score higher than 7 can be able to predict mortality for 18–24 months follow up.[20] It indicates that MIS > 5 has significant risk for 1-year mortality. MIS >5 also used by Harvinder et al on HD and peritoneal dialysis patients. With this cut-off and compared to established guidelines by International Society of Renal Nutrition and Metabolism for Protein Energy-Wasting, MIS had modest sensitivity detect malnutrition in dialysis patients (60–80%).[4] Further diagnostic analysis with higher sample size might be required to support and reveal the fixed and better diagnostic value for MIS cut-off.

As a limitation, our study is merely cross-sectional study. Hence, this is a snapshot representation of association between latent TB and malnutrition, as well as could not determine causal inference of those. Furthermore, other more objective malnutrition assessment tools might be required to accompany the MIS one. As mentioned above, MIS has subjective components of medical history taking that can biased by some condition that commonly occurred in CKD on HD patients, such as depression, fatigue, and cognitive disturbance. These probably affects the assessment. However, our study is the first documentation in Indonesia that investigates the association of nutrition status based on MIS with latent TB among CKD on HD patients. MIS could be used as detection tools of latent TB, even though the further validation and diagnostic investigation are required. Further study to evaluate the causal inference of latent TB and malnutrition is needed.

In conclusion, malnutrition according to MIS > 5 is not statistically associated, but clinically associated with latent TB infection based on IGRA positivity. Further causal inference study is needed to determine, strengthen, and re-evaluate this association.

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