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The Relationship between Nutritional Status and Latent Tuberculosis in Routine Hemodialysis

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Abstract

BACKGROUND: Malnutrition in chronic kidney disease (CKD) patients undergoing hemodialysis (HD) interferes with the natural and adaptive immune response, consequently, increasing the latent tuberculosis (TB) reactivation.

AIM: This study therefore aims to determine the relationship between nutritional status and latent TB in routine HD, using interferon gamma release assays (IGRA), to screen for latent TB.

METHODS AND STUDY DESIGN: This study has an analytical observation cross-sectional design, and was conducted on 120 CKD-HD patients aged 18 years and above, and has been undergoing HD twice weekly for over 3 months, without malignancy, human immunodeficiency virus/acquired immunodeficiency syndrome, history of TB, or radiological evidence at the HD Unit of the Dr. Hasan Sadikin Hospital, Bandung, Indonesia, between March and May 2020, and not currently receiving immunosuppressant or TB therapy. In addition, the age, gender, history of Bacille Calmette-Guerin vaccine, CKD etiology, length of HD, HD adequacy, TB contact history, number of family members, smoking status, body mass index, albumin, malnutrition inflammation score, triceps skinfold thickness (TST), biceps skinfold thickness, suprailiac skinfold thickness (SIST), mid-upper arm circumference (MAC), and normalized protein catabolic rate between positive and negative IGRA groups, of each patient, were determined.

RESULTS: In this study, all the patients met the inclusion and exclusion criteria. Based on the IGRA test, 47 patients (39.17%) tested positive, and 68 (56.67%) tested negative, while the results for the remaining 5 (4.16%) were indeterminate. The malnutrition inflammation score (MIS) score with positive IGRA 23.3 (20.0–26.7) was discovered to differ insignificantly (p value of 0.252) from the negative counterpart 20.0 (16.7–28.4). Meanwhile, in the HD adequacy assessment based on urea reduction rate, a statistically significant difference (p = 0.042) occurred between the positive 70.45 (65.70–76.61) and negative 74.15 (70.71–77.33) IGRA groups. In the smoking status, the positive and negative IGRA were discovered to differ significantly (30 (63.8% vs. 28 (41.2% p = 0.017) OR 2.521 (1.172–5.425). However, in the history of contact with TB patients, the positive and negative IGRA did not differ significantly (4.3% vs. 11.8% p = 0.160). Furthermore, there was a significant difference in TST and MAC, between MIS >5 and MIS ≤5 (p < 0.05).

CONCLUSION: The assessment of nutritional status level, TST, MAC, smoking status, and adequate HD is crucial for CKD patients with routine HD, as these factors present risks of latent TB.

Introduction

Chronic kidney disease (CKD) remains a global health problem, affecting 5–10% of the world's population, with increasing prevalence each year. According to the Global Burden of Disease Study in 2015, CKD is the 12 highest cause of death in the world, causing about 1.1 million deaths worldwide [1]. Meanwhile, tuberculosis (TB) is currently one of the top ten causes of death worldwide, and Indonesia has the highest prevalence of TB in the world (8%) after India (27%) and China (9%) [2].

The occurrence of TB is 10–25 times higher in people with CKD and up to 37 times higher in kidney recipients [3]. This is related to uremic retention in CKD causing impaired immune response due to decreased phagocytosis function of granulocytes and monocytes/macrophages, impaired antigen presentation capacity in antigen presenting cell (APC) cells, decreased number of antigen presentation on dendritic cell surfaces, decreased B lymphocyte production capacity, increased T lymphocyte apoptosis, and cell-mediated immunity (CMI) disorders [4].

In addition to infection in CKD patients, hemodialysis (HD) patients often suffer from protein energy wasting (PEW), and this malnutrition has a detrimental effect [5]. PEW has been shown to be an independent and strong predictor of mortality, life quality, and morbidity in people with CKD, and to be prevalent in about 18–75% of CKD-HD patients [6], [7]. Therefore,

nutritional management is crucial for patients undergoing HD [5].

Furthermore, monitoring the protein-energy nutritional status of dialysis patients is crucial in preventing, diagnosing and treating PEW. A significant longitudinal reduction in anthropometric nutritional parameters, including weight, muscle, and fat mass, as well as an overtime rise in inflammatory markers, including C-reactive protein and pro-inflammatory cytokines, including interleukin-6, is often observed in CKD patients undergoing HD [8].

Meanwhile, a recent study conducted in Korea during 2019, on 90 CKD-HD patients, using the interferon gamma release assays (IGRA) test, reported a 22.2% prevalence of latent TB in CKD patients, and the examination of protein catabolic rate (nPCR) showed that low protein intake was associated with the risk of latent TB in the CKD population [9]. Another study on 375 CKD patients in Taiwan from 2013 to 2017 showed mid-upper arm circumference (MAC), body fat, serum creatinine, uric acid, and dialysis adequacy values were associated with a lower risk of mortality, while inflammation and hyperglycemia are associated with a greater mortality risk.

However, further studies are required to define the relationship between various nutritional markers and latent TB. Furthermore, patients with latent TB and low body mass index (BMI) are at risk of developing active TB, and malnutrition is an important risk factor for TB reactivation in dialysis patients with high risk of latent TB, partly due to the decreased CMI. Conversely, TB patients experience significant weight loss with loss of lean body mass and fat. Thus, cytokine activation and abnormal protein metabolism interact in both directions, with TB and malnutrition [9].

Materials and Methods

The participants of this study were CKD patients undergoing routine HD (CKD-HD) at the Dr. Hasan Sadikin Hospital Bandung, Indonesia, and the inclusion criteria was patients aged 18 years and above, undergoing routine HD twice weekly for over 3 months with HD frequency 2 times a week, while the exclusion criteria was patients with malignancy, human immunodeficiency virus/acquired immunodeficiency syndrome, radiological evidence or history of TB, currently receiving immunosuppressive or TB therapy.

This research is an analytical observation study, with a cross-sectional design, and the patients fulfilling the inclusion and exclusion criteria were subjected to anamnestic, physical, and supporting examinations to eliminate the possibility of active TB. Subsequently, the blood serum levels of the patients without TB symptoms were tested prior to HD, to check for IGRA. Meanwhile, personal data, including the age, gender, history of Bacille Calmette-Guerin (BCG) vaccine, CKD etiology, length of HD, HD adequacy, TB contact history, number of family members, smoking status, BMI, albumin, MIS, triceps skinfold thickness (TST), biceps skinfold thickness (BST), suprailiac skinfold thickness, MAC and nPCR levels of the subjects, were also collected.

This study was conducted after approval was obtained from the health research ethics committee, Faculty of Medicine, Universitas Padjadjaran, and the Dr. Hasan Sadikin Hospital, Bandung, Indonesia. In addition, this research is part of the “TB study in CKD patients, undergoing Routine HD at the Dr. Hasan Sadikin Hospital and Habibie Kidney Special Hospital, Bandung,” with research ethics number LB.02.01/X6.5/302/2019.

Results

In this study, only 120 of the 159 CKD patients undergoing routine HD in the HD Unit of Dr. Hasan Sadikin Hospital, Bandung, Indonesia, met the exclusion and inclusion criteria. Based on the IGRA test, 47 people (39.17%) tested positive, 68 people (56.67%) tested negative, while the results of the remaining 5 (4.16%) were indeterminate.

Table 1 shows the basic characteristics of research subjects. The average age of the research subjects was discovered to be 47 ± 13 years. Meanwhile, in terms of gender distribution, there were more men (54%) in the positive IGRA group, and more women (58.8%), in the negative IGRA group.

Based on the urea reduction rate (URR) value, a statistically significant difference occurred between the positive and negative IGRA groups (70.45 [65.70– 76.61] vs. 74.15 [70.71–77.33]), with p 0.042 (Table 2). In addition, there were more smokers and patients with history of smoking, in the positive IGRA group, compared to the negative counterpart, with a significant difference (30 [63.8% vs. 28 41.2% p = 0.017]). Furthermore, the history of previous contact with TB patients was lower in the positive IGRA group, compared to the negative counterpart; however, the values did not differ statistically.

Discussion

According to this study, the latent TB prevalence based on the IGRA test was discovered to be 39.17%. This prevalence is higher compared to the report by Shu *et al*., at Taiwan, in 2012–2013, stating latent TB with IGRA test was 21.3%, with 3.5% having indeterminate results [10]. Meanwhile, in the

Table 1: Basic characteristics of research subjects

Basic characteristics	Total *n*=118	IGRA (+) *n*=50	IGRA (−) *n*=68	*P* value
Age (years)				
Mean ± SD	47 ± 13	48 ± 12	47 ± 14	0.840[a]
Gender				
Male	55 (46.6)	27 (54.0)	28 (41.2)	0.168[c]
Female	63 (53.4)	23 (46.0)	40 (58.8)	
History of BCG Vaccine				
Yes	73 (61.9)	29 (58.0)	44 (64.7)	0.459[c]
Not	45 (38.1)	21 (42.0)	24 (35.3)	
Length of HD (years)				
Median (Range)	50 (5 – 177)	45 (6 – 177)	53 (5 – 147)	0.442[b]
Body mass index				
Mean ± SD	0.39 ± 0.66	0.32 ± 0.56	0.47 ± 0.76	0.429
Number of Family Members				
1–4 people	78 (66.1)	34 (68.0)	44 (64.7)	0.709[c]
≥5 people	40 (33.9)	16 (32.0)	24 (35.3)	
Smoking status				
Yes	61 (51.7)	32 (64.0)	29 (42.6)	0.022[c]
Not	57 (48.3)	18 (36.0)	39 (57.4)	
CKD etiology				
Hypertension kidney disease	62 (52.5)	28 (56.0)	34 (50.0)	0.760[c]
Diabetic nephropathy	19 (16.1)	9 (18.0)	10 (14.7)	
Uric acid nephropathy	4 (3.4)	2 (4.0)	2 (2.9)	
Lupus nephropathy	2 (1.7)	1 (2.0)	1 (1.5)	
Obstructive nephropathy	1 (0.8)	1 (2.0)	0 (0.0)	
Glomerulopathy	23 (19.5)	7 (14.0)	16 (23.5)	
Chronic pyelonephritis	6 (5.1)	2 (4.0)	4 (5.9)	
Polycystic kidney	1 (0.8)	0 (0.0)	1 (1.5)	
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]
nPCR	0.72 (0.24–0.95)	0.69 (0.38–0.98)	0.70 (0.24–0.98)	0.649[b]

*The analysis utilized the [a]Unpaired t-test, [b]Mann–Whitney, [c]Chi-square, and dFisher Exact assessments. **IGRA: Interferon-gamma release assays, SD: Standard deviation, BCG: Bacille Calmette-Guerin, HD: Hemodialysis, CKD: Chronic kidney disease, nPCR: Normalized protein catabolic rate.

multivariate analysis of the advanced-stage CKD or CKD-HD group, the independent predictors were discovered to be age, serum albumin level, need for dialysis, and history of TB [10]. A study by Chung *et al*., involving 167 patients in Korea, with CKD-HD, reported latent TB with 45.9% positive IGRA [11]. Three years later, Kim conducted an IGRA test on 126 kidney failure patients in the same country, about to undergo kidney transplant, and discovered positive IGRA in 42.1% of the patients [12]. Furthermore, a study by Agarwal, in India, reported positive IGRA in 36% of 185 CKD-HD patients, nearly the same rate as this research [13].

Table 2: Bivariate analysis of research variables (MIS, HD adequacy, smoking status, and TB contact history) on IGRA

Variable	IGRA (+) n = 47	IGRA (−) n = 68	P Value	OR (95% CI)
MIS				
>5	44 (93.6)	55 (80.9)	0.252[a]	3.467 (0.929–12.932)
≤5	3 (6.4)	13 (19.1)		
HD adequacy				
URR	70.45 (65.70 – 76.61)	74.15 (70.71 –77.33)	**0.042**[b]	
<65	11 (23.4)	11 (16.2)	0.333[a]	1.583 (0.622–4.029)
≥65	36 (76.6)	57 (83.8)		
Smoking status				
Smoking	30 (63.8)	28 (41.2)	**0.017**[b]	2.521 (1.172–5.425)
No	17 (36.2)	40 (58.8)		
TB contact history	2 (4.3)	8 (11.8)	0.160[c]	

*The analysis utilized the aMann–Whitney, bChi-square, and cFisher Exact tests. **IGRA: Interferon gamma release assays, OR: Odds ratio, MIS: Malnutrition inflammation score, HD: Hemodialysis, URR: Urea reduction rate, TB: Tuberculosis.

In this study, the mean age of the positive and negative IGRA groups was discovered to differ insignificantly (48 ± 12 vs. 47 ± 14 p 0.669) (Table 1). This is in line with the report by Rao, with a mean age of 46.4 ± 10.4 and 68.7% of the subjects being male [14]. However, in the study by Agarwal, with the mean age was lower, and discovered to be 36.7 ± 12.3 years, with 69.7% of the subjects being male [13]. Meanwhile in the report by Shu, on 303 CKD-HD patients tested for IGRA, the mean age was higher, and found to be 63.5 ± 12.7 p <0.001 [10].

In this study, there are more total female (53%) than male (47%) subjects. However, the positive IGRA group had more men (55.3%), while the negative counterpart had more women, and the two groups differed insignificantly. This is related to the existing risk factors presented by smoking habits and is in accordance with the studies by Agarwal and Rao [13], [14]. Similarly, in the general populace, there is a 2.2 times higher occurrence of TB in men, compared to women [14].

Furthermore, the duration of HD was shorter in the positive IGRA group was shorter (45 [26–80]), compared to the negative counterpart (52 [28–87]); however, the difference was insignificant. This is in line the study by Shu, reporting a longer HD duration in the negative IGRA group (56.4 ± 51.6 vs. 51.6 ± 43.2 months) [10]. Hemodialysis is also able to cause immune deficiency in CKD patients, through a pro-apoptotic effect due to direct blood contact with the dialysis membrane, and this often affects cell-mediated immune reactions [15].

Based on the URR values, HD adequacy was significantly lower in the positive IGRA group, compared to the negative. However, after analysis with logistic regression at URR >65% and URR ≤65%, this difference was discovered to be statistically insignificant, with a p value of 0.333, OR (95% CI) 1.583 (0.622–4.029), and an even higher minimum URR percentage value is possibly required. HD adequacy is closely related to toxic uremic clearance in the form of urea, during hemodialysis sessions. Furthermore, impaired immune response due to uremic retention is caused by decreased phagocytosis function of granulocytes and monocytes/macrophages, impaired antigen presentation capacity on APC cells, decreased

number of antigen presentations on dendritic cell surfaces, decreased production capacity of B lymphocytes, increased T lymphocyte apoptosis, and CMI disorders [4].

Meanwhile, in terms of CKD etiology, most (52.5%) patients suffered from hypertension, followed by diabetes mellitus (DM), primary glomerulopathy, chronic pyelonephritis, uric acid nephropathy, lupus nephropathy, obstructive nephropathy, and polycystic kidney disorder. The etiology of DM was also found to be more prevalent in the positive IGRA group (19.15%) and compared to the negative (13.2%). Furthermore, the incidence of DM has been found to increase the risk of TB, with the Ai study reporting a relative risk between 1.16 and 7.83 [16]. A report by Kumar on the DM population in India, discovered 88 patients at high risk of TB reactivation. Of these 88 patients, 44 patients had been diagnosed with DM, while the remaining 44 had no diabetes [17]. Similarly, a study by Koesoemadinata *et al*. on the DM population in Bandung, also reported a high prevalence of latent TB 38.9% (95% CI 34.7–43.2) [18].

In addition, patients with positive IGRA were discovered to have higher MIS score, compared to the negative group (23.3 [20.0–26.7] vs. 20.0 [16.7–28.4]), without a significant difference (p = 0.252). This was due to subjective components, including medical history as well as physical examination, having a lower value, and objective components, body size and laboratory data, having a greater value.

The previous studies showed an optimal MIS cutoff point (MIS >5) for early malnutrition detection toward TB infection. A report by Ho on 257 stable CKD patients in Taiwan, obtained probability of death in CKD HD with MIS 3, 4, and 5 at 10.40 and 80%. This shows MIS >4–5 has a significant effect on the 1 year risk of death [19]. Meanwhile, a report by Harvinder on the nutritional status examination of 155 HD and 90 PD patients in Malaysia, through MIS, showed MIS ≥5 indications for malnutrition, and malnourishment in 88% of HD subjects, as well as 90% of PD subjects, according to the MIS scores [20].

In terms of smoking status, the positive IGRA group was discovered to have more smoking habits, and this differed statistically from the negative in the bivariate analysis, with an OR of (95% CI) 2,521 (1.172–5.425). These results are also in line with the study by Shu *et al*., stating smoking was the independent risk factor for latent TB is smoking, with an OR of 2.675 (1.061–6.747) [10]. Similarly, a report by Horne showed that the general population in America has an average latent TB prevalence of 5.3%, while the latent TB prevalence among never smokers, current smokers, and non-smokers was 4.1%, 6.6%, and 6.2%, respectively [21]. In the multivariable model, currently smoking was associated with latent TB (OR 1.8; 95% CI, 1.1–2.9).

In this study, no significant differences were recorded in the history of contact with TB patients between the positive and negative IGRA groups (4.3% vs. 11.8% p = 0.160). This is in accordance with the report by Chung on HD patients, stating no significant difference in IGRA results of high and low-risk TB patients (41.2% vs. 44%). Patients with high risk of latent TB are said to have a history of close contact with TB patients, old TB features on chest X-ray examination or a history of TB infection [11]. Similarly, Horne reported no significant relationship between latent TB and TB history, with active TB [21]. Conversely, a study by Fox in Canada, on multivariable household analysis with active TB patients obtained an OR of 14.7; 95% CI 1.6–137.3 [22]. The difference in this study is contact with active TB patients occurred before the occurrence of CKD and undergoing HD.

In addition, the results of albumin level examination were below normal, with a median of 3.36 (3.17–3.54) g/l. The positive IGRA group also showed a tendency to be lower, compared to the negative IGRA (3.35 [3.20–2.46] vs. 3.36 [31703.57] g/dl), with a p value of 0.680. Similarly, a report by Sayarlioglu *et al*., on 89 HD patients on Taiwan, obtained a positive IGRA result of 45% [23]. However, a study by Baek *et al*. reported no significant difference in albumin levels between the two groups (3.8 [3.5–4.0] vs. 3.8 [3.4–3.9]; p = 0.429), while the research by Rao *et al*. in India discovered low albumin (3 g/dl) was a risk factor for TB infection (p <0.001) [9], [14].

Serum albumin is an acute negative reactant phase, and therefore reduces in level, during the inflammatory process. Furthermore, serum albumin is often used to measure protein reserves and possibly compromised by the occurrence of an acute infection in dialysis patients [24], [25]. Chronic infections or other infections are able reduce serum albumin concentrations because of reduced albumin synthesis within the liver, in response to increased production of the reactant acute phase [26], [27]. In the past, albumin levels have been used as a determinant of nutritional status, but this is relatively insensitive to nutritional changes. The substance is present in the body in relatively large amounts and has a half-life of 20 days, with a concentration affected by the patient's hydration state and renal function. This level usually takes 14 days to return to normal when the reserves are exhausted [28].

Meanwhile, no significant difference in nPCR was recorded between the positive and negative IGRA groups (p > 0.05); however, the positive group showed a tendency to has lower values. In the calculation of body size based on weight and height ratio, there was no difference in BMI between the two groups, both having BMI ≥20 kg/m^2. Similarly, Baek *et al*. study on 90 chronic HD patients reported no significant difference in BMI between the positive and negative IGRA groups (23.0 ± 3.1 vs. 23.5 ± 3.5; p = 0.525) [9]. However, in a report by Lee *et al*. on 93 HD patients, 27.3% were malnourished (BMI <20), with a positive IGRA (adjusted OR 0.46; p = 0.21) [29].

A high BMI appeared to offer more protection to CKD-HD patients, as seen in a study by Abbot, reporting patients with BMI >30 kg/m^2 with improved survival (adjusted hazard ratio (HR) 0.89 [95% CI: 0.81–0.99]; p = 0.042) and a better 5-year survival rate of 40%, compared to 32% in patients with a BMI below 30 kg/m^2 (p < 0.01) [26]. In the HEMO study, decreased TST and MAC were associated with risk of infection-related treatment (HR 1.16 [95% CI: 0.98–1.37] and HR 2.45 [95% CI: 1.55–3.88]) as well as all causes of death (HR 1.06 [95% CI: 0.99–1.13] and HR 1.58 [95% CI: 1.29–1.94]), especially at BMI below 25 kg/m^2 [26].

According to the results of analysis in Table 3, significant differences occurred in TST1, TST2, MAC1, MAC2, MAC3, and MAC Mean, between MIS >5 and MIS≤5 (p < 0.05). The median of TST1, TST, MAC2, MAC3, and MAC mean was discovered to be lower at MIS >5, compared to MIS ≤5. This is in line with a study by Yigit *et al*., showing a significant negative correlation between MIS scores and anthropometric examinations ([TSF, BSF, MAC, and mid-arm muscle circumference]) in hemodialysis patients [30]. Similarly, a study in China on 82 HD patients reported a significant relationship between MAC and MIS values [31].

Table 3: Anthropometric measurement based on MIS classification

Variable	Total n = 118	MIS >5 n = 102	MIS ≤5 n =16	Nilai p
TST 1	10 (1–38)	10 (1–38)	12 (7–32)	0.038*
TST 2	10 (1–39)	10 (1–39)	13 (7–34)	0.053
TST 3	10 (1–39)	10 (1–39)	13.5 (7–34)	0.038*
TST Mean	10 (1–39)	10 (1–39)	12.5 (7–33)	0.051
BST 1	6 (1–32)	6 (1–32)	7 (2 - 22)	0.099
BST 2	6 (1–34)	6 (1–34)	7.5 (2–24)	0.076
BST 3	6 (1–34)	6 (1–34)	6.5 (2–26)	0.181
BST Mean	6 (1–33)	6 (1–33)	7 (2–24)	0.104
SIST 1	12 (1–42)	11.5 (1–42)	17 (2–41)	0.197
SIST 2	12 (1–42)	12 (1–42)	16.5 (3–40)	0.287
SIST 3	12 (1–44)	12 (1–44)	16 (3–40)	0.351
SIST Mean	12 (1–43)	12 (1–43)	16.5 (3–40)	0.284
MAC 1	24.0 (17.0–39.4)	23.8 (17.0–39.4)	26.9 (17.1–37.8)	0.042*
MAC 2	24.2 (17.0–39.5)	23.8 (17.0–39.5)	27.0 (17.0–38.0)	0.037*
MAC 3	24.2 (16.8–39.6)	24.0 (16.8–39.6)	27.2 (17.0–38.2)	0.033*
MAC Mean	24.1 (17.0–39.5)	23.85 (17.0–39.5)	27.05 (17.0–38.0)	0.038*

*The analysis utilized the Mann Whitney assessments. **TST: Triceps skinfold thickness, BST: Biceps skinfold thickness, SIST: Suprailiac skinfold thickness, MAC: Mid-upper arm circumference.

In addition, malnutrition in TB infection decreases immune status, due to decreased lymphocyte production and immune cell proliferation ability, and this leads to increased growth of microorganisms and dissemination risk [32], [33]. The reactivation of latent TB or a previous subclinical TB infection is associated with worsened nutritional status [34].

This study is limited by the cross-sectional studies describing the situation at a time (snapshot); therefore, the causal relationship is not determined, and the representativeness is not guaranteed. Furthermore, the MIS assessment requires examination of subjective parameters, including dietary intake, gastrointestinal symptoms, functional capacity, reduced fat reserves, as well as muscle mass, and the presence of depression, fatigue, and cognitive impairment is able to the examination results.

Conclusion

The assessment of nutritional status, through TST, MAC, smoking status, and adequate HD, is crucial, because these factors present risks for latent TB in CKD patients undergoing routine HD.

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