Factors Associated with Sarcopenia in Maintenance Hemodialysis Patients: A Cross-Sectional Study

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ABSTRACT

Background: *Sarcopenia is associated with worse outcomes in maintenance hemodialysis (MHD) patients. Differences in criteria and methods used to diagnose sarcopenia, results in a wide range of prevalence. Factors associated with sarcopenia in MHD have not been well-studied. This study aimed to investigate the prevalence and factors associated with sarcopenia in the MHD population.* ***Methods****: Observational cross-sectional study was done with 96 MHD patients aged ≥18 years old, with dialysis vintage ≥120 days at Cipto Mangunkusumo Hospital March-May 2022. Descriptive, bivariate, and logistic regression analysis were done to find sarcopenia's prevalence and association with Simplify Creatinine Index (SCI), type 2 diabetes (DM), Interleukin-6 (IL-6), nutritional status, physical activity, and phosphate serum level. Asian Working Group for Sarcopenia (AWGS) 2019 criteria used to diagnose sarcopenia, Hand Grip Strength (HGS) to identify muscle strength, Bioimpedance Spectroscopy (BIS) to calculate muscle mass, and 6-meter walk test to evaluate physical performance.* ***Results:*** *The prevalence of sarcopenia was 54.2%. Factors with a significant association in bivariate analysis were phosphate serum level (p=0.008), SCI (p=0.005) and low physical activity (International Physical Activity Questionnaire) (p-0.006). Logistic regression analysis found higher phosphate serum level and high physical activity protective of sarcopenia (OR 0.677;CI95% 0.493-0.93 and OR 0.313;CI95% 0.130-0.755 respectively).* ***Conclusion:*** *The prevalence of sarcopenia in the MHD population was 54.2%. Phosphate serum level, SCI, and physical activity were significantly correlated with sarcopenia. Both high phosphate level and high physical activity were protective against sarcopenia.*

Key words: *Maintenance hemodialysis, AWGS 2019, sarcopenia.*

INTRODUCTION

Sarcopenia is associated with worsened clinical and nutritional outcomes and is an independent predictor of morbidities and mortality in a maintenance hemodialysis patient.[1] The prevalence of sarcopenia in patients with chronic kidney disease (CKD) population ranges between 4%-68% depending on guidelines, tools, and methods used to identify each variables to define sarcopenia. The prevalence in the dialysis population is found at an average of 37%.[2]

Sarcopenia in chronic kidney disease (CKD) is called uremic sarcopenia.[3] Low physical activity and negative protein balance because of prolonged uremic milieu, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, vitamin D deficiency, and oxidative stress were proposed to play a role in uremic sarcopenia.[4] To date, there has been no studies in Indonesian MHD population using AWGS 2019 criteria.

This study aimed to find the prevalence of sarcopenia using AWGS 2019 criteria and factors associated with sarcopenia in Maintenance Hemodialysis (MHD) populations.

METHODS

Study Design, Setting, Participants, and Sample Size

We conducted a cross-sectional study at Cipto Mangunkusumo Hospital Jakarta from March to May 2022. Sampling was done consecutively, inclusion criteria were patients aged ≥ 18 years with dialysis vintage ≥120 days. We excluded hospitalized patients, as well as subjects who were unable to follow procedure, amputated, or refused to join. The sample size of this study was 96.

Ethics

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (Ref. No. KET-175/UN2.F1/ETIK/PPM.00.02/2022).

Variables and Data Sources

Data from medical records were age, dialysis duration, diabetes history, hypertension, Angiotensin Converting Enzyme (ACE) inhibitor/Angiotensin Receptor Blocker (ARB) use, and phosphate binder use. Physical activities were evaluate using the International Physical Activity Questionnaire (IPAQ), while nutritional status was evaluated using the Subjective Global Assessment (SGA). Laboratory examinations taken before the dialysis session for Interleukin-6 (IL-6) level, calcium ion level, haemoglobin, and albumin serum. Simplify Creatinine Index (SCI) assessed with Single Pool Kt/V (SpKt/V). Body composition data for muscle mass calculation was obtained from Body Composition Monitor (Fresenius) and Appendicular Muscle Mass was calculated using the formula by Lin et al.[5] Hand Grip Strength measurement by Jamar hand dynamometer used to identify muscle strength and physical performance was evaluated with 6-meters walk test. We defined sarcopenia based on the criteria suggested by AWGS in 2019.

Statistical Methods

We analyzed the data using SPSS Version 20, involving descriptive analysis to find the prevalence of sarcopenia, bivariate analysis by independent T-test and chi-square to determine the association between phosphate serum level, diabetes, Il-6, physical activity, SCI, and nutritional status with sarcopenia. $P<0.05$ was considered statistically significant. Variables with $P<0.25$ were then analysed with logistic regression (predictive analysis).

RESULTS

The prevalence of this study was 54.2%, with characteristics as shown in **Table 1**.

Table 1. Characteristics of the subject.

Variables	Frequencies (%)	Mean (SD)/ Median (Range)
Sex		
Male	48 (50.0)	
Female	48 (50.0)	
Age (year)		50.82 (14.9)
Dialysis vintage (month)		48 (24-96)
Nutritional status		
SGA A	89 (92.7)	
SGA B	7 (7.3)	
Diabetes Mellitus		
Yes	30 (31.3)	
No	66 (68.8)	
International Physical Activity Questionnaire (IPAQ)		
Light activity	58 (60.4)	
Moderate activity	38 (39.6)	
Hypertension		
Yes	75 (78.1)	
No	21 (21.9)	
Angiotensin-converting Enzyme inhibitor/ Angiotensin Receptor Blocker (ACEi/ARB) use		
Yes	36 (3.5)	
No	60 (62.5)	
Calcium carbonate ($CaCO_3$) use		
Yes	57 (59.4)	
No	39 (40.6)	
Early Referral		
Yes	18 (18.8)	
No	78 (81.3)	
Simplify Creatinine Index (SCI)(mg/kg/day)		23.02 (3.59)
Interleukin-6 (pg/mL)		5.53 (3.93-10.52)
Single Pool (Sp) Kt/V		2.02 (1.76-2.33)
Phosphate serum (mg/dL)		4.08 (1.45)
Creatinine serum (mg/dL)		11.99 (3.77)
Ion calcium (mmol/L)		1.13(1.08-1.21)
Hemoglobin (g/dL)		9.30 (1.38)
Albumin (g/dL)		3.93 (0.38)
Body mass index (kg/m^2)		23.07 (4.91)
Fat mass (kg)		14.15 (9.23-21.30)
Lean tissue mass (kg)		35.35 (30.57-41.80)
Appendicular skeletal muscle mass (ASM) (kg/m^2)		
Male		4.92 (0.84)
Female		3.76 (0.79)
Hand grip strength (kg)		
Male		24 (20-30)
Female		18 (12-20)

Independent T-test analysis showed a significant difference in mean phosphate serum level (p=0.008) and Simplify Creatinine Index (p=0.005). The Chi-Square analysis of physical activity (using IPAQ score) (p=0.006) was significantly associated with sarcopenia (**Table 2**).

Researchers elaborated analysis with a predictive model using variables with p<0.25 and found higher phosphate serum levels (OR 0.677, p=0.016) and higher physical activity (OR 0.313, p=0.01) were protective of and significantly correlated with sarcopenia in MHD population (**Table 3**).

DISCUSSION

Muscle loss is a common finding in CKD patients, especially in the hemodialysis patients. The prevalence of sarcopenia is greatly influenced by the variability of diagnostic criteria and patient characteristics. Sarcopenia in the MHD population's prevalence from various studies ranges from 4-68%.[6,7] The prevalence of sarcopenia in this study population was 54.2%. This study is the first in Indonesia that used AWGS 2019 criteria to diagnose sarcopenia. Researchers use Bio-Impedance Spectroscopy (BIS) to assess Appendicular Skeletal Mass (ASM), Hand Grip Strength (HGS) to assess muscle strength, and 6-meters walk test to evaluate physical performance. The examinations were done before hemodialysis session on the non-AV-shunt arm.

The etiologic factors that contribute to muscle loss in hemodialysis are diverse and can be grouped into factors that contribute to increased protein degradation (reduced energy and protein intake, inflammation, insulin resistance, metabolic acidosis, vitamin D deficiency, and oxidative stress) and factors that related to decreasing protein synthesis (loss of amino acid and protein during dialysis, reduced regenerative stimulus, hormonal derangements, sedentary lifestyle, ageing).[8]

Table 2. Association of SCI, type 2 DM, IL-6, nutritional status, physical activity with sarcopenia.

Variables	Sarcopenia		p
	Yes	No	
Phosphate serum level, mean (SD)	3.73 (SD 1.18)	4.5 (SD 1.63)	0.008
Simplify creatinine index (SCI), mean (SD)	22.09 (SD 3.56)	24.12 (SD 3.35)	0.005
Type 2 DM, n (%)			
Yes	20 (66.7)	10 (33.3)	0.095
No	32 (48.5)	34 (51.5)	
IL6, n (%)			
Normal	33 (56.9)	25 (43.1)	0.507
Above normal level	19 (50.0)	19 (50.0)	
Nutritional status, n (%)			
SGA A	46 (51.7)	43 (48.3)	0.120*
SGA B	6 (85.7)	1 (14.3)	
IPAQ, n (%)			
Light activity	38 (65.5)	20 (34.5)	0.006
Moderate activity	14 (36.8)	24 (63.2)	

Table 3. Multivariate analysis logistic regression.

	Variables	B	SE	Z	P
1	Phosphate serum	0.390	0.162	2.407	0.016
2	Physical Activity	1.162	0.449	2.588	0.010
3	Constant	-3400	0.962	3.534	<0.001

Impaired muscle regeneration also often develops in CKD patients, proven by reduced cell activation and expression of myogenic regulatory factors (a negative regulator of skeletal muscle mass).[9] Furthermore, there is increased catabolism in CKD due to the accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, vitamin D deficiency, oxidative stress, and increased ubiquitination.[4]

Emerging evidence addressed an association between phosphate and muscle function, but only a little attention focused on this issue.[10] High phosphate concentrations are associated with an increased incidence of cardiovascular complications and mortality in CKD patients, hence dietary and pharmacotherapeutic interventions aimed to reduce phosphate serum level.[11] However, a meta-analysis study by Block et al[12] found significant increases in the relative risk of death in lower phosphate serum concentrations (<4.0 mg/dL).

Bivariate analysis in this study showed a significant association between the lower level of phosphate serum with sarcopenia and accordance with the following study by Umakanthan, et al[13], Ren, et al[14], and Cai, et al[15]. The findings suggested that a high protein diet also contained high phosphate, and patient in the uremic milieu usually lost their appetite or even has anorexia. Reduced energy and protein intake will lower phosphate serum levels, causing malnutrition, catabolic protein condition, and sarcopenia. Another mechanism that could explain hypophosphatemia in sarcopenia is that inorganic phosphate also plays a role in cell membrane, energy production, and transduction signal in all body cells.[16] Study by Pesta et al.[17] in animal showed that genetically and diet-induced hypophosphatemic mice has a decreasing muscle ATP synthesis rate.[18]

This study also found a significant correlation between Simplify Creatinine Index (SCI) with sarcopenia (p=0.005). This finding also followed Canaud, et al[19] study which stated that SCI is a reliable and inexpensive marker of muscle metabolism and can be used as a nutritional and skeletal muscle marker in the dialysis population. Yamamoto, et al[20] found that SCI's long term predictive value was comparable with hand grip strength and walking speed.

In this study, physical activity was analysed with IPAQ and had a significant correlation with sarcopenia in this study (p=0.006). Regolisti, et al[21] stated that low physical activity was commonly found in MHD populations and related to muscle disuse which could further cause loss of muscle mass and eventually sarcopenia. Limited physical activity during hemodialysis session and lethargic feelings that are often felt by MHD populations reduce their activity time.

This study did not find a significant correlation between DMt2 and sarcopenia in the MHD population (p=0.095); nevertheless, 66.7% of DMt2 participants in this study were diagnosed with sarcopenia. This finding was following Giglio, et al[1], Hoppe, et al[22], and Visser, et al[23]. This could be explained by the fact that both diabetes and CKD present with chronic inflammation that could disrupt muscle metabolism in the long term.

Nutritional status was assessed with SGA as recommended by KDOQI. The majority of samples in this study (92.7%) have good nutritional status (SGA A). Macedo, et al[24] found that 51.2% of samples in the non-sarcopenia group suffered from malnutrition. Vettoretti, et al[25] also found no significant correlation between sarcopenia and malnutrition and stated that both were different domains of nutrition abnormalities. Similar finding was also found in Ren, et al's study.[14]

The inflammation factor (using IL-6 as a marker) did not meet the significance's requirement in this study (0.507). Many studies found similar results using the same or different markers.[1,14,26,27] This could explained by the fact that inflammation in MHD population are increase in an episodic manner and do not picture the chronic conditions state of the patient.

The logistic regression analysis showed the ideal model to detect sarcopenia, where higher phosphate level and high physical activity were both protective factors to prevent sarcopenia (OR 0.677;CI95% 0.493-0.93 and OR 0.313;CI95% 0.130-0.755 respectively).

This study presented the recent data about the prevalence of sarcopenia in MHD populations

in Indonesia using AWGS 2019 criteria with variables that are proposed to play a role in the pathogenesis of sarcopenia. This study's high prevalence of sarcopenia implies the necessity to address and treat sarcopenia in the clinical setting. Variables used in this study was objective and easily retrieved in hemodialysis centers to diagnose sarcopenia in MHD patient, so the reproducibility of this study was good.

This study was cross sectional, so the causal relationship between variables was not achieved. This study did not include the role of hormones like ghrelin and angiotensin. Bias potentials from this study required considerations were glucocorticoid use and HGS examination in the non-AV shunt arm, which could be the non-dominant arm. Factors that were not significant in logistic regression analysis might reach significance in larger samples study; hence the follow-up study is encouraged.

CONCLUSION

The prevalence of sarcopenia in the MHD population in Cipto Mangunkusumo Hospital was 54.2%. This study's factors significantly associated with sarcopenia were phosphate serum level, SCI, and physical activity. Logistic regression analysis showed that higher phosphate serum level and high physical activity were protective against sarcopenia in the MHD population.

On the basis of these findings, it seems prudent to suggest that early detection of sarcopenia is crucial in MHD populations, and by increasing physical activity and a better control of phosphate serum level could prevent this condition.

AUTHOR'S CONTRIBUTION

RJ designed the study, collected the data, performed data analysis, and drafted the original manuscript. MBM and PN participated in designing the study and revised the manuscript. IR helped in data analysis and revising the manuscript. S, HS, PWL, and IH participated in revised the manuscript. All authors read and approved the final manuscript.

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