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Malnutrition inflammation in chronic kidney disease undergoing hemodialysis in Cipto Mangunkusumo Hospital

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ABSTRACT

Background: Malnutrition was a nutritional problem in hemodialysis with prevalence 50-70% and 2018 study at Cipto Mangunkusumo Hospital showed the prevalence was 39%.

Objectives: This study was team study of Renal and Hypertension Unit RSCM, using cross sectional design, primary data collected in February and May 2018.

Materials and Methods: The sample size used a hypothesis test with total sample of 120 patients. Data obtained through interviews and laboratory data obtained through medical records. Univariate, bivariate and multivariate analysis were carried out to see the determinant factors that influence the Malnutrition Inflammation Score (MIS).

Results: The results showed that there were relationship between sex ($p<0.022$), age ($p<0.031$), etiology chronic kidney disease ($p<0.037$), duration hemodialysis ($p<0.025$), protein intake ($p<0.030$) and grip strength ($p<0.010$). The determinant factors significantly associated with MIS were sex $p<0.0001$, age $p<0.014$, protein intake $p<0.018$, and grip strength $p<0.017$.

Conclusion: The conclusions of this study were the prevalence of inflammatory malnutrition in hemodialysis patients was 55.8%, male had risk of 4.1 malnutrition, age ≥40 years had risk of 3.1, inadequate protein intake had risk 2.8 times malnutrition and less grip strength as a protective variable had a 0.23 times lower risk.

Keywords *: Chronic kidney disease; hemodialysis; malnutrition inflammation; nutritional status*

BACKGROUND

Chronic Kidney Disease (CKD) is a progressive and irreversible impairment of kidney function where the body cannot maintain the balance of fluids, electrolytes and metabolic waste.[1] In Asian populations, the prevalence of CKD varies between 10-18% with the highest rates in Japan (28.8%) and Bangladesh (20.8%) while the smallest CKD population is in Vietnam (3.1%).[2] The global prevalence of malnutrition in CKD ranges from 28-54%, with other studies suggesting a range of 30-40%.[3] High inflammation and metabolism in patients with kidney disease can accelerate the decline in nutritional status, resulting in weight loss and malnutrition. Assessment of nutritional status in CKD patients with hemodialysis therapy can be done in various ways, one of which is by using Subjective Global Assessment (SGA) and Malnutrition Inflammation Score (MIS). Malnutrition Inflammation Score (MIS) has been used by practitioners in assessing the inflammatory status of hemodialysis patients associated with malnutrition inflammatory syndrome. Malnutrition Inflammation Score (MIS) assessment has been recommended by Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) in measuring and assessing nutritional status, especially protein-energy malnutrition. Prevalence of malnutrition in hemodialysis population in Cipto Mangunkusumo was high, it found that more than 30% patients undergoing hemodialysis is malnutrition. Therefore, based on the explanation above, an analysis is needed regarding the determinants of Malnutrition Inflammation Score (MIS) associated with nutritional status in chronic kidney disease patients with hemodialysis therapy.

MATERIALS AND METHODS

This research design used a cross-sectional study design using primary data from collaborative multidisciplinary team conducted by Nephrologist, Dietitian and Nurse in the Hemodialysis Outpatient of the Kidney and Hypertension Unit of Dr. Cipto Mangunkusumo Hospital Jakarta in February and May 2018. Inclusion criteria were: Chronic kidney disease patients aged more than 18 years who undergo chronic hemodialysis for at least 3 months in a week experiencing twice a week dialysis. While the exclusion criteria are: hemodialysis patients which come to Cipto Mangunkusumo Hospital because of traveling to Jakarta or visiting Jakarta that not scheduled for routine hemodialysis, patients in the indication of hospitalization in the last 3 months, patients with cardiac disorders, patients who do not undergo routine hemodialysis at least 2

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times a week, psychological illness such as bipolar disorder and schizophrenia, impaired consciousness in critical ill patients and patients who refuse to be subject of research. Sampling using population hypothesis testing that meets population parameters, with the prevalence of non-malnutrition of hemodialysis patients in Asia at 20% and the prevalence of hemodialysis malnutrition in RSCM at 39%, a sample size of 120 patients was obtained. The study was conducted with intermprofessional cooperation, including: internal medicine specialists specializing in renal hypertension, nutritionists and dietitians, and nurses. Here is the collecting data operational by variables.

Table 1. Collecting Data Method and Variabels

No	Variable	Tools	Method	Categorized
1.	Body Mass Index (BMI)[4]	Seca 703 Acuration: 0.01 kg and 1 cm	Measurement Height and Weight Primary Data	Malnutrition <20 Kg/m^2 and Normal: ≥ 20 Kg/m^2
2.	Malnutrition Inflammation Score (MIS)[5,6]	MIS Questionnaire	Interview and Medical Record	Normal/Well Nourished <6 and Malnutrition ≥ 6
3.	Subjective Global Assessment (SGA)[7]	SGA Questionnaire	Interview and Medical Record	Score A: well nourished, Score B: moderate malnutrition, and Score C: severe malnutrition
4.	Sex	Medical Record	Secondary Data	Female and Male
5.	Age [8]	Medical Record	Secondary Data	≤ 40 Years Old and > 40 Years Old
6.	CKD Etiology	Medical Record	Secondary Data	Not Hypertension and Hypertension
7.	Duration Hemodialysis[9]	Medical Record	Secondary Data	< 5 Years and ≥ 5 Years
8.	Comorbidity[4,5,10]	Malnutrition Inflammation Score	Interview and Medical Record	Without Comorbidity and Have Comorbidity ≥1
9.	Energy Intake	*Food Record*	Food Record 24 hours	Sufficient (≥80%) and Deficit (<80%)
10.	Protein Intake	*Food Record*	Food Record 24 hours	Sufficient (≥80%) and Deficit (<80%)
11.	Grip Test Strength[11]	*Hand Grip*	HGS Test	Normal -Male >26 kg -Female >18 kg Low/Deficit -Male <26 kg -Female <18 kg
12.	Laboratory Test - Albumin Serum - TIBC Serum	Medical Record	Secondary Data	

Data processing was carried out with patient characteristics conclude in body weight change, food appetite, gastrointestinal symptoms, functional capacity, comorbid disease, physical assessment, etiology of CKD, duration hemodialysis, energi and protein intake, hands grip test and malnutrition inflammation score (MIS). Univariate analysis was performed to obtain a description of the variables, bivariate analysis was performed to see the relationship between variables using Chi-Square and multivariate analysis using multiple logistic regression to determine the determinants of MIS and multivariate interaction tests between variables. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia - Dr. Cipto Mangunkusumo Hospital No: 1096/UN2.F1/ETIK/2017.

RESULTS

The National Central General Hospital or RSUPN Dr. Cipto Mangunkusumo, abbreviated as RSCM, is a hospital that serves patient referrals from all regions of Indonesia. The status of this hospital is legally stated in the Regulation of the Minister of Health of the Republic of Indonesia Number 63 of 2019 concerning the Organization and Work Procedures of Dr. Cipto Mangunkusumo National Central General Hospital. The Kidney and Hypertension Division of the Department of Internal Medicine, Faculty of Medicine, University of Indonesia provides health services to patients with kidney disease including kidney examinations, hemodialysis services, CAPD services (Continuous Ambulatory Peritoneal Dialysis or Continuous Independent Peritoneal Dialysis) and kidney transplant services. The nutrition services of the Hypertension Kidney Division of the Department of Internal Medicine of Cipto Mangunkusumo Hospital are included

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outpatient and inpatient nutrition services, Nutritionists and Dietitians provide nutrition and dietetic counseling regarding to with hospital accreditation standards.

Table 2. Malnutrition Inflammation Score Characteristic

Category	N	%
(A) Patient History		
Body Weight Changes (Last 3 – 6 months)		
<0.5 kg	97	80.8
0.5 – 1 kg	6	5.0
≥ 1 Kg - <5%	11	9.9
≥ 5%	6	5.0
Food Appetite		
Good appetite	104	86.7
Suboptimal solid intake	16	13.3
Gastrointestinal Symptoms		
No complaints with good appetite	70	58.3
Mild complaints, poor appetite, frequent nausea	46	38.3
Moderate complaints and occasionally vomiting	2	1.7
Severe anorexia, frequent vomiting and diarrhea	2	1.7
Functional Capacity		
Normal and well	69	57.5
Sometimes difficult to walk or often feel tired	47	39.2
Difficult to do independent activities	2	1.7
Inactivity or bedridden	2	1.7
Comorbid Disease		
Less than 1 year and healthy	16	13.3
1 - 4 years old or mild comorbidities (without major comorbidities*)	52	43.3
More than 4 years, moderate comorbidities (including 1 major comorbid*)	51	42.5
Severe comorbidity, multiple (≥ 2 major comorbidities*)	1	0.8
(B) Physical Assessment		
Fat Storage		
Normal (no change)	73	60.8
Mild	38	31.7
Medium	3	2.5
Severe	6	5.0
Muscle Mass		
No signs of atrophy	70	53.8
Mild	40	33.3
Moderate	4	3.3
Severe	6	5.0
(C) Body Mass Index (BMI)		
Body Mass Index (BMI)		
> 20 Kg/m^2	90	75
18 – 19.9 Kg/m^2	15	12.5
16 – 17.9 Kg/m^2	7	5.8
<16 Kg/m^2	8	6.7
(D) Laboratory Test		
Albumin Serum		
> 4 g/dL	79	65.8
3.5 – 3.9 g/dL	30	25.0
3.0 – 3.4 g/dL	8	6.7
<3.0 g/dL	3	2.5
TIBC Serum		
> 250 µg/dL	31	25.8
200 – 249 µg/dL	46	38.3
150 – 199 µg/dL	39	32.5
<150 µg/dL	4	3.3

*) Major comorbidities include: CHF stage III or IV, AIDS, Coronary Artery Disease (CAD), moderate to severe COPD, major neurologic trauma and metastatic malignancy or with chemotherapy.

Malnutrition inflammation score characteristic at Table 1 showed that sex characteristics in this study found that more than half of the hemodialysis patient population were male with a total percentage of 54.2%, while the female was 45.8%.The age of hemodialysis patients in this study ranged from 22 years to 76 years with a median value of 55 years. The highest proportion of patients was >40 years old (85%) with an average age of hemodialysis patients of 52.9±12.7 years. Hypertension was the etiology of CKD with hemodialysis in 58.3%, diabetes mellitus 26.7%, glumerulonephritis 8.3% and others 6.7%. In this study, more than half of the sample had undergone hemodialysis therapy for >5 years, 57.5%, and 42.5% had undergone therapy for <5 years. The least length of hemodialysis was 1 year and the longest was 19 years with an average of 5.69 years. Most patients had ≥ 1 comorbidity (83.3%) and only 11.9% had no comorbidity. Energy and protein requirements and intake of the patients are showed in Table bellow

Table 3. Energy and Protein Requirements and Intake

Variables	Min	Max	Median	Average ± SD
Requirements				
Energy (Kcal)	1260	2457	1890	1886±261
Protein (gram)	40.8	84.2	64.8	64.6±9.0
Intake				
Energy (Kcal)	1314	2980	1625	1524 ± 491
Protein (gram)	30.1	120	46.8	48.8 ± 17

Table 4. Relationship Between Variables and MIS of Hemodialysis Patients

No	Independent Variable	At Risk of Malnutrition (MIS ≥6)		No Risk of Malnutrition (MIS<6)		*p-Value*	OR	95% CI
		n	%	n	%			
1.	**Sex**							
	- Male	43	66.2	22	33.8	0.022*	2.525	1.204 – 5.293
	- Female	24	43.6	31	56.4			
2.	**Age**							
	- > 40 Years	63	60.0	42	40.0	0.031*	2.125	1.231 – 3.283
	- ≤ 40 Years	7	46.6	8	53.3			
3.	**Etiology CKD**							
	- Hypertension	34	52.9	33	47.1	0.037*	1.420	0.597 – 1.895
	- Not Hypertension	34	68.0	16	32.0			
	1. Diabetes Mellitus	18	56.3	14	44.3	1.000	0.977	0.432 – 2.208
	2. Glomerulonephritis	4	40.0	6	60.0	0.292	2.011	0.537 – 7.529
	3. Others	5	62.5	3	37.5	0.694	0.744	0.170 – 3.265
4.	**Duration Hemodialysis**							
	- ≥ 5 Years	47	68.1	22	31.8	0.025*	1.395	1.185 – 1.843
	- < 5 Years	30	58.8	21	41.1			
5.	**Comorbidities**							
	- ≥ 1 Comorbidities	57	54.3	48	45.7	0.532	0.594	0.190 – 1.857
	- Without Comorbidities	10	66.7	5	33.3			
5.	**Energy Intake**							
	- Deficit	34	55.7	27	44.3	1.000	0.992	0.483 – 2.040
	- Adequate	33	55.9	26	44.1			
6.	**Protein Intake**							
	- Deficit	41	66.1	21	33.9	0.030*	2.403	1.149 – 4.026
	- Adequate	26	44.8	32	55.2			
7.	**Hands Grip Test**							
	- Deficit	34	45.9	40	54.1	0.010*	0.335	0.152 – 0.736
	- Adequate	33	71.7	13	28.3			

*) has a significant value

The smallest energy requirement in the study was 1260 kcal and the highest was 2457 Kcal, and the lowest protein requirement was 40.8 grams and the highest was 84.2 grams. The nutritional adequacy rate of the proportion between insufficient and adequate nutritional adequacy is almost the same, in DRI (Daily Recommended Intake) Energy deficient or deficit as much as 50.8% and sufficient 49.2%. Most of the study samples had normal albumin levels above 3.5 g/dL, namely 90.8%, while in samples with hypoalbuminemia as much as 9.2%. Most TIBC (total iron binding capacity) was in the range of 200 - 249 µg/dL at 38.3% and

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150 - 199 µg/dL at 32.5%. TIBC above 250 µg/dL was 25.8%. The mean TIBC of the study was 220 µg/dL where the lowest value was 138 µg/dL and the highest was 389 µg/dL. More than 50% of the study patients had poor or low grip strength of 61.7% and normal 38.3%. In male, the majority had less grip strength as many as 49 people and women had normal grip strength as many as 30 people. The minimum grip strength was 7.0 Kg with a maximum of 43.2 Kg. The average grip strength of the study was 20 ± 8.2 Kg. More than half of the study sample was at risk of malnutrition, 55.8% while those not at risk of malnutrition were 44.8%. The highest MIS score was 20 with an average score of 6.15.

Variables that have a significant relationship with MIS in hemodialysis patients at Dr. Cipto Mangunkusmo Hospital were variables: sex, age, CKD etiology, length of hemodialysis, protein intake and grip strength. In the sex variable, there is a difference in the proportion between sex and the risk of malnutrition ($p<0.05$) with an Odds Ratio of 2.5, this means that male has a risk of inflammatory malnutrition 2.5 times higher compared to the female with 95% CI: 1.204 – 5.293. The second variable that significant with malnutrition inflammation was age (p=0.031) with an OR of 2.1, which means that at the age of more than 40 years has a risk of inflammatory malnutrition in hemodialysis as much as 2.1 times compared to less than 40 years with 95% CI: 1.231 – 3.283. The third variable that has an association is CKD etiology with p=0.037 and OR 1.4 which means that hemodialysis patients with hypertensive etiology have a risk of 1.4 times inflammatory malnutrition compared to non-hypertensive 95% CI 0.597 - 1.895. The fourth variable is the length of hemodialysis which is associated with inflammatory malnutrition (p=0.025) with an OR of 1.4 or patients with a length of hemodialysis of more than 5 years have a risk of 1.4 times experiencing inflammatory malnutrition 95% CI 1.185 - 1.843. The fifth variable that was significantly associated was protein intake (p=0.030) with an OR of 2.4, meaning that patients with insufficient protein intake had a risk of inflammatory malnutrition 2.4 times compared to adequate protein intake 95% CI 1.149 - 4.026. The last variable that was significantly associated was hand grip strength (p=0.010) with an OR of 0.3 95% CI 0.152 - 0.736, which means that the variable lack of hand grip strength has a 0.3 times risk of inflammatory malnutrition but the OR value does not exceed 1 and has the smallest odds compared to all variables associated.

Table 5. Determinant Multivariate Model

Variables	*p value*	OR	95% CI
Sex	0.0001	4.167	2.733 – 7.224
Age	0.014	3.181	1.454 – 4.267
Protein Intake	0.018	2.882	1.262 – 4.937
Hands Grip Strength	0.017	0.238	0.073 – 0.772

Multivariate model test showed determinant variables that were significantly associated with the incidence of Malnutrition Inflammation Score were sex, age, protein intake and grip strength. The results of the analysis obtained the Odds Ratio (OR) of the sex variable is 4.167 (95% CI: 2.733 - 7.224), meaning that the sex variable has the greatest risk of inflammatory malnutrition in hemodialysis. The second variable was age which was significantly associated (p=0.014) and had the second largest risk with an OR of 3.181 967 (95% CI: 1.454 - 4.267), meaning that age over 40 years had a 3.1 times risk of inflammatory malnutrition. The third variable that was strongly associated was protein intake with p=0.018 and OR 2.882 (95%CI: 1.262 - 4.937) which means that protein intake is less at a risk of 2.8 times inflammatory malnutrition in hemodialysis patients. The variable of grip strength is significantly associated with inflammatory malnutrition ($p<0.05$), but the relationship is not strong OR<1 with the OR interval value not exceeding 1. This means that the variable of grip strength is a protective variable against inflammatory malnutrition. Patients with less grip strength have a lower risk of inflammatory malnutrition which is 0.23 times compared to normal grip strength. The result of multivariate and interaction test provided at Table 5.

Table 6. Multivariate Interaction Test

Variabel	B	*p value*	OR	95% CI
Sex	1.656	0.005	3.238	1.666-4.463
Age	1.870	0.030	2.489	1.193-4.283
Protein Intake	0.900	0.088	1.461	0.874-6.928
Grip Strength	2.053	0.106	0.128	0.011-1.552
Grip Strength by Sex	0.976	0.473	1.653	0.185-5.036
Grip Strength by Age	0.022	0.989	0.978	0.038-4.379
Grip Strength by Protein Intake	0.927	0.312	0.396	0.065-2.392

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After the multivariate logistic regression determinant model was carried out, the interaction test was carried out on variables that were suspected of having an interaction that are: sex, age, protein intake, grip strength tested by sex, age and protein intake. Table 5 showed interaction test found no interaction relationship between age and protein intake with grip strength.

DISCUSSION

Study shown that male had higher risk of hemodialysis than women, other study mentioned that men had a higher proportion of hemodialysis (68%) than women (32%).[4] The proportion of female is lower in CKD risk because kidney function is influenced by sexual hormones. Estrogen in women has an important role in the progressivity of kidney disease. This hormone acts as a component of nephron cells and is protective against grumerulosclerosis, fibrosis, and renal cell receptor regeneration.[5,6]

The age proportion was obtained at the age of <40 years as much as 15% and 85% of patients aged >40 years with a maximum age of 76 years and an average of 52.9 years. Based on research in 2019 conducted in Europe at several hemodialysis service centers, showed that after the age of 40 the kidneys will experience decreased function, and atrophy and immunity of the renal cortex will decrease. The estimated decrease in kidney function based on age per decade is around 10 ml/min/1.73m2, with a GFR value of 60 - 89 ml/min/1.73m2 or equal to a decrease in kidney function of around 10%. In addition, CKD epidemiological research in the Middle East states that men aged >50 years' experience the initiation of hemodialysis as renal replacement therapy (RRT) in end-stage CKD,[8] while in Indonesia, research at Dr. M Djamil Padang Hospital found that the highest proportion of CKD patients was male with an age of >40 years undergoing hemodialysis.[9]

The national prevalence of CKD on dialysis in Indonesia based on Riskesdas 2018 is 19.3% and DKI Jakarta Province is the area with the highest proportion of dialysis in Indonesia, which is 38.7%. Non-communicable diseases (NCDs), especially hypertension and diabetes, play a major role in the progressivity of CKD. Riskesdas stated that the prevalence of hypertension is 34.1% and diabetes is 2.0%, DKI Jakarta Province were the highest prevalence of hypertension at 9.5% and diabetes in Indonesia at 3.4%. The most common etiology of hemodialysis in this study was hypertension at 58.3% or as many as 70 patients had hypertension, diabetes 26.7%, grumeluronephritis 8.3% and others 6.7%.

The length of hemodialysis and comorbid diseases suffered by patients can affect the patient's metabolic condition. The longer hemodialysis is accompanied by comorbidities, the more the body will adapt to catabolic conditions characterized by weight loss, decreased fat reserves and muscle mass, and body mass index[16]. In this study, the length of hemodialysis ≥5 years had a proportion of 57.5% and the length of hemodialysis <5 years was 42.5% with an average of 5.69 ± 3.6 years. An observational study in Japan in 2017 showed that 735 hemodialysis patients with a hemodialysis duration of 103.7±89.3 months or 8.5 years had a mortality risk proportion of 32.8%. Most deaths on hemodialysis are due to cardiovascular disease, malnutrition, inflammation and fluid overload.[11]

The results showed that more than 80% of patients had comorbidities of more than 1 disease with a length of hemodialysis> 4 years, there were only 11.9% who did not have additional diseases or comorbidities. Patients who undergo hemodialysis have a high prevalence of comorbidities, including Atherosclerosis Cardiovascular Disease (ACVD), Congestive Heart Failure (CHF), hypertension, diabetes mellitus and cognitive impairment, these comorbidities are one of the risk factors for death on hemodialysis. Research shows that 66% of 250 hemodialysis patients have comorbidities and the presence of various comorbidities will increase the symptoms experienced by patients and have an impact on hospital visits, length of stay, cost of care and death.[12]

The average energy intake of the study (Table 2) was 1524 ± 491 kcal when compared with the needs, as many as 50.8% of patients had a deficit in energy intake and 49.2% of patients had sufficient energy intake. In this study, 44.3% of patients had insufficient energy intake and were significantly ($p<0.05$) at risk of 1.251 times inflammatory malnutrition compared to adequate energy intake with 95%CI: 1.045 – 1.633. Deficits in energy intake in hemodialysis patients can result in muscle breakdown as a manifestation of glycogenolysis resulting in muscle atrophy, inflammation and malnutrition, this condition makes energy wasting which increases morbidity and mortality.[13] Protein intake based on Table 2 showed in this study was 48.8 ± 17 grams, when compared to protein adequacy requirements, it was categorized as a deficit with 60% of patients consuming protein <80% DRI (daily recommended intake). Protein intake has an important role in metabolism in hemodialysis patients. Diagnosis of CKD can be done by assessing serum ureum and creatinine levels,

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creatinine is the result of creatine metabolism which is muscle nitrogen. The amount of creatinine produced and secreted is proportional to muscle mass, so protein intake reflects the body's creatinine metabolism and muscle protein stores.[14]

In this study, the average grip strength was 20 ± 8.2 kg, most hemodialysis patients had less grip strength, namely 61.7% and normal 43.2% of patients, with less grip strength at risk of inflammatory malnutrition ($p < 0.05$) compared to normal grip strength. In addition, the lack of grip strength in men is higher than women, 66.2% of men have less grip strength and women with less grip strength are 38.8%. The test between variables found that grip strength was significantly associated with sex, etiology, and comorbidities ($p<0.05$). The difference in Hand Grip strength between men and women in this study is related to etiological conditions and comorbidities that are higher in men, namely 57.1% of male patients have ≥ 1 comorbidity. Hands grip strength thresholds are associated with malnutrition inflammation (MIS) in maintenance hemodialysis patients, research states that males are 1.8 times more at risk of developing PEW due to malnutrition and inflammation which can increase morbidity and mortality.[15]

Based on the results of the study, the variables that have a significant relationship with MIS in hemodialysis patients at Dr. Cipto Mangunkusmo Hospital are variables: sex, age, CKD etiology, length of hemodialysis, protein intake and grip strength. In the sex variable, there is a difference in the proportion between sex and the risk of malnutrition ($p<0.05$) with an Odds Ratio of 2.5, this means that the male sex has a risk of inflammatory malnutrition 2.5 times compared to the female with 95% CI: 1.204 – 5.293. Men have a higher risk than women at 66.2%. A meta-analysis of 25 recent studies also stated that men are at more risk of developing CKD with hemodialysis than women 1.39 times (95%CI: 1.15 - 1.69), and only 12 studies showed no difference in the risk of CKD in men and women OR 0.95 (95CI: 0.75 - 1.49).[16]

Patient age is associated with MIS ($p=0.031$) with an OR of 2.1 which means that at the age of more than 40 years has a risk of inflammatory malnutrition in hemodialysis as much as 2.1 times compared to less than 40 years with 95% CI: 1.231 – 3.283. In terms of age, patients aged >40 years have the greatest risk of inflammatory malnutrition as much as 60% compared to less than 40 years of age by 26.7%. Research in America also supports the results of this hemodialysis study, namely the speed of the aging process in individuals varies, influenced by genes, environment and risk factors. Kidney in its manifestation of physiological decline that begins at the age of 30 years due to continuous loss of nephrons and gromelolus damage with a risk of 7 - 14% decrease in kidney function every decade due to glomeruloscreloris and kidney damage that occurs is irreversible or cannot return to normal as before.[17] A study conducted in Canada stated that at the age of >45 the CKD population with hemodialysis increased by 70% to have a 40% risk of morbidity and 22.5% mortality with an OR of 1.31 (95%CI: 1.12 – 1.52).[18]

In addition to sex and age, CKD etiology has an association with MIS ($p=0.037$) and OR 1.4 which means that hemodialysis patients with hypertensive etiology are at risk of 1.4 times inflammatory malnutrition compared to non-hypertensive 95% CI 0.597 - 1.895. Hypertension is the disease that is the biggest etiology in CKD in this study as much as 52.9% are at risk of inflammatory malnutrition and 47.1% of hypertensive patients are not at risk. Research in Thailand mentioned the etiology of hypertension is the cause of inflammation especially in CKD with OR 1.8 (95%CI: 1.1 - 3.4) while diabetes has a risk of 1.6 times (95%CI: 1.0 - 3.4) with hemodialysis, so therapeutic management of hypertension and diabetes is needed to prevent the progressiveness of CKD.[19] Another study stated that the risk factors for hypertension associated with hemodialysis are dietary intake ($p=0.005$), inadequate dialysis adequacy or only getting one time hemodialysis therapy per week ($p=0.01$) and lifestyle ($p=0.002$).[20]

Hemodialysis patients with more than 5 years of hemodialysis therapy are at risk of inflammatory malnutrition by 53.6% while less than 5 years are at risk of inflammatory malnutrition 68.6%. Whereas in patients who were not at risk of inflammatory malnutrition in hemodialysis duration of more than 5 years as much as 46.6% and less than 5 years 31.4%. Length of hemodialysis associated with inflammatory malnutrition ($p=0.025$) with OR 1.4 or patients with hemodialysis duration of more than 5 years have a risk of 1.4 times experiencing inflammatory malnutrition 95% CI 1.185 - 1.843. This is supported by research in Korea which states that hemodialysis patients with a length of therapy of 5.2 years have a risk of decreasing BMI by 1.4 times (95%CI 1.253 - 2.361). This study also mentioned that the longer duration of hemodialysis will increase patient morbidity and mortality by 1.2 times (95%CI: 0.854 - 1.890).[21]

In protein intake, 66.1% of patients had insufficient protein intake and were higher risk of malnutrition, while only 44.8% had sufficient intake and were lower risk of malnutrition. Chi-square test found that protein intake was significantly associated with MIS ($p=0.030$) with OR 2.4, meaning that patients with insufficient

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protein intake had a risk of inflammatory malnutrition 2.4 times higer compared to adequate protein intake 95% CI 1.149 - 4.026. Inadequate protein intake can lead to malnutrition in hemodialysis patients, high catabolism that is not balanced with intake will reduce body stores, decrease muscle mass, BMI and inflammation[16]. The study mentioned inadequate protein intake <1.2 g/kgBBI/day in hemodialysis patients had a risk of malnutrition 3.4 times higher and increased mortality by 4.98 times.[3]

The handgrip strength test using the Hand Grip Test found that 70 patients had less handgrip strength with 45.9% at risk of inflammatory malnutrition. Handgrip strength was significantly associated with MIS (p=0.010) with OR 0.3 95% CI 0.152 - 0.736, which means the variable of less handgrip strength has a risk of 0.3 times inflammatory malnutrition. The OR value of handgrip strength does not exceed 1 or in other words, handgrip strength has a protective effect on MIS. Handgrip strength research states that patients on hemodialysis have reduced handgrip strength with an average handgrip strength of 18.09±8.05 kg, high oxidative stress and inflammatory status. Handgrip strength was associated with serum albumin (p=0.004) but not with inflammation or oxidative stress.[22]

This study also found no relationship between grip strength and SMI (Scalp Muscle Index) (p=0.810), this is because almost all patients have normal Muscle Index values. Poor grip strength is in line with the MIS assessment component of physical activity and coordination where 40% of patients often feel tired and have difficulty walking. This is in line with a Korean study that assessed grip strength for the diagnosis of sarcopenia and walking speed in the elderly.[23] Handgrip strength (HGS) has stood out as a method of assessing nutritional status, and it is feasible in clinical practice for measuring voluntary muscle strength, it is strongly correlated to body mass, making it possible to identify patients who had a significant reduction in nutritional status before any change occurred. In the scientific literature, few studies have evaluated HGS as a parameter for nutritional assessment in hemodialysis patients. In addition, higher MIS scores are associated with a higher inflammation, risk of death and hospitalizations in HD patients. Although not associated with inflammatory malnutrition, other studies have suggested that grip strength is strongly associated with mortality in CKD patients on hemodialysis, functional status and prognosis.[24]

After examining the relationship between variables and Malnutrition Inflammation Score (MIS) through Chi Square test, multivariate modeling of MIS determinants was conducted. The results of bivariate selection on the variables of sex, age, CKD etiology, duration of hemodialysis, comorbidities, energy intake, protein intake and grip strength obtained six variables that had a p value <0.25, that are sex, age, CKD etiology, duration of hemodialysis, protein intake and grip strength. However, because some variables were considered important by the researchers, all variables were included in the multivariate modeling. Comorbidity variables were included referring to the research of which suggests that comorbidities in hemodialysis patients can increase morbidity and mortality, especially in cardiovascular disease related to malnutrition and vascular inflammation in several diseases including hypertension, diabetes mellitus and heart disease.[24]

Energy intake variables were included in multivariate modeling because insufficient energy intake can increase the risk of protein energy malnutrition, wasting, reduce quality of life and increase morbidity and mortality.[25] Energy intake also plays an important role in suppressing uremic syndrome in hemodialysis patients, because if there is an imbalance between intake and needs in hemodialysis patients, it will cause metabolic disorders, weight loss, muscle mass, fat reserves, inflammation and malnutrition.[26] Energy and protein intake have an important role in suppressing the increased catabolic rate in hemodialysis, adequate and sufficient intake can replace protein lost during the hemodialysis process, maintain normal body weight, reduce the risk of morbidity and mortality.[13] After going through a series of multivariate modeling processes using logistic regression analysis, the determinant model obtained variables that affect the Malnutrition Inflammation Score or MIS are: sex has a strong significant association with MIS p<0.0001 (OR 4.167; 95%CI: 2.733 - 7.224). Sex is the biggest determinant associated with MIS when viewed from the p-value and the largest OR among other variables. Age had a significant association with MIS p<0.014 (OR 3.181; 95%CI: 1.454 - 4.267). According to the study, age has the second largest risk after sex for inflammatory malnutrition conditions at 3.1 times more risk at the age of ≥ 40 years. Protein intake was significantly associated with MIS p<0.018 (OR 2.882; 95%CI: 1.262- 4.937). High catabolism in hemodialysis if not balanced with protein intake will risk 2.8 times of inflammatory malnutrition. Handgrip strength was significantly associated with MIS p<0.017 (OR 0.238; 95%CI: 0.073- 0.772), but the OR value was less than 1 and the OR range did not exceed 1 so it can be said that handgrip strength is a protective variable against inflammatory malnutrition. Less grip strength had a 0.23 times higher risk of malnutrition compared to normal grip strength. The study showed the opposite result from previous study mentioned above, the less grip strength is influenced by protein intake and

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sex, study found male with less protein intake high hands grip test. Few research the vascular grip exercise in hemodialysis can influence hand muscle and increasing hands grip test.[28]

The most powerful determinant of MIS was sex after controlling for age, protein intake and grip strength. In this study, low grip strength is of a protective variable against malnutrition, in line with previous research that the average patient with Maintenance Hemodialysis has less average grip strength and is not associated with inflammation and oxidative stress, but is associated with serum albumin.[22] In this study, it can also be concluded that male hemodialysis patients with age ≥40 years will be at great risk of inflammatory malnutrition and increase if coupled with inadequate protein intake.

The interaction test was conducted to see if there was an interaction between variables, especially on grip strength as a protective variable in this study. Research on grip strength states that grip strength is related to sex, men have higher grip strength than women and grip strength can be used to assess sarcopenia.[27] In this study, the opposite results were obtained that the average grip strength of patients was less with male in the malnutrition risk group, another study in India stated that the average grip strength of CKD patients with Hemodialysis was less and was not associated with weight, BMI and oxidative stress but was associated with morbidity.[22]

The results of the interaction test also found no interaction relationship between age and protein intake with grip strength. Insufficient protein intake is assumed to be in line with low muscle mass stores and the resulting lack of grip strength, while in this study it was found that the average Skeletal Muscle Mass (SMI) in CKD patients with hemodialysis was normal so that it was not reflected or opposite to the results of reduced grip strength. In CKD with hemodialysis, it is recommended to train grip strength through a rubber ball that is squeezed or pressed, this exercise is also needed in strengthening vascular access because during the dialysis process it can cause cramps, especially the hands and feet.[24] Cimino access exercises (hemodialysis access vessels) in addition to squeezing using a rubber ball can be done using a Hand Grip Dynamometer by pressing or grasping the Hand Grip tool and releasing it quickly, the exercise interval is carried out for 10 minutes for 6 times a day.[28]

CONCLUSIONS

The prevalence of inflammatory malnutrition in hemodialysis CKD patients in this study was 55.8% and variables associated with inflammatory malnutrition were sex, age, CKD etiology, duration of hemodialysis, protein intake and grip strength ($p<0.05$). Male and hemodialysis patients aged ≥40 years had higher risk of inflammatory malnutrition. Hand grip strength had higher risk of inflammatory malnutrition compared to normal grip strength and was a protective variable.

The results of the interaction test between the variable grip strength with sex, age and protein intake showed that in this study there was no interaction relationship to Malnutrition Inflammation Score (MIS). Inflammation is a very important factor associated with malnutrition in hemodialysis patients, further research is needed in looking of inflammatory conditions in hemodialysis patients, especially by conducting biochemical examinations of CRP (C-reactive protein) and inflammatory cytokines, especially IL-1, IL-6 and TNF-α which are pro-inflammatory cytokines that are directly involved in CKD patients with hemodialysis.

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