ORIGINAL ARTICLE

Factors Associated With Poor Nutritional Status Among Hemodialysis Patients in Malaysia

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ABSTRACT

Introduction: Poor nutritional status is prevalent among hemodialysis patients, with limited studies available on how it is being influenced by other factors in the local context. The current study aimed to determine the nutritional status and its associated factors among hemodialysis patients. **Methods:** This was a study undertaken in a total of 455 hemodialysis patients (256 men and 199 women). The main outcome measure was Malnutrition Inflammation Score (MIS), which was utilized to identify nutritional and inflammatory status of the hemodialysis patients. Other evaluation tools included anthropometry and biochemical measurements as well as dietary assessment. **Results:** A high proportion of hemodialysis patients were malnourished (64.4%) and presented with inflammation (67.5%). Using multiple linear regression analysis, factors contributing to malnutrition were older age, lower lean body mass, higher interdialytic weight gain (IDWG), inadequate intakes of energy and protein, as well as presence of comorbidities and inflammation. **Conclusion:** The presence of malnutrition and inflammation were prevalent among hemodialysis patients. Several determinants of poor nutritional status of hemodialysis patients were modifiable and should be recognized while formulating and implementing appropriate intervention plans for this vulnerable group.

Keywords: Hemodialysis patients, Malnutrition Inflammation Score, Inflammation, Modifiable determinants, Nutritional status

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INTRODUCTION

Despite the advancement in dialysis technology, mortality rate remains high among hemodialysis patients. Of all, cardiovascular disease (CVD) is widely reported as the primary cause of death among patients undergoing hemodialysis (HD) besides infection (1), with growing evidence that the often co-exist malnutrition and inflammation as the two most common determinants of CVD. Malnutrition and inflammation are highly prevalent in hemodialysis patients and are associated with poor clinical outcomes including lower quality of life and increased mortality (2-5). In Malaysia, more than 90% of end stage renal disease patients depend on HD as a treatment modality (6). While HD prolongs the life expectancy of patients, malnutrition is common (7-9). Data pertaining to the nutritional status and inflammatory state of hemodialysis patients are still limited at the local context. Identification of determinants of poor nutritional status and early initiation of interventions may prevent the progression of malnutrition among these patients. Hence this study was undertaken to ascertain the nutritional status and its determinants among hemodialysis patients.

MATERIALS AND METHODS

Study design, study location and subjects

This was a baseline data of a quasi-experiment study which aimed to determine the effectiveness of a nutrition intervention on nutritional status of hemodialysis patients. This study employed purposive sampling method, with the details being described elsewhere (10). Briefly, the patients were recruited from dialysis centers operated by non-government organizations, located within 50 km radius from the university. Study inclusion criteria include patients had received regular hemodialysis for four-hour thrice weekly for a minimum of three months prior to study enrollment, aged 18 years

and above and absence from major acute diseases or psychological disorders. A total of 455 patients from 14 hemodialysis centers, meeting the selection criteria and consented to participate were enrolled into the study. The sample size was calculated based on equation suggested by Aday and Cornelius (2006) for multivariate analysis (11). The Medical Research Ethics Committee of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia approved the study protocol in accordance with Good Clinical Practice guidelines and conforms to the provisions of the Declaration of Helsinki. Permission was obtained from all dialysis centres prior to data collection. Upon approval from ethics review board, the detailed of the study was explained to potential participants. Anonymity and confidentially were assured before individual written informed consent was obtained. A total of 521 eligible patients were approached with 455 consented to study, giving a response rate of 87.3%.

Measurements

Medical history and routine laboratory measurements including serum albumin, total iron binding capacity and creatinine were retrospectively retrieved from medical records of patients. Arrangement was made to withdraw additional of 4 ml blood samples from the patients for the analysis of high sensitivity interleukin-6 (IL-6), a pleiotropic inflammatory cytokine, at the same time point when routine laboratory measurements were performed. Briefly, serum samples were obtained from whole blood stored in serum-separator tubes after 30 minutes clotting and centrifuged at 1500xg for 10 minutes. Samples were analyzed using commercial kits of enzyme-linked immunosorbent assay (ELISA) method as per the manufacturer's protocol (Invitrogen, California, USA). The adequacy of dialysis was determined according to the delivered dose of dialysis (Kt/V urea) while patients' comorbidity scores was ascertained according to modified Charlson's Comorbidity Index which has been validated among dialysis patients (12).

Means for dry weight and interdialytic weight gain (defined as mean weight gain between two consecutive dialysis sessions for the past three months, IDWG) were obtained retrospectively from patient's dialysis record. Achievement of IDWG of less than 4% of dry weight which was associated with lower risk of overall fluid overload hospitalizations (13), was used as an indicator for fluid compliance in this study. Mid-arm circumference (MAC) was made on the non-vascular access arm with the use of fibergrass measurement tape. Skinfold thicknesses at four sites (Triceps, biceps, subscapular and iliac crest) were performed with Lange skinfold caliper (Cambridge Scientific Instruments, Cambridge, Maryland, USA), using standard techniques described elsewhere (14-15), to allow the estimation of percentage of body fat (16). All measurements were ascertained after the termination of dialysis treatment when the patients were at dry weight. This is crucial as skin turgor and hydration may affect subcutaneous skinfold thickness (17). All measurements were taken three times 20 minutes after the dialysis session, unless the first two were the same. Mid-arm muscle circumference (MAMC) was calculated by which the triceps skinfold thickness multiplied by 0.314 was subtracted from the MAC while lean body mass (LBM) was calculated by subtracting total fat mass from dry weight. As all the anthropometric measurements were performed by the same dietitian, the intra-observer technical error of measurement (TEM) and relative TEM (%TEM, serves as a measure of coefficient of variance) among 20 respondents were computed using the following equations (18):

$$\text{Technical Error of Measurements (TEM)} = \sqrt{\sum d^2/2N}$$

$$\text{Relative TEM (\%TEM)} = \text{TEM/mean X } 100$$

where d is the difference between measurement and N is the number of individuals measured. The relative TEM for intra-examiner measurements ranged from 2.4 to 3.8% and were all within acceptable limit (<5%), denoting an acceptable degree of precision (19).

Dietary intakes of energy and protein of patients were obtained using two days dietary records (comprising of one dialysis day and one non-dialysis day), with the aids of food photo album, three-dimensional food replicas and standard household measuring sets. Type of foods, portion size, method of preparation and cooking as well as brand name for certain foods were recorded. Dietary data was analyzed using Nutritionist Pro ™ software version 2.5 (First Data Bank, USA, 2005) whereby food databases including the Malaysian Food Composition Tables (20), Food Composition Guide Singapore (21), Singapore Food Facts (22), China Food Composition 2002 (23), and ASEAN Food Composition Tables (24) were used to complement the existing databases available in Nutritionist Pro™. All the dietary records were reviewed by dietitian, probing for inaccurate and omitted responses. Adequacy of energy and protein intake was ascertained comparing to National Kidney Foundation KDOQI clinical practice guidelines for nutrition in chronic renal failure (25). In light of the high prevalence of underreporting of energy intake among hemodialysis patients (26), possibility of underreporting of energy intake of the patients was ascertained according to established protocol (27). A total of 19.3% of the patients had energy intake to resting energy expenditure ratio (EI:REE) of less than 1.27, which was much lower as compared to earlier studies (26-27). An effort was made to exclude the dietary data of patients with suspected underreporting energy intakes, however, this did not seem to influence the outcomes of multiple linear regression analysis. Hence all dietary data were included in the analysis for this paper. Nutritional status of the patients was determined using quantitative Subjective Global Assessment (SGA) (28) and Malnutrition Inflammation Score (MIS) (29). For

SGA, the 4-item (changes in body weight, the degree of anorexia, the loss of subcutaneous tissue and muscle mass and signs of muscle wasting) 7-point system was used. Score for individual item was summed up to generate a global score, together with clinical judgment of the researchers, this allowed the nutritional status of the patients to be classified as normal, moderate to mild malnutrition or severe malnutrition. On the other hand, the MIS is a score which incorporate SGA and three additional components of body mass index (BMI), serum albumin and total iron-binding capacity, which hence allowed the determination of inflammation status of patients. MIS has been reported as a user-friendly and reliable nutritional scoring system (30) and able to predict the mortality and clinical outcomes of patients preciously (29). The detailed calculation of MIS has been described previously (29). The scoring of MIS (ranges from 0 to 30, with higher score denote higher degree of malnutrition and inflammation) was performed within 5-15 minutes before anthropometric measurements. Measurement on the consistency of MIS scoring was performed by the same dietitian on 10 patients at two different occasions with two weeks apart. The intrarater reliability was measured using intra-class efficiency and was reported to be 0.80, denoting a good degree of reproducibility.

Statistical analysis

Analyses were performed using the IBM Windows Version 22 (Chicago, IL). Explanatory Data Analysis was carried out to determine the normality and homogeneity of the data prior to further data analysis. Continuous variables were presented as mean ± standard deviation while categorical variables were expressed as percentage. The associations between MIS with continuous and categorical variables were computed using Pearson's product moment correlation coefficients or Spearman correlation coefficients, respectively. Stepwise multiple linear regression analysis was performed to determine factors predicting nutritional status of hemodialysis patients, with MIS score as the dependent variable. Statistical significance was defined at $p < 0.05$.

RESULTS

Patients' characteristics are presented in Table I. Mean age of patients was 63.4 ± 10.7 years. Slightly more than one-third of them had MIS score equal or exceeded 8 (34.9%). Presence of co-morbidities was common, with a mean Charlson's Comorbidity Score of 5.20 ± 2.05. Hypertension was dominant and diabetes mellitus was prevalent in our sample. Adequate dialysis (determined as Kt/V urea ≥ 1.2) was identified in approximately 90% of the patients. Approximately 87% of the patients had excess IDWG and hence giving an overall poor fluid compliant of 13.2%. Both hypoalbuminemia and hyperphosphatemia were highly evident in this studied cohort. Mean serum concentration of proinflammatory cytokine, IL-6 was high and this was attributed to the high proportion of patients (67.5%) presented with state of inflammation (defined as serum IL-6 > 6.5 ng/ml).

Based on SGA classification, more than 60% of our cohort were malnourished, either mild-moderately

Table I: Demographics, clinical and laboratory characteristics of patients (n = 455)

Characteristics		Mean (SD)	Frequency n (%)
Age (years)		63.4 (10.7)	
Sex	Male		256 (56.3)
	Female		199 (43.7)
Charlson's Co-morbidity Score		5.20 (2.05)	
Presence of co-morbidity	Hypertension		303 (66.6)
	Diabetes mellitus		210 (46.2)
	Ischaemic heart disease		69 (15.2)
MIS		7.9 (2.3)	
	MIS ≥ 8		159 (34.9)
Hemodialysis treatment measures	Duration of dialysis (months)	65.7 (38.4)	
	Dialysis dose (Kt/V)	1.25 (0.4)	
	Kt/V ≥ 1.2		400 (87.9)
Body composition	Dry weight (kg)	56.4 (14.0)	
	IDWG (kg)	4.3 (1.2)	
	IDWG > 4.0% of dry weight		395 (86.8)
	BMI (kg/m^2)	21.3 (6.5)	
	Waist circumference (cm)	92.4 (3.8)	
	Triceps skinfold > 50th percentile		154 (33.8)
	Mid-arm circumference > 50th percentile		147 (32.3)
	LBM (kg)	38.2 (7.5)	
Biochemical measurements	Albumin (g/L)	35.6 (6.5)	
	Albumin < 40 g/L		283 (62.2)
	Creatinine (mg/dL)	3.5 (1.1)	
	Creatinine ≥ 1.2 mg/dL		455 (100)
	Phosphate (mmol/L)	1.9 (0.5)	
	Phosphate ≥ 1.6 mmol/L		371 (81.5)
	Interleukin-6 (ng/ml)	8.85 (5.24)	
	Interleukin-6 > 6.5 ng/ml		307 (67.5)
SGA classification	Well-nourished		162 (35.6)
	Mild-moderately malnourished		256 (56.3)
	Severely malnourished		37 (8.1)
Dietary measures	DEI (kcal/kg/day)	24 (8)	
	DEI ≥ 30-35 Kcal/kg/day		115 (25.3)
	DPI (g/kg/day)	0.73 (0.4)	
	DPI ≥ 1.0-1.2 g/kg/day		93 (20.4)

Data are reported as Mean (SD) or n (%); BMI: Body mass index; DEI: dietary energy intake; DPI: dietary protein intake; IDWG: interdialytic weight gain; Kt/V: Dialysis dose; LBM: Lean body mass; MIS: Malnutrition Inflammation Score; SGA: Subjective Global Assessment

(56.3%) or severely malnourished (8.1%). Mean intakes for dietary energy and protein were low at 24±8 kcal/kg/day and 0.73±0.40 g/kg/day, respectively. Inadequate intakes of energy and protein were highly evident. A comparison with The Dialysis Outcome Quality Initiative (DOQI) guidelines (25) shows that less than 10% of the patients had adequate intakes for both energy and protein. Meanwhile, there were 16.5% had adequate energy but inadequate protein intakes while 11.2% had adequate protein intake but inadequate energy intake, respectively.

The correlation between MIS and selected variables are shown in Table II. There were moderate positive relationships between MIS with age (r = 0.485, p<0.01) and hemodialysis vintage (r = 0.457, p<0.01), denoting the higher possibility for hemodialysis patients who are older and had longer duration of dialysis to have more severe degrees of PEM and inflammation. Higher family income was associated with lower MIS, hence better nutritional status. Kt/V, an indicator for dialysis adequacy was negatively correlated with MIS (r = -0.240, p<0.05). As expected, IL6, a well-known surrogate inflammatory marker was found to have moderate positive correlation with MIS (r = 0.415, p<0.01). MIS was negatively correlated with LBM (r = -0.322, p<0.01) but positively associated with IDWG (r=0.272, p<0.05), triceps skinfolds (r=0.221, p<0.05) and waist circumference (r=0.162, p<0.05). There were significant negative correlations between MIS with creatinine (r = -0.241, p<0.05), dietary energy (r = -0.337, p<0.01) and protein intakes (r = -0.255, p<0.05). MIS was moderately associated with Charlson's comorbidity score (r = 0.384, p<0.01), denoting that the presence of more comorbid diseases were associated with poorer nutritional status. Sex, level of education and employment status had no significant correlations with MIS.

Table II: Correlation between selected variables and Malnutrition Inflammation Score (MIS) (n= 455)

Variables		*r*	*p*-value
Age		0.485	**0.008**
Sex		0.174	0.122
Education level		0.120	0.138
Employment status		0.163	0.420
Family income		-0.283	**0.007**
Hemodialysis vintage		0.457	**0.006**
Kt/V		-0.240	**0.035**
Nutrition parameters	Interleukin-6	0.415	**0.005**
	IDWG	0.272	**0.038**
	Triceps skinfolds	0.221	**0.041**
	Waist circumference	0.162	**0.038**
	LBM	-0.332	**0.005**
	Mid arm circumference	-0.260	**0.007**
	Creatinine	-0.241	**0.035**
	DEI	-0.337	**0.040**
	DPI	-0.255	**0.036**
Charlson's Comorbidity Score		0.384	**0.008**

DEI: dietary energy intake;
DPI: dietary protein intake; IDWG: interdialytic weight gain; Kt/V: Dialysis dose; LBM: lean body mass

Significant regression model predicting MIS was summarized in Table III. Higher MIS score (representing poorer nutritional status) was predicted by a combination of factors including higher comorbidity score, longer duration of dialysis, higher level of inflammation as indicated by higher IL6, lower dietary energy and protein intake, advanced age, lower LBM, less adequately dialyzed, higher IDWG and lower serum creatinine. Morbidity Score, duration of hemodialysis, interleukin 6 and Kt/V contributed 8.1%, 2.9%, 4.4% and 1.3% of variances in the malnutrition inflammation score (MIS), respectively. On the other hand, modifiable factors such as dietary energy intake, lean body mass, dietary protein intakes and IDWG contributed to a total of approximately 8% of variances in the MIS. Taken all together, these factors explained approximately 25% of the variance in the MIS and the model indicated the complexity of predicting MIS.

Table III: Factors contributing to Malnutrition Inflammation Score (MIS) among hemodialysis patients (n= 455)

Variables	Standardized coefficients (β)	t	p	R	R^2	Δ R^2
Charlson's Comorbidity Score	0.361	3.514	<0.001	0.285	0.081	0.081
Haemodialysis vintage	0.238	3.300	0.001	0.332	0.110	0.029
Interleukin-6	0.234	3.275	0.008	0.392	0.154	0.044
Dietary energy intake	-0.190	3.131	0.006	0.431	0.186	0.032
Age	0.189	2.925	0.009	0.463	0.214	0.028
Lean body mass	-0.178	2.213	0.036	0.488	0.238	0.024
Kt/V	-0.163	2.201	0.035	0.501	0.251	0.013
Dietary protein intake	-0.152	2.145	0.041	0.513	0.263	0.012
IDWG	0.142	2.071	0.042	0.520	0.270	0.007
Creatinine	-0.115	1.989	0.042	0.526	0.277	0.007

Kt/V: dialysis dose; IDWG: interdialytic weight gain

DISCUSSION

Malnutrition is highly evident in this cohort. The prevalence of chronic inflammation is high in our hemodialysis patients and is comparable with the reported prevalence of inflammation (31). More than one third of the patients had MIS score exceeded 8 predicting a poorer clinical outcome (mortality and hospitalization) (32). Insufficient intakes of energy and protein contributed to malnutrition among hemodialysis patients. These findings were consistent with an earlier study (33). Although we ascertained that both adequate intakes of protein

and energy are needed to ensure satisfactory level of nutritional status among hemodialysis patients, inadequate intakes of energy and protein were however highly prevalent among our patients. Similar findings were reported among hemodialysis patients in other populations (2, 34) and such phenomenon is believed to impose a great challenge to the patients and health care teams.

Interdialytic weight gain and LBM remained as the significant predictor variables while other body composition parameters (waist circumference or triceps skinfolds) were not significant in the stepwise multivariate analysis. In the present study, LBM is a promising factor in predicting nutritional status. As LBM indicates the presence and degree of muscle mass, the lower the LBM, the greater the loss of muscle mass and more profound malnutrition is therefore expected. Recently, lean mass, but not high BMI or fat mass, was reported to be associated with lower composite outcome of death or cardiovascular events (35), which has clinical importance to emphasize adequate attainment of lean mass among the dialysis population.

The non-compliance rate on fluid restriction in this study remained high and was relatively higher than previous studies (36), attributed to the high temperature in our country in the entire year. Fluid restriction is always necessary for hemodialysis patients to prevent long term cardiovascular complications and large ultrafiltration-related intradialytic hypotension. Despite this, several earlier studies have reported positive correlations between higher IDWG with nutritional status (37-39) and better survival outcomes (37). Higher IDWG however does not predict better nutritional status in our study. As better compliance to fluid restriction was associated with better nutritional status, the importance of fluid restriction should therefore be emphasized in the routine management of hemodialysis patients.

The relationship between the MIS and the dialysis adequacy, as expressed by Kt/V, deserves further discussion. Our study echoed previous studies that the nutritional status of patient undergoing for hemodialysis is closely related to the dialysis dose delivered (40-43). Adequate dialysis has been associated with lower protein catabolism by alleviating uneasiness of the gastrointestinal tract, metabolic acidosis and insulin resistance (44). There is a growing body of evidence that adequate dialysis was associated with improved better nutritional status among dialysis patients (40-43). This finding supports the necessity of having adequate dialysis to ensure satisfactory levels of nutrition and inflammatory status among hemodialysis patients (42). On the other hand, despite many other measures such as C-reactive protein or interleukin-6 correlate well with clinical outcome (24), such blood tests are expensive and generally not measured routinely. Charlson's comorbidity score has been validated in predicting clinical outcomes (7, 45) and costs (7, 46) in dialysis population. Routine screening of malnutrition among HD patients is seldom carried out in Malaysia beyond monitoring of serum albumin levels (7). The strong positive associations between MIS with Charlson's comorbidity score and interleukin-6 in this study suggest the use of MIS as a relatively simple, cost-effective and valid screening tool for early identification of poor nutritional status as well as determination of clinical outcomes among hemodialysis population in Malaysia.

Our study revealed that the MIS has significant relationship with inflammatory marker, which further supported an earlier study that MIS can be used as a reliable marker for both inflammation and malnutrition (21). Although it is unclear how inflammation and malnutrition are correlated with each other, the evidence is however convincing that inflammatory cytokines regulate appetite and food intake (47). In view of the strong evidence of associations between inflammation and all-cause and cardiovascular mortality (48-50), there is an urgent need to further delineate determinants contributing to higher inflammatory status among patients undergoing for hemodialysis treatment in the future study.

Our study design was cross-sectional in nature which could limit the cause-effect interpretation and generalisation of finding. Selection bias is also possible where only patients who were generally healthier or more health conscious were more likely to participate in the study. The current study employed only two days dietary record, which could be further extend to three days to include the dietary record on weekend. Despite its limitation, the present study has demonstrated that MIS as a relatively simple and valid screening tool for early identification of poor nutritional status among hemodialysis population in Malaysia.

CONCLUSION

In conclusion, we confirmed that adequacy of dialysis and presence of inflammation are important factors determining MIS. It is however worth-noting that several factors which influence the nutritional status of hemodialysis patients are indeed modifiable. These include lean body mass, interdialytic weight gain, intakes of dietary energy and protein. Through appropriate dietary intervention and counseling, nutritional status of hemodialysis patients can be greatly improved and prevalence of malnutrition can be highly prevented. Health care professionals should recognize the potential impact of modifiable factors while developing and implementing individual care plans for patients undergoing hemodialysis treatment.

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