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## The relationship of nutrition status and dietary intake with hospitalization and mortality in hemodialysis patients; a single-center observational cohort study

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### ABSTRACT

**Introduction:** No single nutrition parameter can accurately assess nutritional status, to predict outcomes and to drive the priorities for nutrition care in patients undergoing hemodialysis (HD).

**Objectives:** The aim of this study was to assess the nutritional status of HD patients using two validated assessment tools; the “7-point subjective global assessment” (SGA) and “malnutrition inflammation score” (MIS); to determine participants’ daily energy intakes (DEI) and daily protein intakes (DPI); and also to examine the relationship of these parameters with hospitalization and mortality.

**Patients and Methods:** This is a 12-month prospective, single HD-center study that recruited 77 HD participants from an outpatient center in South Florida. For the purpose of this analysis, participants with SGA  $\leq 5$  and MIS  $> 7$  and were considered to have an inadequate nutritional status represented by SGA-I and MIS-I, respectively. Inadequate energy (DEI-I) and inadequate protein (DPI-I) intake were defined using cutoff values. The outcomes and endpoints of this study were hospitalizations and mortality, registered over 12 months.

**Results:** Fifty-five male and 22 female patients from a single HD center participated in the study. During the 12-month study, 63.6% of participants were hospitalized, 7% transplanted and 13% died. The group of participants with an inadequate nutritional status (defined as SGA-I and MIS-I) and inadequate energy intake (defined as DEI-I) had an increased hazard ratio for mortality [SGA-I and DEI-I [HR: 7.18 (95% CI: 1.18–43.43;  $P=0.032$ )] and [MIS-I and DEI-I [HR: 13.23, 95% CI: 2.1–83.2;  $P=0.006$ ]] and the likelihood of hospitalization increased almost 3-fold [HR: 2.73, 95% CI: 1.09–6.842;  $P=0.031$ ], in the case of MIS-I.

**Conclusion:** These results indicated that energy intake lower than 25 kcal/kg/day increases the risks of hospitalization and mortality for those HD patients with an impaired nutritional status.

### *Implication for health policy/practice/research/medical education:*

The current study indicates a deleterious effect of a daily energy intake below 25 kcal/kg in combination with inadequate nutritional status which may be an important consideration in determining the nutrition goals and priorities among malnourished patients living with hemodialysis.

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### Introduction

In the United States, over 450 000 people are currently receiving hemodialysis (HD) for renal disease (1). Malnutrition in renal disease patients has been described

as a complex syndrome rather than a single condition or clinical marker, one that interacts with nutrient intake, inflammation, and comorbid conditions and contributes to decreased quality of life, hospitalization and mortality (2,3).

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The overall number of hospitalizations and deaths in patients diagnosed with end-stage renal disease (ESRD) is still very high despite improvements in renal replacement therapies (4). In 2013, an average of 1.7 admissions per patient-year and a mortality rate of 169 deaths per 1000 patient-years were reported in the United States (4). The evaluation of the nutritional status of dialysis patients has become a vital part of their routine care since various studies have reported a high prevalence of malnutrition irrespective of the assessment tool employed (2,5).

Several markers have been used to recognize and treat malnutrition (5,6). However, no single parameter alone can accurately describe nutritional status or drive nutritional care of patients. For example, low-serum albumin levels are strongly associated with high mortality and hospitalization rates (7), however have limited predictive power since levels may also change due to non-nutritional factors, including inflammation, acute or chronic stress and fluid status (8). It is well-known that overall inadequate dietary intake is a crucial contributor of malnutrition in the context of renal disease (2,5); however, it remains unclear, the degree to which adequate energy and protein intake prevent hospitalization and death among patients living with HD (9).

There is a need to improve the routine assessment of nutritional status and dietary intake in order to establish nutrition care priorities and consequently, increase survival, prevent hospitalizations and improve overall quality of life (1,4). Understanding the contributors of malnutrition in dialysis patients is crucial for practitioners in the field to facilitate personalized patient care, as well as to establish treatment strategies (10).

Therefore, prompt and sensitive malnutrition detection through the continuous monitoring of patient nutritional status, followed by a timely development of patient-centered dietary interventions, is decisive in improving the well-being of patients living with dialysis (2,11).

## Objectives

This study aimed to evaluate the nutritional status of participants using 7-point “subjective global assessment” (SGA) and “malnutrition inflammation score” (MIS) to measure their daily dietary intakes (energy and protein), and to examine the relationship of these nutrition parameters with hospitalization and mortality over one year.

## Patients and Methods

### Study design

The study evaluated the nutritional status and daily energy and protein intake of maintenance HD patients from a single outpatient center in South Florida by means of two different assessment tools. The endpoints of this

study were hospitalizations and mortality, registered over 12 months.

### Sample

For this study, seventy-seven maintenance HD patients (21 years of age or older) were enrolled from May 2017 to June 2017 and gave informed consent. The inclusion criteria were; receiving treatment three times weekly for more than 90 days and being medically stable. Patients were excluded if they had an acute infection, were receiving nutritional support by intradialytic parenteral nutrition or artificial feedings; if they were undergoing cancer treatment; if they had any medical condition that could interfere with completing the questionnaires; or if they refused to participate.

### Measures

Biochemical variables of interest and participant’s demographic were collected from clinical charts. The demographic variables included age, ethnicity, gender, HD start date, baseline body mass index (BMI) and diabetes mellitus (DM) diagnosis. The biochemical variables included serum albumin, “total iron binding capacity” (TIBC) and “dialysis adequacy” (Kt/V).

The nutritional status of participants was determined at baseline using the modified SGA from the CANUSA (Canada-USA) study in 1996 (12). Overall SGA score was determined using a 7-point Likert scale, described elsewhere (12). The registered dietitian responsible for the nutrition assessment, evaluation and management of these HD patients determined the total 7-point SGA score. A score of seven indicates no nutritional loss and a score of one indicates severe nutritional loss. An overall score of seven or six denoted being “well-nourished” or “having very mild malnutrition risk”; scores of five, four or three denoted “mild-to-moderate malnutrition”; and scores of two or one denoted “severe malnutrition” (12). Based on a previous multi-center study published by Steiber et al (13), participants with a 7-point SGA score >5 were considered to have an adequate nutritional status (SGA-A) and participants with a 7-point SGA score ≤5 were considered to have an inadequate nutritional status (SGA-I).

MIS was also employed to assess the nutritional status of participants, described in more detail elsewhere (14). The total sum of all components ranges from 0 to 30, representing no symptoms of malnutrition or inflammation to severe malnutrition and inflammation. Although higher the MIS scores represent worse nutritional statuses, there is no universally agreed-upon cut-off value for a malnutrition diagnosis (2). In this study, the authors defined abnormal nutrition status with the associated presence of malnutrition and inflammation using a cut-

off value of MIS >7 based on the work of Borges et al (15), who showed that MIS >7 is an independent predictor of mortality in maintenance HD patients (15). Participants with MIS ≤7 were considered to have an adequate nutritional status (MIS-A) and participants with MIS >7 to have inadequate nutritional status (MIS-I).

During their regular dialysis treatment, all HD patients in this study received specific and individualized dietary counselling together with menu examples, strategies and advice based on “Clinical Practice Guidelines for Nutrition in Chronic Renal Failure” established by the “Kidney Disease Outcomes Quality Initiative (KDOQI-2000)” (16). In this study, the dietary intake of the enrolled participants was assessed using three consecutive 24-hour diet recalls, representing dialysis and non-dialysis days. The daily energy and protein intakes were calculated as a representative average of the three 24-hour diet recalls applying software from “NutriBase 1986-2019 version 11.64” by CyberSoft, Inc.

For dietary intake adequacy, the nutritional cut-off points previously suggested by Antunes et al (17) and Araújo et al (18) for the prevention of developing protein energy wasting and the prevention of death were employed. Participants were classified as having adequate energy intake (DEI-A; ≥ 25 kcal/kg/day) or -inadequate (DEI-I; <25 kcal/kg/day) and adequate protein intake (DPI-A; ≥1.0 g/kg/day) or -inadequate (DPI-I; <1.0 g/kg/day). The ideal body weight was used in the calculations of energy and protein intake as per the review article published by Uribarri (19).

Hospitalization event was considered as any hospital visit with a full admission; hospitalizations due to transplants were not included in the analysis. The incidence of all hospitalization events was recorded over 12 months, including medical diagnosis and cause for hospitalization. All deaths were documented during the study period.

### Data analysis

The outcomes of interest in this study were hospitalizations and deaths. Values were reported as mean, standard deviation and median and data normality was assessed. Categorical variables were described with absolute number and percentage and differences were tested by chi-square test. For the inferential statistics, normal data distribution was first determined using the Kolmogorov-Smirnov test and the equality of variances was confirmed applying the Levene's test. Comparisons of variables between the different groups were performed by the independent T test and the Mann-Whitney U test, as appropriate. Cox proportional hazard analysis was applied to evaluate independent nutritional predictors (nutritional status and dietary intake indicators) of outcomes (hospitalization and survival). Independent predictors were analyzed

between two groups stratified by the presence or absence of adequate nutrition. Cox proportional hazards models were used to estimate the association between “SGA, MIS” and “dietary intake adequacy” at baseline with hospitalization and mortality in a bivariate and multivariate regression analysis, adjusted for age, gender, dialysis vintage and DM. Additionally, two different models for the multivariate analysis were employed; one to examine the interaction of SGA with dietary intake adequacy and the other to examine the interaction of MIS with dietary intake adequacy. The adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

The differences between SGA groups, MIS groups and dietary intake adequacy criteria were assessed by the log-rank test. The cumulative hospitalization and survival probabilities were estimated by Kaplan-Meier analysis. All statistical tests were performed with “SPSS version 20 software” (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at  $P < 0.05$ .

### Results

Fifty-five men and twenty women with a mean age of  $63.2 \pm 15.7$  years participated in this study. Around 18.2% of participants were Hispanic, 39% were Black, 31.2% were White and 11.7% were West Indian. Their mean length of dialysis treatment was  $6.2 \pm 4.2$  years, since 58.4% of the patients had a DM diagnosis in their medical chart. In total, 42.9% (33/77) were classified as SGA-I and 24.6% (19/77) as MIS-I. Only 54.5% (42/77) of the participants met KDOQI (16) energy recommendations and only 35% (27/77) met protein recommendations.

During the 12-month study period, around 64% of participants had at least one hospital admission. More than half of the registered hospitalizations were related to dialysis access malfunction and fluid overload (55%) and the rest were attributed to infections and other causes. Ten, out of seventy-seven participants, (13%) died, all from cardiovascular disease.

Data concerning the comparison of demographic, clinical, nutritional status and intake characteristics between “not-hospitalized” and “hospitalized” patients and between “survivors” and “deceased” patients are shown in Table 1.

In the comparison of not-hospitalized with hospitalized participants, those without registered hospitalization had higher mean BMI ( $29.11 \pm 5.44$  kg/m<sup>2</sup> versus  $26.22 \pm 5.34$  kg/m<sup>2</sup>;  $P=0.027$ ) and lower MIS score ( $5.50 \pm 2.06$  versus  $7.08 \pm 3.42$ ;  $P=0.029$ ), but neither the percentage of participants with SGA-I and MIS-I nor mean DEI and DPI differed significantly between the two groups.

The percentage of participants with inadequate nutrition status at baseline was found to be higher among deceased participants compared to those who survived [SGA-I

**Table 1.** Table of baseline characteristics comparing not-hospitalized versus hospitalized and non-survivors versus survivors

Variable	Not- Hospitalized (n=28)	Hospitalized (n=49)	P value	Survivors (n=67)	Non-Survivors (n=10)	P value
Age	63.21± 14.79	63.3 ± 16.46	0.981 <sup>a</sup>	62.7±17.23	67.1±12.28	0.415 <sup>a</sup>
Female	28.6%	28.6%	0.607 <sup>b</sup>	29.9%	20.0%	0.411 <sup>b</sup>
Ethnicity						
Hispanic	17.9%	18.4%	0.307 <sup>c</sup>	17.9%	20.0%	0.354 <sup>c</sup>
White	32.1%	30.6%		32.8%	20.0%	
AA	46.4%	34.7%		40.3%	30.0%	
West Indian	3.6%	16.3%		9.0%	30.0%	
Diabetes	50.0%	63.3%	0.185 <sup>a</sup>	55.2%	80.0%	0.126 <sup>a</sup>
Years in dialysis	7.15 ± 4.83	5.65 ± 3.73	0.132 <sup>a</sup>	6.30 ± 4.28	5.53 ± 3.74	0.592 <sup>a</sup>
BMI	29.11 ± 5.44	26.22 ± 5.34	<b>0.027<sup>a</sup></b>	27.56 ± 5.58	25.36 ± 4.92	0.243 <sup>a</sup>
Albumin	3.77 ± 0.30	3.81 ± 0.26	0.501 <sup>a</sup>	3.80 ± 0.28	3.75 ± 0.26	0.574 <sup>a</sup>
KtV	1.50 ± 0.19	1.49 ± 0.21	0.828 <sup>a</sup>	1.51 ± 0.19	1.40 ± 0.26	0.157 <sup>a</sup>
SGA	5.64 ± 1.39	5.16 ± 1.57	0.184 <sup>a</sup>	<b>5.50 ± 1.43</b>	<b>4.2 ± 1.61</b>	<b>0.010<sup>a</sup></b>
MIS	<b>5.50 ± 2.06</b>	<b>7.08 ± 3.42</b>	<b>0.029<sup>a</sup></b>	<b>6.17 ± 2.88</b>	<b>8.70 ± 3.59</b>	<b>0.015<sup>a</sup></b>
SGA-I	35.7%	46.9%	0.237 <sup>c</sup>	38.8%	70.0%	0.065 <sup>c</sup>
MIS-I	14.3%	30.6%	0.091 <sup>c</sup>	<b>17.9%</b>	<b>70.0%</b>	<b>0.002<sup>c</sup></b>
DEI (kcal/kg)	29.21 ± 6.64	27.15 ± 6.91	0.207 <sup>a</sup>	28.27 ± 6.97	25.40 ± 5.55	0.218 <sup>a</sup>
DPI (g/kg)	1.21 ± 0.26	1.14 ± 0.21	0.183 <sup>a</sup>	1.18 ± 0.23	1.04 ± 0.19	0.075 <sup>a</sup>

<sup>a</sup> Student t test; <sup>b</sup> Fisher's exact test; <sup>c</sup> Likelihood ratio chi-square; statistically significant results are shown in bold.

BMI, body mass index; Kt/V, dialysis clearance; SGA, 7-point Subjective Global Assessment; MIS, Malnutrition Inflammation Score; DEI = daily energy intake; DPI, daily protein intake; kcal/kg, kilocalories per kilogram of ideal body weight; g/kg, grams protein per kilogram of ideal body weight.

(70.0 versus 38.8%;  $P=0.065$ ) and MIS-I (70.0% versus 17.9%;  $P=0.002$ )]. However, only the difference in MIS-I was statistically significant. Likewise, non-survivors had significantly lower mean SGA scores and higher mean MIS scores than survivors ( $P < 0.05$ ), which indicated that patients who survived had a better nutritional status at baseline. Mean DEI and DPI did not significantly differ between survivors and non-survivors nor between not-hospitalized patients compared with hospitalized participants ( $P > 0.05$ ).

Table 2 shows the HRs and 95% CIs for hospitalization and mortality at 12 months according to SGA-I, MIS-I, DEI-I and DPI-I, as well as the combination of DEI-I and DPI-I. All analysis were adjusted for gender, age, dialysis

vintage and DM diagnosis. In this model, the variables SGA-I, DEI and DPI, analyzed individually, were not significant predictors of hospitalization or mortality. Only MIS-I showed significant association with mortality [HR: 9.58 (95% CI: 2.36-38.91;  $P=0.002$ )], though not with hospitalizations.

Table 3 shows the results of multivariate Cox regression models analyzing combinations of dietary intake indicators for 12-month hospitalization and mortality, grouped by SGA and MIS cutoffs. The goal of this analysis was to exam whether there exists a combination of dietary intake indicators that could better predict hospitalization and mortality in this cohort of HD-patients. Models were adjusted for gender, age, dialysis vintage and diabetes

**Table 2.** Univariate Cox proportional hazards analysis of 12 month-hospitalization and mortality in hemodialysis patients

Covariates	Mortality		Hospitalization	
	Adjusted* HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
SGA-I	<b>2.98 (0.72-12.26)</b>	0.129	1.42 (0.78-2.61)	0.246
MIS-I	9.58 (2.36-38.91)	<b>0.002</b>	1.78 (0.96-3.32)	0.067
DEI-A vs. DEI-I	0.36 (0.10-1.34)	0.130	0.80 (0.44-1.44)	0.467
DPI-A vs. DPI-I	0.41 (0.11-1.54)	0.190	0.83 (0.44-1.57)	0.570
DEI-A & DPI-A vs. DEI-A & DPI-I	0.33 (0.08-1.42)	0.139	0.925 (0.51-1.67)	0.799

CI, confident interval; HR, hazard ratios; BMI, body mass index; Kt/V, dialysis clearance; SGA, 7-point Subjective Global Assessment; SGA-I ( $\leq 5$ ); MIS, Malnutrition Inflammation Score; MIS-I ( $>7$ ); DEI, daily energy intake; DPI, daily protein intake.

\*Adjusted for gender, age, dialysis vintage and presence of diabetes.

mellitus diagnosis. As can be observed, the group of participants with inadequate nutrition status (SGA-I) but with adequate DEI had a hazard risk for mortality 84% [HR: 0.16 (95% CI: 0.03-0.90;  $P=0.038$ )], lower than those participants with adequate DEI. However, adequate DPI by itself was not significant ( $P=0.170$ ). This makes clear that energy intake is predictive of mortality for patients with inadequate nutritional status. Participants with inadequate nutritional status that did not achieve at least 25 kcal/kg/day and 1.0 g/kg/day of protein had a hazard risk for mortality 91% lower than patients that did not consume enough energy or protein [HR: 0.09 (95% CI: 0.01-0.99;  $P=0.049$ )]. To account for any collinearity issues between energy and protein intake, additional adjustments were performed using each other variable, which showed that energy intake and not protein intake, is a significant predictor (Table 3). Similar results were observed with MIS. The concomitant effect of having inadequate nutritional status (MIS-I) however adequate energy intake (DEI-A) showed a 93% lower risk

for mortality than MIS-I patients with inadequate energy intake [HR: 0.07 (95% CI: 0.01-0.83;  $P=0.035$ )]. In this model, none of the variables were significantly associated with hospitalizations.

Table 4 depicts a multivariate Cox proportional hazards analysis of hospitalization and mortality aimed at corroborating the joint effect of inadequate nutritional status with dietary intake adequacy. The models show that participants that were both SGA-I and DEI-I had a high HR for mortality [HR: 7.18 (95% CI: 1.18-43.43;  $P=0.032$ ); however, the HR for hospitalization was not statistically significant,  $P=0.091$ . Patients that were both MIS-I and DEI-I had a likelihood of death 13 times higher than MIS-I patients with adequate energy intake [HR 13.23, 95% CI: 2.1-83.2;  $P=0.006$ ], since their likelihood of hospitalization was almost three times greater [HR 2.73, 95% CI: 1.09-6.842;  $P=0.031$ ].

In addition, longitudinal comparisons of survival for one year using the Kaplan-Meier survival curves showed that the probability of survival was not significantly associated

**Table 3.** Multivariate Cox proportional hazards analysis of 12 month-hospitalization and mortality in hemodialysis patients

Covariates	Adequate nutrition status		Inadequate nutrition status	
	Adjusted* HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
<b>Hospitalization</b>				
<b>SGA-A</b>			<b>SGA-I</b>	
DEI-A	0.82 (0.36-1.87)	0.215	0.65 (0.27-1.55)	0.337
DPI-A	0.73 (0.31-1.70)	0.471	1.23 (0.42-3.53)	0.699
DEI-A+DPI-A	0.909 (0.40-2.05)	0.820	1.06 (0.41-2.71)	0.897
DEI-A**	0.89 (0.37-2.12)	0.799	0.66 (0.27-1.59)	0.361
DPI-A***	0.76 (0.31-1.85)	0.548	1.14 (0.40-3.24)	0.802
<b>MIS-A</b>			<b>MIS-I</b>	
DEI-A	1.08 (0.51-2.26)	0.839	0.41 (0.12-1.32)	0.136
DPI-A	0.93 (0.39-2.19)	0.868	1.18 (0.28-4.96)	0.820
DEI-A+DPI-A	1.22 (0.58-2.56)	0.597	0.62 (0.18-2.15)	0.457
DEI-A**	0.54 (0.03-8.33)	0.662	0.40 (0.12-1.32)	0.134
DPI-A***	0.39 (0.01-8.51)	0.554	1.10 (0.33-3.61)	0.872
<b>Mortality</b>				
<b>SGA-A</b>			<b>SGA-I</b>	
DEI-A	1.05 (0.08-12.82)	0.964	<b>0.16 (0.03-0.90)</b>	<b>0.038</b>
DPI-A	0.57 (0.04-7.49)	0.675	0.29 (0.05-1.69)	0.170
DEI-A+DPI-A	1.81 (0.09-14.41)	0.898	<b>0.09 (0.01-0.99)</b>	<b>0.049</b>
DEI-A**	1.17 (0.96-14.41)	0.898	<b>0.14 (0.02-0.84)</b>	<b>0.031</b>
DPI-A***	0.56 (0.04-7.40)	0.660	0.23 (0.03-1.48)	0.122
<b>MIS-A</b>			<b>MIS-I</b>	
DEI-A	0.88 (0.07-10.94)	0.922	<b>0.07 (0.01-0.83)</b>	<b>0.035</b>
DPI-A	4.13 (0.25-67.86)	0.320	0.79 (0.09-6.74)	0.836
DEI-A+DPI-A	1.15 (0.08-15.23)	0.914	0.25 (0.02-2.66)	0.255
DEI-A**	0.54 (0.03-8.33)	0.662	<b>0.09 (0.01-0.84)</b>	<b>0.035</b>
DPI-A***	0.48 (0.2-11.96)	0.658	1.02 (0.14-7.11)	0.983

CI, confident interval; HR, hazard ratios; BMI, body mass index; Kt/V, dialysis clearance; SGA, 7-point Subjective Global Assessment; MIS, Malnutrition Inflammation Score; DEI, daily energy intake; DPI, daily protein intake.

Statistically significant  $P<0.05$ . \* Adjusted for gender, age, dialysis vintage and presence of diabetes; \*\* Additionally adjusted to protein intake  $\geq 1$  g/kg/day; \*\*\* Sdditionally adjusted for energy intake  $\geq 25$  kcal/kg/day.



**Table 4.** Multivariate Cox proportional hazards analysis of 12-month hospitalization and mortality in hemodialysis patients examining the interaction between specified threshold of energy intake and inadequate nutritional status

Covariates	Mortality		Hospitalization	
	Adjusted* HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
SGA-I & DEI-I	7.18 (1.18-43.43)	<b>0.032</b>	2.16 (0.88-5.3)	0.091
MIS-I & DEI-I	13.23 (2.1-83.2)	<b>0.006</b>	2.73 (1.09-6.84)	<b>0.031</b>

CI, confident interval; HR, hazard ratios; BMI, body mass index; SGA, 7-point Subjective Global Assessment; MIS, Malnutrition Inflammation Score; DEI, daily energy intake.

Statistically significant  $P < 0.05$ .

\*Adjusted for gender, age, dialysis vintage and presence of diabetes.

with solely nutrition status adequacy, employing both diagnostic tools, [SGA; log rank test,  $P = 0.68$ ] (Figure 1A) nor [MIS; log rank test  $P = 0.916$ ] (Figure 1C). However, when adding to it the effect of achieving an adequate energy intake of 25 kcal/kg/day (DEI-A) then the probability of survival improved in patients, utilizing both diagnostic tools, [SGA-I; log rank test ( $P = 0.020$ )] (Figure 1B) and [MIS-I (log rank test;  $P = 0.02$ )] (Figure 1D). The comparison of hospitalizations did not achieve statistical significance in Kaplan–Meier analysis ( $P < 0.05$ ).

## Discussion

This study examined the predictive value of nutritional status and diet adequacy on hospitalization and mortality in HD patients. Our results showed that participants with an inadequate nutritional status who did not fulfil 25 kcal/kg/day of dietary energy intake had an increased

risk for mortality and hospitalizations compared to those who did. This effect was found to be more relevant in the case of mortality which increased up to 13-fold than in hospitalizations (~3 fold). Our study showed that the survival of patients with moderate-to-malnourished was prolonged if DEI was least 25 kcal/kg, which suggests the importance of nutrition interventions focusing on increasing energy intake, or the use of calorie enhancers, in HD patients with impaired nutritional status.

In this study, around 43% of participants were classified as having some degree of malnutrition conducting the 7-point SGA and 25% patients were so classified using the MIS metric. This wide range for the prevalence of malnutrition (25% to 43%) is similar to the range reported by Carrero et al (2), who estimated that malnutrition occurs in 28–54% of HD patients worldwide, depending mostly on the assessment tool used (2). In our models,

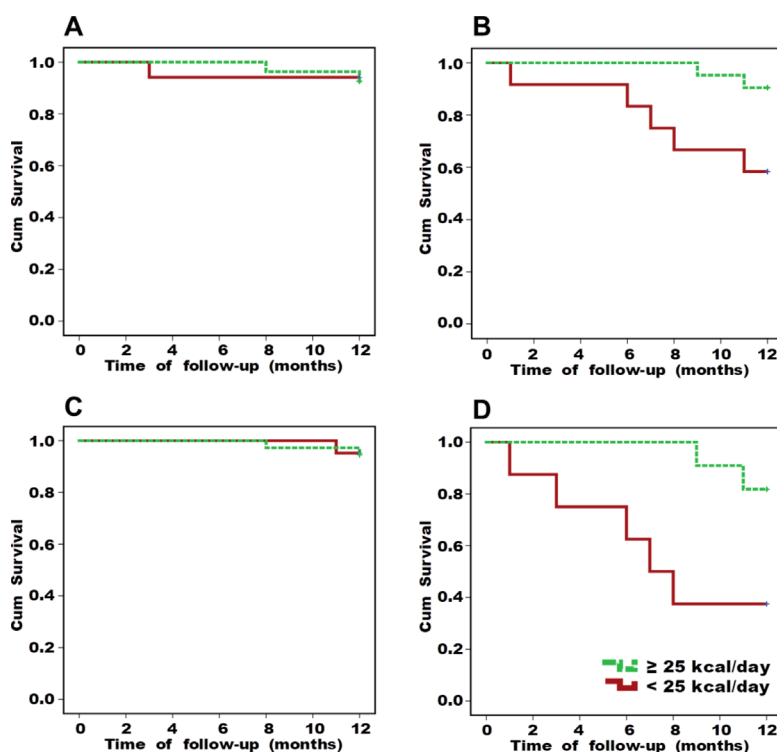


Figure 1. Kaplan–Meier estimates of mortality to analyze the association between nutrition adequacy and energy intake in HD patients.

SGA score was not an independent predictor of either hospitalizations or mortality, unlike prior studies that have reported SGA score as a significant predictor of mortality in patients undergoing HD (5,11,13). One possible explanation for this finding is the small sample size of this study (77 HD participants), which could have limited the statistical power of the analysis. In addition, for the purpose of our analysis, SGA score was not analyzed as a continuous variable but was dichotomized as either well-nourished (adequate) or moderately-to-severely malnourished (inadequate). As the precise nutritional scores indicate different stages of malnutrition, using a dichotomous approach may affect the results of this study.

Interestingly, SGA score was a predictor of mortality when analyzing the interaction of nutrition status with dietary energy intake. Participants with an inadequate nutritional status who met energy recommendations of at least 25 kcal/kg/day had a decreased risk for mortality, employing both nutrition status diagnostic tools (SGA and MIS), compared to those patients that did not meet energy recommendations. The risk was further decreased if they also met DPI of at least 1 g/kg/day, but protein alone did not predict mortality or hospitalization.

While SGA score alone is not predictive of mortality or hospitalization, our results show that MIS score was an independent predictor of mortality, which comports with other studies (14,15). Despite the lack of consensus on cutoff value, increasing MIS scores are correlated with worsened nutritional-inflammation status and clinical markers, including hospitalizations and mortality (11,14). Our study found that patients with MIS scores >7 had a 9.58-fold increase in the risk of one-year mortality.

In this analysis, neither energy nor protein intake were independent predictors of hospitalization and mortality. However, the interaction of nutrition status and diet intake was a predictor of outcomes. The joint effect of nutritional status and calorie intake on clinical outcomes was evident using both nutritional assessment tools. Based on these results, participants who had an inadequate nutritional status but who met an energy intake of at least 25 kcal/kg/day had a dramatically reduced risk of death: 93% lower when using MIS scores and 84% lower when utilizing SGA scores. These findings are consistent with those of Kang et al (20), who found that energy intake below 25 kcal/kg/day in combination with increased MIS (MIS >5) was associated with increased risk of 10-year mortality in HD patients. These results expand the existing literature about the modifying effect of diet, and especially of energy intake, on patients' outcomes.

It has been suggested that an insufficient energy intake might lead to inadequate levels of essential nutrients in HD patients, which could then cause adverse clinical outcomes (21). Some authors have argued that the effect

of energy intake on disease outcomes is greater than the effect of protein intake (22). One possibility for this disparity in effect is that inadequate energy intake, even with adequate protein intake, causes a negative nitrogen balance in patients, resulting in both dietary protein and muscular tissue protein being used as a fuel for energy (21).

Finally, some research has indicated that excessive protein intake is associated with increased phosphorus levels, which can drive mortality and should be avoided (22-24). Unfortunately, dietitians and nephrologists often emphasize the importance of eating a high protein diet while, at the same time, enforcing several dietary restrictions (phosphorus, potassium, sodium, fluid intake, carbohydrate and fats) upon HD patients, leaving them with limited food choices and restricted diets to fulfill their energy needs (25).

In this study, we determined the nutritional status using two different nutritional assessment tools (SGA and MIS), and the participants' average protein and energy intakes were assessed through using the average of three 24-hour diet recalls taken on dialysis and non-dialysis days by a trained dietitian. Our findings highlight that inadequate energy intake has a deleterious impact on hospitalization and mortality risk, especially in those patients with an impaired nutritional status who already are facing nutritional losses.

## Conclusion

Our findings underscore that energy intake below 25 kcal/kg/day in combination with inadequate nutritional status was associated with adverse outcomes in HD patients. Therefore, dietary recommendations to promote overall energy intake and not dietary restrictions should be a nutrition priority among malnourished patients living with HD.

## Limitations of the study

Limitations should be considered when interpreting the study's findings. Firstly, the sample size was small and included participants from a single HD center, and its generalizability to other populations is therefore limited. Secondly, given that it is an observational study, it is difficult to separate the multifarious interactions of variables.

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## Authors' contribution

Conceptualization: JDM, CB and IDE.

Investigation: JDM.

Formal analysis: IDE.

Writing—original draft preparation: CB.

All authors have read and agreed to the published version of the manuscript.

### Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ongoing studies and analysis.

### Conflicts of interest

The authors declare no conflict of interest.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Florida International University approved this study (IRB# 17-0198-CR01). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from PhD thesis of Janet Diaz Martinez at this university [Thesis #FIDC007708, “The Relationship of a Novel Marker of Inflammation (Neutrophil-to-Lymphocyte Ratio) to Nutritional Status, Diet and Clinical Outcomes in Hemodialysis Patients” (2019). FIU Electronic Theses and Dissertations. 4276; <https://digitalcommons.fiu.edu/etd/4276>]. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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