



Applied nutritional investigation

## Nutritional status of older patients on hemodialysis: Which nutritional markers can best predict clinical outcomes?



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### ABSTRACT

**Objective:** The aim of this study was to investigate nutritional status in older patients undergoing maintenance hemodialysis (MHD) to determine the prevalence of nutritional markers indicating protein-energy wasting (PEW) as assessed by subjective global assessment (SGA) and other methods, and to explore which nutritional markers can best predict clinical outcomes.

**Methods:** The study included 173 patients (median age 69 y; 65% men; 38% diabetes) undergoing MHD for >3 mo. Nutritional markers included SGA, malnutrition-inflammation score (MIS), geriatric nutritional risk index (GNRI), handgrip strength (HGS), midarm muscle circumference (MAMC), triceps skinfold thickness (SKF), calf circumference, and albumin. Associations between PEW (diagnosed by different measures and thresholds) and risk for hospitalization (by Poisson regression) and all-cause mortality (by Cox proportional hazards model) were analyzed.

**Results:** Depending on methods and thresholds used, the prevalence of nutritional markers indicating PEW varied from 6.9% to 59.5%. In the Poisson models adjusted for age, sex, dialysis length, and diabetes, low SGA, HGS, albumin, and high MIS score were associated with high hospitalization events, whereas in the bivariate Cox regression models adjusted for the same variables, low SGA, GNRI, BMI, calf circumference, and high MIS score were associated with high hazard ratio (HR) for mortality. In addition, in the multivariate models, SGA showed the strongest association with mortality (HR, 2.32; 95% confidence interval [CI], 1.27–4.24) and together with MIS (HR, 2.09; 95% CI, 1.20–3.64), the highest values of C-statistics.

**Conclusions:** Among older MHD patients, the prevalence of nutritional markers indicating PEW varies substantially depending on methods applied. SGA, MIS, BMI, GNRI, calf circumference, and HGS predicted worse outcomes. SGA and MIS showed the strongest association with hospitalization and mortality risk in the adjusted models.

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### Introduction

The number of individuals  $\geq 65$  y of age worldwide is steadily increasing and global projections forecast a further increase of >1.6 billion by 2050 [1]. The aging population represents an important challenge because senescence is associated with accelerated development of many chronic non-communicable diseases associated with burden of lifestyle, such as diabetes, hypertension, and cardiovascular disease, and chronic kidney disease (CKD) is no exemption. Consequently, the growing number of older individuals with end-stage renal disease (ESRD) is staggering, and close to one-third of patients undergoing dialysis in European and North and South American countries are >65 y of age [2–4].

Considering the inherent changes in nutritional status and body composition that occur with aging, studies comprising patients on

maintenance hemodialysis (MHD) and aiming to investigate the usefulness of methods commonly applied to assess nutritional status in adult patients are warranted. However, to our knowledge, few studies so far have focused on evaluation of methods to assess nutritional status in older patients with CKD [5] and ESRD [6,7]. These studies reported that 51% to 68% of the patients had signs of protein–energy wasting (PEW) as assessed by subjective global assessment (SGA), indicating the importance of careful nutritional assessment in this subsample of patients. Moreover, Çelik et al. [8], when comparing older versus younger adult MHD patients, reported that older patients had significantly lower muscle mass, serum creatinine, normalized protein nitrogen appearance, serum albumin, and prealbumin, but significantly higher fat mass than younger patients, suggesting that older patients on MHD are prone to obese sarcopenia and may present a distinct profile of PEW.

Validating methods for nutritional assessment of older patients on MHD aligns with the clinical practice guidelines on management of older patients with CKD stage 3b or higher [9]. These guidelines reinforce the importance of conducting studies that test whether the nutritional parameters suggested by the expert panel of the International Society in Renal Nutrition (ISRNM) for adult patients on MHD is also associated with higher mortality rates in older adults on MHD [10]. Studies testing the ability of methods commonly applied in adult patients undergoing dialysis to screen for PEW in older adults on dialysis are lacking. Therefore, we aimed to assess the prevalence of nutritional markers indicating PEW by different methods and to evaluate whether established cutoff values for adult dialyzed patients are associated with hospitalization events and overall survival in older patients on MHD.

## Methods

### Participants

We recruited 173 patients on MHD from six dialysis units in Rio de Janeiro and one in São Paulo, Brazil. Patients >60 y of age undergoing MHD for >3 mo were included, and those who were institutionalized; used a wheelchair; or had amputated limbs, cancer, or degenerative diseases, as described elsewhere [11], were not included. Written informed consent was obtained from each patient before enrollment. The study was approved by the Ethics and Research Committee of Rio de Janeiro State University.

### Study and design protocol

This was an observational, longitudinal prospective study. Patients were included from March 2010 to February 2014. Hospitalization events and overall survival were recorded up to 36 mo after the first assessment, with a mean follow-up of median (interquartile range [IQR]) 23.6 (12–34.4) mo.

### Anthropometric measurements and muscle strength

At baseline, all participants had body weight, height, midarm muscle circumference (MAMC), triceps skinfold thickness (SKF), and calf circumference measured after 30 to 60 min of dialysis, according to the protocol proposed by Lohman [12]. The dominant arm without fistula was preferably used. Two experienced dietitians carried out all anthropometric measurements. Height (m) was assessed using a stadiometer and body weight (kg) by an electronic scale at the nearest 0.1 kg. The triceps SKF (mm) was assessed by the Lange Skinfold Caliper (Cambridge Scientific Industries Inc., Cambridge, MD, USA), and the circumferences of arm and calf (cm) were measured by a non-stretchable tape. Body mass index (BMI) was calculated as body weight (kg) divided by square height (m<sup>2</sup>) [13] and MAMC with the following equation [14]:

$$\text{MAMC (cm)} = \text{MAC (cm)} - (\pi \times \text{triceps SKF}).$$

Standard values of MAMC and triceps SKF were calculated by the equation: (measured value – value on P<sub>50</sub>) × 100.

Muscle strength was assessed by handgrip strength (HGS; kg) with a handgrip dynamometer (Baseline Fabrication Enterprises Inc., Elmsford, NY, USA).

Measurements were taken three times in both hands, with arms along the body encouraging the patient to press with maximum strength in response to a voice command. The highest value of the two last measurements from the opposite hand of the arteriovenous fistula was registered and the mean value was used.

### Subjective global assessment, malnutrition-inflammation score, and geriatric nutritional risk index

The nutritional status was assessed by the 7-point SGA [15] and malnutrition-inflammation score (MIS) [16] forms, both translated and validated into Portuguese [17]. In addition, the geriatric nutritional risk index (GNRI), developed by Bouillanne et al. [18], was calculated with the following equation:

$$\text{GNRI} = [1.489 \times \text{albumin (g/dL)}] + [41.7 \times (\text{body weight/ideal body weight})].$$

### Laboratory data

Blood samples were collected pre- and post-dialysis, on a midweek dialysis day, for assessment of serum creatinine, urea (pre- and post-dialysis), albumin (bromocresol green method), and high-sensitivity C-reactive protein (hs-CRP). Urea Kt/V was calculated according to Daugirda's formula [19].

### Definition of nutritional markers indicating the presence of PEW and low muscle strength

The nutritional markers indicating presence of PEW in CKD, as described by Fouque et al. [10], were used to test whether these individual markers, when applied to a group of older individuals undergoing MHD, were associated with higher hospitalization and mortality rates. Therefore, nutritional markers indicating low values of serum chemistry (serum albumin), body stores (BMI, body fat percentage), and muscle mass (MAMC, calf circumference) were tested, in addition to SGA and MIS. The thresholds applied to define low values of nutritional markers indicating PEW and low muscle strength were defined following the guidelines on nutrition for patients with CKD [10,15,20–23] or for older adults [24–26] and are listed in Table 1.

### Clinical outcomes

Any hospital admission that entailed at least one overnight stay was defined as a hospitalization event. Access-related hospitalizations were recorded by medical record and by contacting the patient's family to confirm information, if necessary. Cardiovascular mortality was defined as a demise resulting from coronary heart disease, sudden death, stroke, or peripheral vascular disease. Length of survival was recorded from the baseline up to 36 mo; median follow-up time was 23.6 mo (IQR 12–34.4). Changes in dialysis modality, kidney transplantation, and transfer to other units were considered as dropout and were censored.

### Statistical analysis

Values are presented as mean ± SD for normally distributed or as median (IQR) for skewed variables. The Shapiro–Wilk test was applied to test normality. Categorical variables are described as absolute number and percentage. Comparisons

**Table 1**  
Thresholds applied to define nutritional markers indicating protein–energy wasting and low muscle strength

Variable	Threshold	References
BMI (kg/m <sup>2</sup> )	<23	Fouque et al., 2007 [21]
Standard MAMC (%)	<90	NKF/KDOQI, 2000 [20]
Standard triceps SKF (%)	<90	NKF/KDOQI, 2000 [20]
Calf circumference (cm)	<31	Landi et al., 2014 [25]
7-point SGA (score)	≤5	Steiber et al., 2007 [15]
MIS (score)	≥8	Rambod et al., 2009 [23]
GNRI	≤91.2	Yamada et al., 2008 [22]
Albumin (g/dL)	<4	NKF/KDOQI, 2000 [20]; Fouque et al., 2007 [21]
	<3.8	Fouque et al., 2008 [10]
HGS (kg)		
Male	<30	Cruz-Jentoff et al., 2012 [24]
Female	<20	
Male	<27	Cruz-Jentoff et al., 2019 [25]
Female	<16	

BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; HGS, handgrip strength; MAMC, midarm muscle circumference; MIS, malnutrition-inflammation score; NKF/KDOQI, National Kidney Foundation/Kidney Disease Outcomes Quality Initiative; SGA, subjective global assessment; SKF, skinfold thickness.

of demographic, clinical, and nutritional parameters between the survival and non-survival groups and between the hospitalized and non-hospitalized groups were performed by the independent *t* test and Mann–Whitney U test, as appropriate. The log-rank test was used to evaluate hospitalization and survival curves. The risk for hospitalization was calculated in an adjusted model using Poisson regression, and it was expressed as a hazard ratio (HR) with 95% confidence interval (CI). The Cox proportional hazards models were performed to estimate the association between PEW (diagnosed by different measures and thresholds) and mortality in a bivariate and multivariate regression analysis adjusted for age, sex, dialysis vintage, and presence of diabetes mellitus (DM). Two different models for the multivariate analysis were constructed, where SGA and MIS were included as independent variables in different models owing to the collinearity between SGA and MIS. Potential covariates applied in the adjustment of Cox model were also adjusted for in the Poisson model. Harrell's C-statistic was calculated for every survival test to assess the best predictive accuracy of each test [27]. Values of the C-statistic range from 0.5 to 1, and the higher value, the better the model's accuracy power.  $P < 0.05$  was used for statistical significance. The statistical analyses were performed using SPSS version 20 (IBM, Chicago, IL, USA) and STATA version 13 (StataCorp, College Station, TX, USA).

## Results

Figure 1 describes the flowchart of the study. Of 254 eligible patients, 173 were included after 81 patients declined to participate. No significant differences between those included in the study group and those who declined to participate were found regarding sex, age, dialysis length, BMI, or comorbidities (data not shown). Moreover, 86 (49.7%) of 173 patients had at least one hospitalization event and 61 (35.2%) died during the follow-up of 23.6 mo (IQR 12–34.4). The causes of dropout and deaths are described in the flowchart (Fig. 1). For patients included in the study, median age at baseline was 69.4 y (range 64.5–75.4), most were men ( $n = 112$ ; 65%), median dialysis length was 2.89 y (1.27–5.65) and median urea Kt/V 1.48 (IQR 1.45–1.63). Of the cohort, 38.2% had diabetes and 77.4% had hypertension. The prevalence of nutritional markers indicating PEW assessed by different methods and thresholds varied from 6.9% to 59.5%, and the prevalence of low muscle strength assessed by HGS varied from 51.4% to 35.8%, as described in Figure 2.

Data regarding the comparison of demographic, clinical, and nutritional characteristics between hospitalized and non-hospitalized patients and between living and deceased patients are shown

in Table 2. Those with hospitalization events had significantly lower muscle strength and serum albumin and higher MIS scores, indicating worse nutritional status. Patients who died were older and had worse nutritional status as indicated by lower values of triceps SKF, HGS, and SGA, and higher MIS score. They also had higher hs-CRP.

The comparisons between the hospitalization and survival curves performed by the log-rank test are described in Table 3. As depicted, hospitalized patients with  $\text{GNRI} \leq 91.2$ , albumin ( $< 3.8$  and  $< 4$  g/dL) and  $\text{hs-CRP} > 1$  mg/dL showed a higher hospitalization rate during the follow-up. Similarly, a worse survival rate was observed for those with  $\text{BMI} < 23$  kg/m<sup>2</sup>, calf circumference  $< 31$  cm, HGS  $< 30$  kg for men and  $< 20$  kg for women, SGA score  $\leq 5$ , MIS score  $\geq 8$ , and  $\text{GNRI} \leq 91.2$ .

Table 4 shows the HR and 95% CI for hospitalization and mortality according to the thresholds tested to indicate worse nutritional status adjusted for sex, age, dialysis length, and DM. As can be seen, patients with worse nutritional markers assessed by SGA, MIS, serum albumin, and low HGS had a significantly higher risk for hospitalization events. Regarding mortality events, except for standard triceps SKF, MAMC, and serum albumin, patients diagnosed with signs of PEW by the remaining methods had higher risk for death. Of note, SGA showed the strongest association with mortality (HR, 2.32; 95% CI, 1.27–4.24). Moreover, SGA, MIS, and calf circumference were the methods with higher values of C-statistic, indicating higher prediction accuracy for death. Regarding muscle strength, lower HGS was associated with higher risk for death when the cutoffs  $< 30$  kg for men and  $< 20$  kg for women were used.

SGA and MIS, indices based on similar components to evaluate nutritional status, showed higher HR for mortality. In Table 5, two multivariate models were constructed separately for SGA and MIS, aiming to test whether there would be a combination of nutritional markers that could better predict mortality in elderly patients on MHD. Each model was adjusted for sex, age, dialysis vintage, and DM, in addition to the markers of nutritional status that significantly increased HR for death in the bivariate model showed in Table 4. The models for SGA showed that, except for model 4 (SGA + GNRI + BMI + calf circumference + HGS  $< 30$  kg for men and

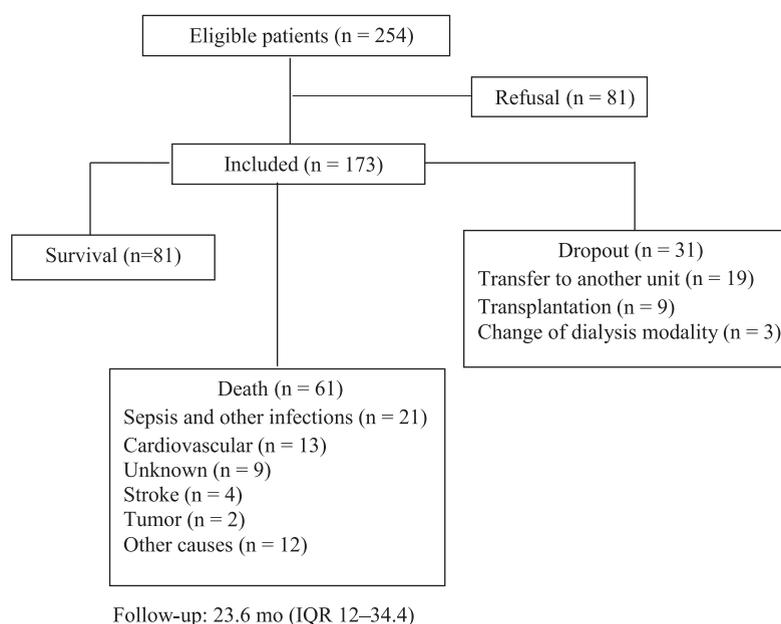
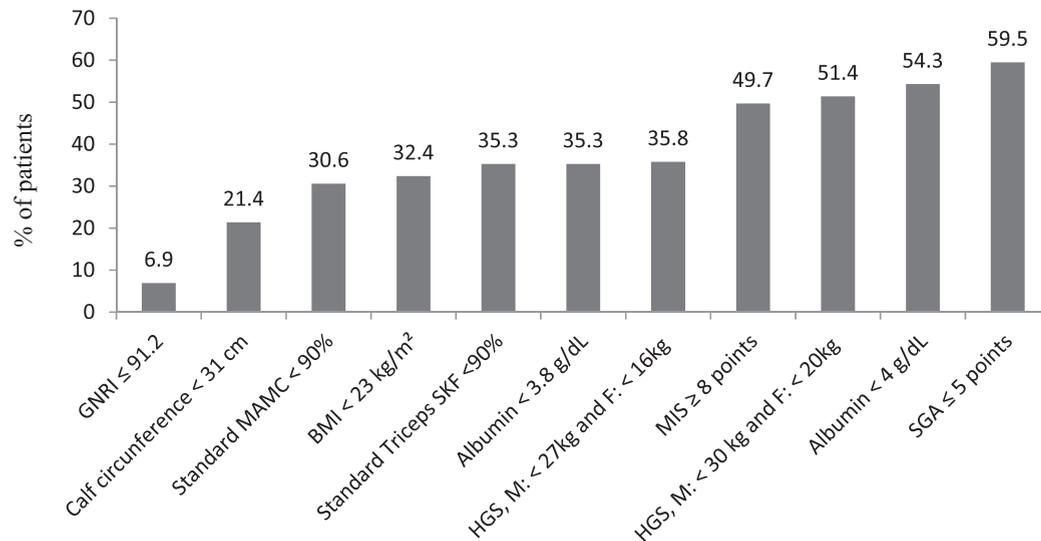


Fig. 1. Flowchart of the study. IQR, interquartile range.



GNRI: Geriatric Nutritional Risk Index; MAMC: Mid Arm Muscle Circumference; BMI: Body Mass Index; SKF: Skinfold Thickness; MIS: Malnutrition Inflammation Score; HGS: Handgrip Strength; F: Female; M: Male; SGA: Subjective Global Assessment.

**Fig. 2.** Prevalence of nutritional markers indicating protein energy wasting and low muscle strength in elderly on maintenance hemodialysis according to the thresholds proposed in the literature (N = 173).

<20 kg for women) that had borderline significance ( $P=0.05$ ), the combination of SGA with the remaining nutritional markers showed a significant and higher risk for mortality, although it was attenuated as additional nutritional markers were included in the model. Similar results were observed in the models tested

for MIS. The threshold of HGS <27 kg for men and <16 kg for women were not associated with death in combination with the remaining nutritional markers. When we compared the discrimination of the Cox models using C-statistics, for both SGA and MIS, adding nutritional markers in the model significantly

**Table 2**  
Comparison of demographic, clinical, and nutritional data between hospitalized and non-hospitalized patients and between surviving and deceased patients on maintenance hemodialysis (N = 173)

	Hospitalization events			Mortality		
	Non-Hospitalized (n = 87)	Hospitalized (n = 86)	P-value*	Surviving (n = 112)	Deceased (n = 61)	P-value*
Age (y)	70.1 ± 7.4	70.9 ± 7.1	0.46	69.5 ± 6.7	72.4 ± 7.7	<b>0.01</b>
Male n (%)	53 (47.3)	59 (52.7)	0.34	73 (65.2)	39 (63.9)	0.87
Dialysis length (y)	3.0 (1.2–5.7)	2.8 (1.3–5.6)	0.76	2.8 (1.1–5.3)	3 (1.4–6)	0.34
Diabetes n (%)	32 (37.2)	34 (39.1)	0.79	44 (39.3)	22 (36.1)	0.74
BMI (kg/m <sup>2</sup> )	25.7 ± 5.1	25.3 ± 3.9	0.54	25.5 ± 4.1	25.4 ± 5.2	0.79
Triceps SKF (mm)						
Male	14.5 ± 6.4	15.3 ± 7.6	0.56	15.1 ± 7.3	14.3 ± 6.6	0.54
Female	22.6 ± 8.1	19.3 ± 7.4	0.11	22.6 ± 7.8	18.4 ± 7.6	<b>0.05</b>
Standard triceps SKF (%)	118.4 ± 61.1	115.9 ± 56.4	0.78	120.2 ± 59	111.9 ± 57	0.42
MAMC (cm)						
Male	26.1 ± 3.7	24.9 ± 3.2	0.08	25.8 ± 3.6	24.8 ± 3.2	0.09
Female	23.1 ± 3.9	24.3 ± 2.6	0.17	23.4 ± 3.1	24.1 ± 3.9	0.44
Standard MAMC (%)	99.3 ± 15.4	97.2 ± 14	0.77	98.5 ± 13.9	97.7 ± 16.1	0.52
Calf circumference (cm)						
Male	34.7 ± 4.3	34.2 ± 3.5	0.46	34.9 ± 3.7	33.6 ± 3.9	0.11
Female	33.6 ± 3.8	33.1 ± 3.1	0.62	33.8 ± 3.2	32.7 ± 3.8	0.27
HGS (kg)						
Male	29.5 ± 7.0	26.3 ± 8.1	<b>0.03</b>	29.5 ± 7.2	24.7 ± 7.8	<b>0.01</b>
Female	20.3 ± 6.5	15.6 ± 6.1	<b>0.01</b>	18.8 ± 6.6	17.2 ± 6.9	0.39
SGA	5.3 ± 1	5.1 ± 0.9	0.13	5.4 ± 0.9	4.9 ± 0.9	<b>0.01</b>
MIS	7.4 ± 3.1	8.4 ± 3.4	<b>0.04</b>	7.3 ± 3.2	8.9 ± 3.2	<b>0.01</b>
GNRI	107.8 ± 11	105.1 ± 8.9	0.08	106.9 ± 9.4	105.7 ± 11.4	0.44
Albumin (g/dL)	4.0 ± 0.4	3.8 ± 0.4	<b>0.04</b>	3.9 ± 0.4	3.8 ± 0.4	0.06
hsCRP (mg/dL)	0.36 (0.21–1.21)	0.49 (0.20–0.90)	0.98	0.34 (0.18–0.83)	0.59 (0.27–1.49)	<b>0.01</b>

BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; HGS, handgrip strength; hs-CRP, high-sensitivity C-reactive protein; MAMC, midarm muscle circumference; MIS, malnutrition-inflammation score; SGA, subjective global assessment; SKF, skinfold thickness.

\*Independent t test or Mann–Whitney U test.

Male (n = 112); Female (n = 61).

Values are expressed as mean ± SD; median (interquartile range); or n (%) and significant values were described in bold.

**Table 3**

Comparison between hospitalization and survival curves according to the methods and thresholds tested to assess nutritional status in older adults undergoing maintenance hemodialysis (N = 173)

	P-value* for hospitalization	P-value* for overall survival
Age $\geq$ 75 y	0.90	0.06
BMI <23 kg/m <sup>2</sup>	0.99	<b>0.01</b>
Standard Triceps SKF <90%	0.44	0.16
Standard MAMC <90%	0.14	0.23
Calf circumference <31 cm	0.78	<b>0.01</b>
HGS (men <30 kg, women <20 kg)	0.44	<b>0.01</b>
HGS (men < 27 kg, women < 16 kg)	0.09	0.09
SGA $\leq$ 5 points	0.89	<b>0.01</b>
MIS $\geq$ 8 points	0.22	<b>0.01</b>
GNRI $\leq$ 9 1.2	<b>0.03</b>	<b>0.04</b>
Hs-CRP $\geq$ 1 mg/dL	<b>0.01</b>	0.06
Albumin <3.8 g/dL	<b>0.01</b>	0.19
Albumin <4 g/dL	<b>0.01</b>	0.06

BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; HGS, handgrip strength; hs-CRP, high-sensitivity C-reactive protein; MAMC, midarm muscle circumference; MIS, malnutrition-inflammation score; SGA, subjective global assessment; SKF, skinfold thickness.

Significant values were described in bold.

\*Log-rank test.

improved the predictive accuracy for death beyond that observed for SGA or MIS alone.

## Discussion

The prevalence of individuals  $\geq$ 65 y of age undergoing MHD has been increasing over recent decades [2–4], the importance of geriatric nephrology research, including methods for assessment of nutritional status in the  $\geq$ 65 population, as aging itself leads to lower food intake, lower thirst, lower synthesis of somatic proteins, decrease in height, and changes in body composition, characterized by a higher deposition of body fat with a concomitant decrease in muscle mass [28,29].

Bearing that in mind, we evaluated the prevalence of nutritional markers applied for the diagnosis of PEW and tested whether the cutoffs commonly applied to screen for PEW in adult patients on dialysis are associated with poor outcomes in a sample comprised by older adults on MHD. The findings from the present study showed that the prevalence of nutritional markers indicating PEW varied widely, from 6.9% to 59.5%, depending on the method

applied. In addition, among the methods and thresholds tested, we report that signs of malnutrition assessed by SGA, MIS, BMI, GNRI, and calf circumference were associated with higher death risk in models adjusted for sex, age, dialysis vintage, and DM. Similar associations for hospitalization events were found for SGA, MIS, and lower serum albumin. Regarding muscle strength, lower HGS was associated with higher number of hospitalization events and higher risk for death with the threshold <30 kg for men and <20 kg for women, but not for mortality events when the threshold <27 kg for men and <16 kg for women was used. These findings suggest that these methods and thresholds normally applied in patients with CKD and ESRD predict worse outcome in a sample of older individuals on MHD. Although reduced muscle strength using the cutoffs proposed in the revised consensus on sarcopenia [25] did not show association with mortality, the cutoffs from the previous consensus [24] were associated with hospitalization and mortality. One reason that might explain this finding is the diminished sample classified with low muscle mass, which may lead to diminished statistical power, as shown by the P-value indicating borderline significance ( $P=0.09$ ).

The wide variation of the prevalence of nutritional markers indicating PEW was similar to that found in adults on dialysis [6,30–35]. By applying the SGA and the diagnostic criteria from the International Society in Renal Nutrition (including the evaluation of serum albumin, prealbumin, cholesterol, energy and protein intake, BMI, body fat, and muscle wasting), Essadik et al. [36] observed that the prevalence of PEW evaluated by each method and criteria varied from 7.1% to 80.9% [36]. This wide range can be explained by the fact that these methods, when considered as a single marker, assess different aspects of PEW, such as a distinct body compartments or visceral protein stores or energy and protein intake. As PEW is characterized by a conjunction of several concomitant nutritional deficiencies, it is preferable to choose a method that assesses these deficiencies as a whole. In this respect, SGA and MIS, which consider the clinical history, appetite, spontaneous loss of body weight, physical function, muscle mass, and fat stores can be a method of choice. In addition, in a previous publication including older adults on MHD, we showed that both methods differentiated well-nourished patients from those with PEW when compared with other objective nutritional measurements [37]. Adding to these findings, we now demonstrate that patients diagnosed with malnutrition by SGA and MIS had higher risk for hospitalization and death and that these conditions were highly

**Table 4**

Risk for hospitalization events and mortality, expressed as HR, according to specified thresholds of nutritional parameters tested in older patients undergoing maintenance hemodialysis (N = 173)

Methods	Hospitalization		Mortality		
	HR (95% CI)*	P-value	HR (95% CI)†	P-value	C-statistic
SGA $\leq$ 5 points	1.38 (1.03–1.85)	<b>0.03</b>	2.32 (1.27–4.24)	<b>0.01</b>	0.64
MIS $\geq$ 8 points	1.40 (1.06–1.87)	<b>0.02</b>	2.09 (1.20–3.64)	<b>0.01</b>	0.65
GNRI $\leq$ 9 1.2	1.05 (0.61–1.78)	0.86	2.37 (1.00–5.59)	<b>0.04</b>	0.61
BMI <23 kg/m <sup>2</sup>	1.00 (0.74–1.35)	0.99	1.85 (1.09–3.14)	<b>0.02</b>	0.62
Calf circumference <31 cm	1.21 (0.87–1.71)	0.25	2.27 (1.27–4.05)	<b>0.01</b>	0.64
Standard triceps SKF <90%	0.90 (0.68–1.21)	0.52	1.54 (0.91–2.59)	0.11	0.59
Standard MAMC <90%	1.08 (0.80–1.46)	0.59	1.19 (0.69–2.06)	0.53	0.58
HGS (men <30 kg; women <20 kg)	1.82 (1.37–2.43)	<b>0.01</b>	1.98 (1.12–3.48)	0.02	0.58
HGS (men <27 kg; women <16 kg)	1.64 (1.22–2.20)	<b>0.01</b>	1.37 (0.78;2.42)	0.26	0.58
Albumin <3.8 g/dL	1.39 (1.06–1.83)	<b>0.02</b>	1.29 (0.76–2.18)	0.35	0.59
Albumin <4 g/dL	1.72 (1.29–2.29)	<b>0.01</b>	1.44 (0.85–2.47)	0.18	0.60

BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; HGS, handgrip strength; hs-CRP, high-sensitivity C-reactive protein; MAMC, midarm muscle circumference; MIS, malnutrition-inflammation score; SGA, subjective global assessment; SKF, skinfold thickness.

Significant values were described in bold.

\*Each variable was tested by Poisson regression, adjusted for sex, age, dialysis vintage, and presence of diabetes.

†Each variable was tested by bivariate Cox proportional regression, adjusted for sex, age, dialysis vintage, and presence of diabetes.

**Table 5**  
Risk for mortality events, expressed as HR,\* and associations of nutritional parameters and strength with mortality events, when evaluating nutritional status using SGA and MIS, and combinations with other specified nutritional parameters in older patients undergoing maintenance hemodialysis (N = 173)

Models <sup>†</sup>	Mortality			Models <sup>‡</sup>	Mortality		
	HR (95% CI)*	P-value	C-statistic		HR (95% CI)*	P-value	C-statistic
SGA	2.32 (1.27–4.24)	<b>0.01</b>	0.64	MIS	2.09 (1.20–3.64)	<b>0.01</b>	0.65
Model 1	2.23 (1.21–4.1)	<b>0.01</b>	0.65	Model 5	1.97 (1.11–3.50)	<b>0.02</b>	0.65
Model 2	2.08 (1.11–3.88)	<b>0.02</b>	0.66	Model 6	1.86 (1.04–3.33)	<b>0.03</b>	0.66
Model 3	1.95 (1.03–3.68)	<b>0.04</b>	0.67	Model 7	1.78 (0.99–3.22)	0.05	0.68
Model 4	1.86 (0.99–3.53)	0.05	0.68	Model 8	1.72 (0.95–3.12)	0.07	0.69

BMI, body mass index; CC, calf circumference; GNRI, Geriatric Nutritional Risk Index; HGS, handgrip strength; hs-CRP, high-sensitivity C-reactive protein; MIS, malnutrition-inflammation score; SGA, subjective global assessment.

Significant values were described in bold.

\*Multivariate Cox proportional regression, adjusted for sex, age, dialysis vintage, and diabetes.

<sup>†</sup>**Model 1** (SGA): SGA + GNRI + cofounders; **Model 2** (SGA): SGA + GNRI + BMI + cofounders; **Model 3** (SGA): SGA + GNRI + BMI + CC + cofounders; **Model 4** (SGA): SGA + GNRI + BMI + CC + HGS <30 kg for men and <20 kg for women + cofounders; **Model 5** (MIS): MIS + GNRI + cofounders; **Model 6** (MIS): MIS + GNRI + BMI + cofounders; **Model 7** (MIS): MIS + GNRI + BMI + CC + cofounders; **Model 8** (MIS): MIS + GNRI + BMI + CC + HGS <30 kg for men and <20 kg for women + cofounders.

predictive according to the C-statistics test. These findings are in accordance with the European Best Practice Guidelines for older adult patients with CKD stages 3b or higher, which recommended SGA as a preferred method for the assessment of nutritional status [9]. In addition, the same expert panel suggested using a score composed by serum albumin, BMI, serum creatinine, and protein nitrogen appearance normalized by body weight to assess nutritional status of older adults with CKD [9]. However, when we tested whether combining other nutritional measurements to SGA or MIS would increase the risk for death, we found that adding GNRI, BMI, calf circumference, and HGS (<30 kg for men and <20 kg for women) to the model marginally increased the prediction of death and, perhaps surprisingly, diminished the risk for death. Our hypothesis is that SGA and MIS already contemplate the nutrition deficiencies assessed by the other measurements and therefore, the addition of other measurements to the regression model did not increase the association with worse outcomes. Thus, our finding suggest that by using SGA or MIS, one can adequately assess the nutritional status of older patients on MHD. This concurs with a study with a large proportion of older patients that showed that SGA was a valid assessor of nutritional status and an independent predictor of all-cause mortality both in CKD non-dialysis and dialysis patients, and that SGA outperformed non-composite nutritional markers as prognosticator [38].

Of note, lower serum albumin concentration was associated with higher risk for hospitalization, but not with increased mortality hazard ratio in the models adjusted for age, sex, length of dialysis, and DM, even when this marker was evaluated as a continuous variable or when categorized with different cutoffs (<4 and <3.8 g/dL). The fact that only individuals >60 y of age were included might explain these results because aging itself is related to lower albumin synthesis [37]. This means that a lower albumin concentration can be expected and, therefore, does not differentiate mortality in this subsample of older patients on MHD. Moreover, it also can be speculated that low serum albumin is related to higher mortality only when systemic inflammation is present, as recently reported in a study comprising patients on dialysis [39]. On the other hand, patients with serum values of albumin <3.8 and <4 g/dL had an HR of 1.39 (95% CI, 1.06–1.83) and 1.72 (95% CI, 1.29–2.29) for hospitalization events, respectively, indicating that those with lower albumin had increased risk for hospitalization [39]. The fact that hospitalized individuals are prone to more comorbidities and increased inflammation likely accounts for these findings.

The effect of sex on outcomes according to the nutritional markers was not tested in this study, but it was noticeable that deceased men presented significantly lower HGS than survivors, whereas the same was not true for women where low values of

triceps SKF had significantly worse outcome. Similar results also could be observed in men with low HGS in a study that aimed to evaluate separately men (n = 126) and women (n = 80) close to starting dialysis and predicted outcome according to S-albumin, SGA, HGS, lean body mass, fat mass, and other clinical markers [40].

The strengths and limitations of the present study should be noted. Regarding strengths, we present data of a well-characterized sample of older patients on MHD using several methods for assessment of nutritional status. We focused investigations on the use of methods that are easy to use on a routine basis in this population, a topic not well studied yet, to our knowledge. Regarding limitations, because this is a convenience sample, we might have selected a group of adults with better health status not fully representing the group of older adults on dialysis. Some markers, such as MIS, have no defined cutoff to diagnose for PEW. Although we adopted a cutoff that showed association with higher mortality rates and lower measurements of nutritional status in patients on hemodialysis (15), we cannot rule out that patients with MIS score <8 might have signs of malnutrition as well. We did not test the performance of these measurements to assess longitudinal changes, but in a previous publication we showed that a one-unit change of SGA and MIS were associated with changes of anthropometrics, muscle strength, and bioelectrical impedance analysis parameters during 12 mo of follow-up [11]. Finally, the lack of a control group comprised of young adults did not allow us to investigate the association of these measurements with worse outcomes in young compared with older patients on MHD.

## Conclusion

We reported that the prevalence of nutritional markers indicating PEW among older patients on MHD varies from 6.9% to 59.5%, depending on the method applied. Moreover, among the methods and cutoffs applied, SGA, MIS, BMI, GNRI, and calf circumference predict worse outcomes in this older population on MHD. SGA and MIS stand out as key predictors of increased hospitalization and mortality risk, even when other nutritional markers are added to the model. This information can be used by dietitians in the daily routine when choosing the method to assess nutritional status, and thus to improve the nutritional care given to older adults on MHD.

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## References

- [1] He W, Goodkind D, Kowal P. An aging world: 2015. U.S. Census Bureau, International Population Reports, P95/16–1, Washington DC: U.S. Government Publishing Office; 2016.
- [2] Kramer A, Pippias M, Noordzij M, Stel VS, Afentakis N, Ambühl PM, et al. The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. *Clin Kidney J* 2018;11: 108–22.
- [3] Sesso RC, Lopes AA, Thomé FS, Lugon JR, Martins CT. Brazilian Chronic Dialysis Survey 2016. *J Bras Nefrol* 2017;39:261–6.
- [4] United States Renal Data System. 2017 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
- [5] Windahl K, Faxén Irving G, Almquist T, Lidén MK, van de Luijngaarden M, Chesnay NC, et al. Prevalence and risk of protein-energy wasting assessed by Subjective Global Assessment in older adults with advanced chronic kidney disease: results from the EQUAL study. *J Ren Nutr* 2018;28:165–74.
- [6] Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, et al. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int* 1998;53:773–82.
- [7] Cianciaruso B, Brunori G, Traverso G, Panarello G, Enia G, Strippoli P, et al. Nutritional status in the elderly patient with uraemia. *Nephrol Dial Transplant* 1995;10(suppl 6):65–8.
- [8] Celik G, Oc B, Kara I, Yılmaz M, Yucaektas A, Apiliogullari S. Comparison of nutritional parameters among adult and elderly hemodialysis patients. *Int J Med Sci* 2011;8:628–34.
- [9] Farrington K, Covic A, Aucella F, Clyne N, de Vos L, Findlay A, et al. Clinical Practice guideline on management of older patients with chronic kidney disease stage 3 b or higher (eGFR <45 mL/min/1.73 m<sup>2</sup>). *Nephrol Dial Transplant* 2016;31(suppl 2):iii1–66.
- [10] Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008;73:391–8.
- [11] Santin F, Rodrigues J, Brito FB, Avesani CM. Performance of subjective global assessment and malnutrition inflammation score for monitoring the nutritional status of older adults on hemodialysis. *Clin Nutr* 2018;37:604–11.
- [12] Lohman TR, Roche AF, Martorell R. Anthropometric standardization reference manual. 1<sup>th</sup> ed. Champaign, IL: Human Kinetics Books; 1991.
- [13] Quetelet LA. A treatise on man and the development of his faculties. 1842. *Obes Res* 1994;2:72–85.
- [14] Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981;34:2540–5.
- [15] Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, et al. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. *J Ren Nutr* 2007: 336–42.
- [16] Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001;38:1251–63.
- [17] Fetter RL, Bigogno FG, de Oliveira FG, Avesani CM. Cross-cultural adaptation—Portuguese of tools for assessing the nutritional status of patients on dialysis. *J Bras Nefrol* 2014;36:176–85.
- [18] Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Ncolis I, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 2005;82:777–83.
- [19] Daugirdas JT. 2nd-generation logarithmic estimates of single-pool variable volume Kt/V – An analysis of error. *J Am Soc Nephrol* 1993;4:1205–13.
- [20] National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kid Dis* 2000;35:S1–140.
- [21] Fouque D, Vennegoor M, Wee P, Wanner C, Basci A, Canaud B, et al. EBPG guideline on nutrition. *Nephrol Dial Transplant* 2007;22(suppl 2):ii45–87.
- [22] Yamada K, Furuya R, Takita T, Maruyama Y, Yamaguchi Y, Ohkawa S, et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am J Clin Nutr* 2008;87:106–13.
- [23] Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, et al. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis* 2009;53:298–309.
- [24] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;39:412–23.
- [25] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised european consensus on definition and diagnosis. *Age Ageing* 2019;48:16–31.
- [26] Landi F, Onder G, Russo A, Liperoti R, Tosato M, Martone AM, et al. Calf circumference, frailty and physical performance among older adults living in the community. *Clin Nutr* 2014;33:539–44.
- [27] Harrell FE, Lee Jr KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87.
- [28] Raguso CA, Kyle U, Kossovsky MP, Roynette C, Paoloni-Giacobino A, Hans D, et al. A 3-year longitudinal study on body composition changes in the elderly: role of physical exercise. *Clin Nutr* 2006;25:573–80.
- [29] St-Onge MP, Gallagher D. Body composition changes with aging: the cause or the result of alterations in metabolic rate and macronutrient oxidation? *Nutrition* 2010;26:152–5.
- [30] Aparicio M, Cano N, Chauveau P, Azar R, Canaud B, Flory A, et al. Nutritional status of haemodialysis patients: a French national cooperative study. French Study Group for Nutrition in Dialysis. *Nephrol Dial Transplant* 1999;14:1679–86.
- [31] Cianciaruso B, Brunori G, Kopple JD, Traverso G, Panarello G, Enia G, et al. Cross-sectional comparison of malnutrition in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Am J Kidney Dis* 1995;26:475–86.
- [32] Nascimento MM, Qureshi AR, Stenvinkel P, Pecoits-Filho R, Heimbürger O, Cederholm T, et al. Malnutrition and inflammation are associated with impaired pulmonary function in patients with chronic kidney disease. *Nephrol Dial Transplant* 2004;19:1823–8.
- [33] Bazanelli AP, Kamimura MA, da Silva CB, Avesani CM, Lopes MG, Manfredi SR, et al. Resting energy expenditure in peritoneal dialysis patients. *Perit Dial Int* 2006;26:697–704.
- [34] Tayyem RF, Mrayyan MT. Assessing the prevalence of malnutrition in chronic kidney disease patients in Jordan. *J Ren Nutr* 2008;18:202–9.
- [35] Young GA, Kopple JD, Lindholm B, Vonesh EF, De Vecchi A, Scalamogna A, et al. Nutritional assessment of continuous ambulatory peritoneal dialysis patients: an international study. *Am J Kidney Dis* 1991;17:462–71.
- [36] Essadik R, Msaad R, Lebrazi H, Taki H, Tahri EH, Kettani A, et al. Assessing the prevalence of protein-energy wasting in haemodialysis patients: a cross-sectional monocentric study. *Nephrol Ther* 2017;13:537–43.
- [37] Santin FG, Bigogno FG, Dias Rodrigues J, Cuppari L, Avesani CM. Concurrent and predictive validity of composite methods to assess nutritional status in older adults on hemodialysis. *J Ren Nutr* 2016;26:18–25.
- [38] Dai L, Mukai H, Lindholm B, Heimbürger O, Barany P, Stenvinkel P, et al. Clinical global assessment of nutritional status as predictor of mortality in chronic kidney disease patients. *PLoS One* 2017;12:E0186659.
- [39] Alves F, Sun J, Qureshi AR, Dai L, Snaedal S, Bårány P, et al. The higher mortality associated with low serum albumin is dependent on systemic inflammation in end-stage kidney disease. *PLoS One* 2018;13:e0190410.
- [40] Stenvinkel P, Barany P, Chung SH, Lindholm B, Heimbürger O. A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. *Nephrol Dial Transplant* 2002;17:1266–74.