A Comparative Analysis of Nutritional Assessment Using Global Leadership Initiative on Malnutrition Versus Subjective Global Assessment and Malnutrition Inflammation Score in Maintenance Hemodialysis Patients

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Objective: Malnutrition is a prevalent condition in maintenance hemodialysis (MHD) patients. This study aimed to evaluate the performance of the recently developed GLIM (Global Leadership Initiative on Malnutrition) in MHD by assessing the agreement, accuracy, sensitivity, specificity, and survival prediction of GLIM when compared to 7-point subjective global assessment (7p-SGA) and malnutrition inflammation score (MIS).

Design and Methods: We investigated 2 cohorts: MHD_{Italy} (121 adults from Italy; 67 ± 16 years, 65% men, body mass index 25 ± 5 kg/m^2) and MHD_{Brazil} (169 elderly [age > 60 years] from Brazil; 71 ± 7 years, 66% men, body mass index 25 ± 4 kg/m^2), followed for all-cause mortality for median 40 and 17 months, respectively. We applied the 2-step approach from GLIM: (1) screening and (2) confirming malnutrition by phenotypic and etiologic criteria. For 7p-SGA and MIS, a score ≤5 and ≥8, respectively, defined malnutrition.

Results: Malnutrition was present in 38.8% by GLIM, 25.6% by 7p-SGA, and 29.7% by MIS in the MHD_{Italy} cohort, and in 47.9% by GLIM, 59.8% by 7p-SGA, and 49.7% by MIS in the MHD_{Brazil} cohort. Cohen's kappa coefficient (κ) showed only "fair" agreement between GLIM and SGA (MHD_{Italy}: $\kappa = 0.26$, $P = .003$; MHD_{Brazil}: $\kappa = 0.22$, $P = .003$) and between GLIM and MIS (MHD_{Italy}: $\kappa = 0.33$, $P < .001$; MHD_{Brazil}: $\kappa = 0.25$, $P = .001$). Cox regression analysis showed that all 3 methods were able to predict mortality in crude analysis; however in the adjusted model, the association seemed more consistent and stronger in magnitude for 7p-SGA and MIS.

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Conclusion: In MHD patients, GLIM showed low agreement, sensitivity, and accuracy in identifying malnourished subjects by either 7p-SGA or MIS. Considering the specific wasting characteristics that predominate in MHD, the well-established 7p-SGA and MIS methods may be more useful in this clinical setting.

Introduction

MALNUTRITION IS HIGHLY prevalent in maintenance hemodialysis (MHD) patients as indicated by a global meta-analysis of 65 studies from 10 geographical regions, showing that half of the studies reported a malnutrition prevalence (assessed by subjective global assessment [SGA] or malnutrition inflammation score [MIS]) of 43% or higher.[1] The causes of malnutrition or rather protein-energy wasting (PEW) syndrome in CKD are multifactorial and include metabolic acidosis, low-grade chronic inflammation, increased protein degradation, and loss of amino acids and proteins during the dialysis procedure, as well as decreased appetite and insufficient food intake.[2,3] Collectively, these conditions, which lead to loss of muscle mass and body fat, are closely associated with increased risk for all-cause mortality.[4,5]

The assessment of nutritional status in MHD patients should consider specificities related to CKD per se and the impact of MHD including the following: (1) nutrient losses into dialysate; (2) an altered hydration status that changes at each dialysis session with subsequent body weight fluctuations; (3) a decreased serum albumin level in large part due to low-grade inflammation; and (4) a pattern of overall food intake that often varies between dialysis and a non-dialysis day. Based on a systematic review of available evidence, the 2020 Updated Clinical Practice Guideline for Nutrition in CKD published by the National Kidney Foundation/Kidney Disease Outcome Quality Initiative recommended the 7-point SGA (7p-SGA) and MIS for the assessment of nutritional status in patients with CKD stage 5 (glomerular filtration rate < 15 mL/min/1.73 m^2) not on dialysis and for those on MHD.[6]

In 2018, a special committee from the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed a consensus definition for an etiology-independent diagnosis of malnutrition in adults independent of the clinical setting.[7] The main motivation was the need to build a universal score to standardize the definition of malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) was developed and is composed of a 2-step approach including a first screening to select patients at risk and a second assessment for the diagnosis and grading of the severity of malnutrition.[7] Because GLIM is a new nutritional score and not yet validated in the setting of renal care, we designed a study aiming at evaluating its applicability in MHD patients. For this purpose, we analyzed the agreement, accuracy, sensitivity, and specificity of GLIM compared to 7p-SGA and MIS, which are well-established tools for nutritional assessment in MHD patients. In addition, we evaluated the survival prediction of GLIM compared with that obtained with 7p-SGA and MIS.

Methods

Study Design and Patients

This is an observational, longitudinal, prospective cohort study involving 2 cohorts of patients on MHD, one from Italy and the other from Brazil. The Italian cohort (MHD Italian) comprised 121 patients aged older than 18 years recruited between December 2015 and December 2016 and followed for median 40 months (interquartile range [IQR] 27-46). The main objective of the MHD Italian study was to assess the correlation between nutritional parameters and muscle mass as assessed by ultrasound.[8] The Brazilian cohort (MHD Brazilian) comprised 169 patients older than 60 years recruited between March 2010 and February 2014 and followed for median 17 months (IQR 12-31). The primary objective of the MHD Brazilian study was to evaluate the nutritional marker that could best predict a worse clinical outcome in older adults on MHD.[5] In both cohorts, only patients on MHD for at least 3 months and on standard dialysis scheme (3 times weekly every other day; 3.5-4 hours each dialysis session) were included. The exclusion criteria for the MHD Italian cohort were the presence of malignancy and conditions with mandatory immobilization and for the Brazilian cohort patients who were living in elderly home care, use of wheelchair, presence of amputated limbs, or malignant and degenerative diseases. Both protocols were approved by the respective Local Ethical Committees and all participants gave their informed consent before enrollment in the study.

Anthropometrics Measurements

Patients from both cohorts had their nutritional status assessed by experienced dietitians. Anthropometric measurements included body weight, height, mid-arm circumference, and triceps skinfold thicknesses (SKF) assessed 20-60 minutes after the dialysis session. Body weight (kg) was assessed by an electronic scale at the nearest 0.1 kg and height (m) using a stadiometer. Triceps SKF (mm) was assessed by the Lange Skinfold Caliper (Cambridge Scientific Industries Inc., Cambridge, MD), and arm circumference was measured by a nonstretchable tape. Body mass index (BMI) was calculated as body weight (kg) divided by square height (m^2), and mid-arm

muscle circumference (MAMC) was calculated using the following equation: MAMC (cm) = mid-arm circumference (cm) − (π × triceps SKF). Standard values of MAMC were calculated using the following equation: (measured value/value on 50th percentile) × 100.[9]

Seven-Point Subjective Global Assessment and Malnutrition Inflammation Score

The 7p-SGA and MIS are composite tools to evaluate the nutritional status and are composed of nutritional history (changes in body weight and dietary intake, presence of gastrointestinal symptoms), functional capacity, disease-related comorbidities, and physical examination (loss of subcutaneous fat, muscle wasting, and clinical edema). MIS adds the objective assessments of BMI, serum albumin, and serum transferrin.[10] These conditions were assessed by trained dietitians and rated according to each tool. For SGA, the 7-point scale was used, and patients were classified as well-nourished malnutrition (score 7 to 6), mild to moderate malnutrition (score 5 to 3) and severe malnutrition (score 2 to 1).[10] For analysis purposes, patients with SGA score 5 to 1 were grouped as malnourished. For MIS, we used the cutoff proposed in our previous study for older adults on MHD, in which patients with MIS higher or equal to 8 were considered malnourished.[5]

Global Leadership Initiative on Malnutrition

The GLIM comprises 2 steps: (1) screening for malnutrition and (2) confirming and grading malnutrition by phenotypic and etiologic criteria.[7] For screening, we used the proposed diagnostic criteria for PEW in patients with kidney failure.[11] Patients screened at risk when at least one of the following criteria was present: BMI <23 kg/m^2, nonvolitional weight loss >5% during the previous 3 months, MAMC <90% of the value considered to be adequate (reduction >10% in relation to 50th percentile of reference population), serum albumin <3.8 g/dL, and normalized protein equivalent of nitrogen appearance (nPNA) <0.8 g of protein/kg/day.[11] In the second step, patients identified as being at risk for malnutrition at the screening were retested with GLIM's phenotypic criteria: nonvolitional weight loss >5% the previous 3 months or low BMI (<20 kg/m^2 if <70 years, or <22 kg/m^2 if >70 years) and reduced muscle mass (MAMC <90% of value considered to be adequate). Because MHD patients are often inflamed and have a reduced food intake, suffer from other chronic disease-related etiologic factors, and, furthermore, are exposed to dialysis, which is a catabolic procedure, all patients included in the present study were considered to fulfill the etiologic criteria for the diagnosis of malnutrition proposed by the GLIM original paper.[7]

Laboratorial Measurements

Blood samples were collected predialysis and postdialysis, on a midweek dialysis day, for assessment of serum creatinine (predialysis), urea (predialysis and postdialysis), albumin (predialysis, bromocresol green method), and high-sensitivity C-reactive protein (predialysis). The nPNA was calculated to estimate dietary protein intake based on urea kinetic modeling, and normalized by actual body weight.[12]

Statistical Analysis

Continuous variables are presented as median and interquartile range, or mean and standard deviation, depending on its normality distribution (assessed by Kolmogorov-Smirnov test). Categorical variables are shown as the absolute value and percentage. The agreement between GLIM with 7p-SGA and MIS muscle mass was evaluated by kappa test. The kappa value of agreement can be interpreted as follows: 0.20 poor, 0.21-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 very good.[13] The sensitivity and specificity of GLIM compared to 7p-SGA and MIS were assessed through a cross-reference table, and the area under the curve (AUC) by the receiver operating characteristics curve analysis, using 7p-SGA and MIS as the reference method. Diagnostic accuracy was deemed excellent for AUC values in the range of 0.90-1.00, good or discrete for 0.80-0.70; poor for 0.60-0.70, and absent for values between 0.50 and 0.6.[14] Statistical significance was defined as *P*-values below .05. The Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS, Inc., Chicago, IL) was used for the statistical analyses.

Results

As shown in Table 1, both cohorts had a majority of men, an average BMI tending to overweight, and an average 7p-SGA and MIS indicating some degree of malnutrition. Mean serum albumin was below 4.0 mg/dL in both cohorts, and the Brazilian cohort had a high-sensitivity C-reactive protein indicative of chronic low-grade inflammation.

The prevalence of malnutrition according to 7p-SGA, MIS, and GLIM was highest in the MHD Brazilian cohort. In both cohorts, the prevalence of malnutrition showed opposite patterns depending on the method used: within the MHD Italian cohort, GLIM showed the highest prevalence of malnutrition (38.8%), while within the MHD Brazilian cohort, GLIM showed the lowest prevalence (47.9%). Overall, the lowest prevalence (25.6%) was observed when applying 7p-SGA in the MHD Italian cohort, while the highest prevalence (59.8%), also for 7p-SGA, was observed in the MHD Brazilian cohort (Fig. 1).

When assessing the agreement between GLIM with 7p-SGA and MIS (Table 2), the results of the kappa test showed a moderate degree of agreement in both cohorts. As for the AUC, a discrete degree of accuracy of GLIM to diagnose malnutrition was observed in comparison to 7p-SGA and MIS in both cohorts. Aligned with this

Table 1. Main Characteristics of the 2 Cohorts of Maintenance Hemodialysis Patients

Variables	MHD Italian (n = 121)	MHD Brazilian (n = 169)
Male, n (%)	79 (65)	111 (65.7%)
Mean age (y)	66.8 ± 16.1	70.6 ± 7.3
Age (y), interquartile range	24-94	64-76
Dialysis vintage (y)	4.1 (1.55-7.7)	2.9 (1.27-5.6)
Kt/V	1.49 (1.28-1.70)	1.46 (1.30-1.62)
BMI (kg/m^2)	24.8 ± 4.6	25.4 ± 4.5
7p-SGA (points)	5.8 ± 0.97	5.2 ± 0.9
MIS (points)	6.7 ± 3.8	7.9 ± 3.3
Serum albumin (g/dL)	3.60 ± 0.39	3.89 ± 0.41
hsCRP (mg/L)	1.41 (0.34-3.84)	4.2 (2.0-11.0)

7p-SGA, 7-point subjective global assessment; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; MHD, maintenance hemodialysis; MIS, malnutrition inflammation index.

Data are expressed as mean ± standard deviation, or median and interquartile range.

findings, the sensitivity (true positives) of GLIM for malnutrition was low because only 61%-72% of the patients in both cohorts were being diagnosed as malnourished by GLIM and 7p-SGA and by GLIM and MIS, meaning that if 7p-SGA and MIS are taken as reference, GLIM would have missed the diagnosis of malnutrition in 39%-28% of the patients.

We followed patients for median 40 (IQR 27-46) months in the MHD Italian cohort and for 17 (IQR 12-31) months in the MHD Brazilian cohort. In this period, there were 45 deaths (37%) in the MHD Italian cohort and 48 deaths (28%) in the MHD Brazilian cohort. The survival analysis showed that patients diagnosed as malnourished by the 3 score systems had worse survival curves compared with those diagnosed as well nourished (Fig. 2A and B). In the Cox regression analysis, the hazard ratio for mortality was also higher for malnourished patients by the 3 score systems in both cohorts, but when adjusted for age and sex, in the MHD Italian cohort, only patients malnourished by MIS had a statistically significant higher risk for mortality, while in the MHD Brazilian cohort, patients malnourished by GLIM, 7p-SGA, and MIS remained at higher risk for mortality (Table 3).

Discussion

The routine assessment of nutritional status in patients on MHD remains a challenge. Although a detailed nutritional assessment based on a combination of methods that include assessment of body composition, muscle function, laboratorial parameters, and nutrient intake is considered the reference for nutritional care, it is time consuming and not always possible to implement in clinical practice. The 7p-SGA and MIS, on the other hand, are methods easy to perform, simple, inexpensive, and recommended by the 2020 National Kidney Foundation/Kidney Disease Outcome Quality Initiative Nutrition guidelines for routine nutritional assessment.[6] Recently, the ESPEN society proposed the GLIM score for the assessment of nutritional status,[7] but as such it does not consider the particularities of MHD patients. Therefore, in the present study, we assessed the agreement, specificity, sensitivity, and association with mortality risk of GLIM in comparison to the 7p-SGA and MIS in MHD patients. When applying

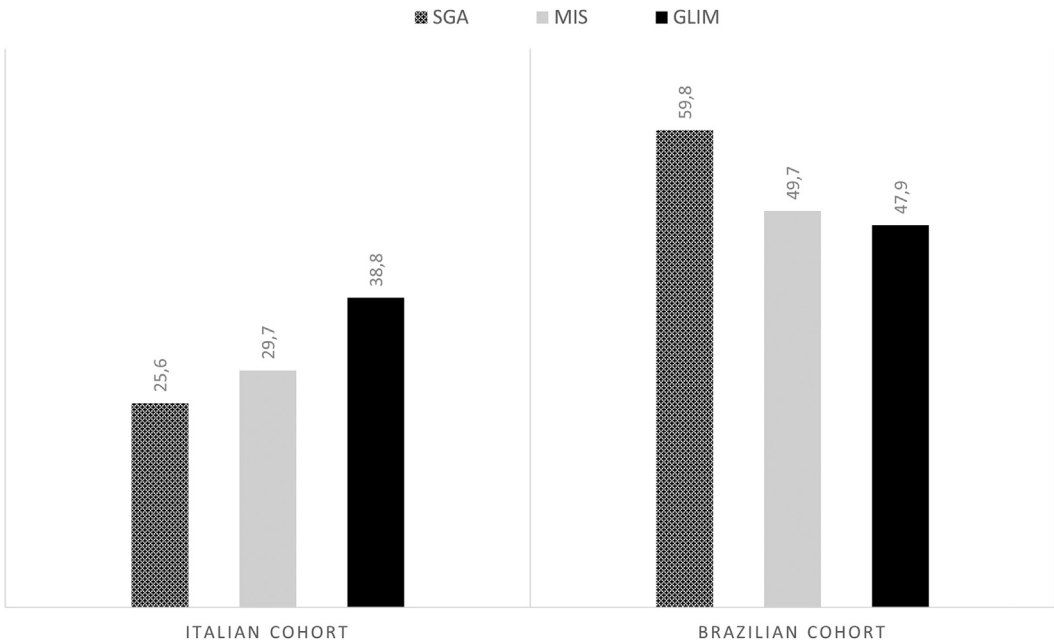

Figure 1. Prevalence of malnutrition in maintenance hemodialysis patients according to the different tools for the Italian cohort (n = 121) and the Brazilian cohort (n = 169). 7p-SGA, 7-point subjective global assessment; GLIM, Global Leadership Initiative on Malnutrition; MIS, malnutrition inflammation index.

Table 2. Agreement Among GLIM, SGA, and MIS for the Assessment of Malnutrition in 2 Cohorts of Maintenance Hemodialysis Patients

Variables	Kappa (*P* Value)	Sensitivity (%)	Specificity (%)	AUC (95% CI)
MHD Italian (n = 121)				
GLIM × 7p-SGA	0.26 (.003)	61	69	0.65 (0.537-0.765)
GLIM × MIS	0.33 (<.001)	64	72	0.68 (0.571-0.785)
MHD Brazilian (n = 169)				
GLIM × 7p-SGA	0.22 (.003)	72	51	0.61 (0.529-0.699)
GLIM × MIS	0.25 (.001)	63	62	0.63 (0.543-0.712)

7p-SGA, 7-point subjective global assessment; AUC, area under the curve; CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition; MHD, maintenance hemodialysis; MIS, malnutrition inflammation index.

these 3 tools in 2 cohorts of MHD patients, GLIM identified the highest prevalence of malnutrition in the MHD Italian cohort, but, in the Brazilian MHD cohort, GLIM identified the lowest prevalence in comparison to 7p-SGA and MIS. This variability resulted only in a fair agreement between 7p-SGA and MIS with GLIM, with poor diagnostic accuracy for GLIM, characterized by AUC ranging from 0.61 to 0.68. This finding is similar to that found by Karavetian et al[15] in which there was a fair agreement between GLIM and MIS (kappa = 0.202) and a higher prevalence of malnutrition by GLIM (54.3%) than by MIS (48.6%) in adult MHD patients. The difference in structure between the tools likely played an important role in these findings. Although MIS and 7p-SGA were adapted from the original SGA to identify malnourished patients in CKD and MHD patients, GLIM was built for a broader use in different clinical settings. In addition, GLIM has a 2o-step approach: it first uses a screening tool and then a combination of objective parameters (BMI or weight loss and muscle mass), plus an etiologic criterion to confirm the diagnosis of malnutrition. In the current study, the presence of one positive parameter of the PEW diagnostic criteria as a screening tool was used because these measurements are well-established predictors of poor outcome in HD patients[11] and it is one of the screening tools suggested by the

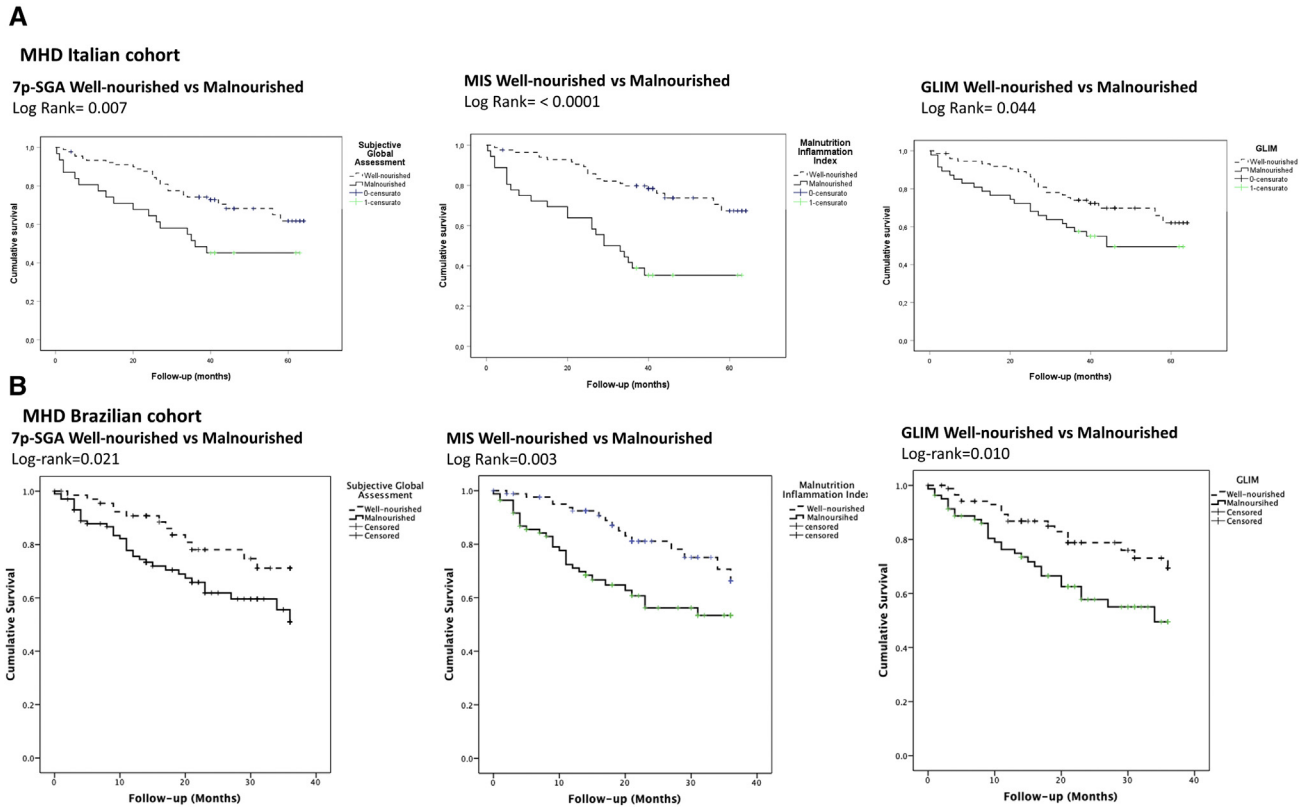

Figure 2. Kaplan-Meier survival curves according to the different tools in maintenance hemodialysis patients for the Italian cohort (n = 121) (A) and the Brazilian cohort (n = 169) (B). 7p-SGA, 7-point subjective global assessment; GLIM, Global Leadership Initiative on Malnutrition; MHD, maintenance hemodialysis; MIS, malnutrition inflammation index. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3. Risk for Mortality Events Associated With Malnutrition as Defined by GLIM, SGA-7p, and MIS in Maintenance Hemodialysis Patients

	Crude		Adjusted*	
Variables	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
MHD Italian (n = 121)				
7p-SGA malnourished	2.25 (1.23-4.11)	.009	1.52 (0.81-2.88)	.196
MIS malnourished	3.70 (2.04-6.70)	<.001	2.42 (1.28-4.59)	.007
GLIM malnourished	1.81 (1.01-3.25)	.04	1.38 (0.75-2.55)	.306
MHD Brazilian (n = 169)				
7p-SGA malnourished	2.07 (1.09-3.92)	.025	1.96 (1.01-3.79)	.045
MIS malnourished	2.40 (1.31-4.39)	.004	2.24 (1.20-4.16)	.011
GLIM malnourished	2.10 (1.17-3.78)	.013	2.09 (1.13-3.86)	.018

7p-SGA, 7-point subjective global assessment; CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition; MHD, maintenance hemodialysis; MIS, malnutrition inflammation index.

*Adjusted for age and sex.

GLIM working group.[7] For etiologic criterion, all patients were considered positive due to the underlying disease and the MHD treatment, a procedure known to increase protein degradation and protein catabolism predisposing to muscle wasting.[16] We cannot rule out that these specificities might have reduced the sensitivity and specificity of GLIM to diagnose malnutrition in our study.

The performance of GLIM has been investigated in other clinical settings, including liver disease,[17] cancer,[18] inflammatory bowel disease,[19] and in healthy community-dwelling elderly individuals.[20] The results from these studies showed a fair-to-moderate agreement between GLIM and other nutritional markers like the ESPEN 2015 criterion, the patient-generated SGA, and nutritional risk screening tool.[17-20] Of note, in hospitalized patients with diverse diseases, GLIM was shown to have high accuracy to screen for malnutrition compared to the mini-nutrition assessment tool using a cut-off <9 for severe malnutrition (AUC 0.92, $P < .01$) and <11 for moderate malnutrition (AUC 0.90, $P < .01$).[21] This suggests that the performance of GLIM varies depending on the patient group and that GLIM might show better performance to diagnose malnutrition in a diverse group, such as hospitalized patients, in which the use of specific tools may be complicated by factors related to the cause of hospitalization and the severity of the disease.

The predictive validity for all-cause mortality risk associated with malnutrition was evaluated in our study by the 3 tools. We found that patients classified as malnourished by all 3 tools had lower survival than well-nourished patients in the crude analysis. We interpret the loss of statistical significance in some scores after adjustment for age and sex as a general lack of power in our study. However, the magnitude of the hazards was similarly elevated throughout. Our results are in line with multiple previous studies in MHD,[4,5] as well as studies using GLIM in community-dwelling elderly individuals,[20] or oncologic patients,[18] emphasizing the prognostic role that alterations in nutritional status have. Moreover, as shown by our AUC analysis the MIS score appeared superior in predicting mortality, especially in younger patients. We speculate that the inclusion in the MIS score of BMI, serum albumin, and serum transferrin, 3 factors known to predict mortality, increases its prognostic capacity over and above the more traditional 7p-SGA.[22-26]

Some strengths and limitations of our study should be addressed. The use of 2 different cohorts of diverse age and geographical distribution, and the observation of similar results regardless, may increase the generalizability of our findings. One important limitation is that we did not use a gold standard method of body composition assessment to test the validity of the GLIM score. However, because GLIM is a composite tool, comparing it to 2 other well-established and validated composite tools seemed appropriate. Another limitation is our potentially lack of power, which makes our results warrant confirmation in future studies. Until then, we believe our results may have clinical implications and can inform decisions on the choice of nutritional assessment tools to adopt for the everyday clinical practice for this particular patient population. Finally, it is important to underline that kidney patients may not be an eligible/suitable group for applying indices and guidelines developed for the nonrenal population.

In conclusion, GLIM score did not perform better than 7p-SGA and MIS in diagnosing malnutrition in MHD patients. This was shown by a low agreement, sensitivity, and accuracy of GLIM in identifying malnourished subjects by either 7p-SGA or MIS as reference. Although all methods predicted death risk in crude analysis, the association seemed more consistent and stronger in magnitude for 7p-SGA and MIS. Considering the specific wasting characteristics that predominate in MHD, we conclude that the

well-established 7p-SGA and MIS methods may be more useful in these patients.

Practical Application

Considering the specific wasting characteristics that predominate in MHD, this specific patient population may not be an eligible/suitable group for applying indices and guidelines developed for the nonrenal population. Based on our findings, the well-established 7p-SGA and MIS methods may be more useful for the diagnosis of malnutrition in patients on MHD and should be preferred by clinicians.

CRediT Authorship Contribution Statement

Carla Maria Avesani: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Supervision, Project administration, Funding acquisition. **Alice Sabatino:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Supervision, Project administration, Funding acquisition. **Alessandro Guerra:** Conceptualization, Writing – original draft. **Juliana Rodrigues:** Methodology, Validation, Investigation, Writing – review & editing. **Juan Jesus Carrero:** Writing – review & editing. **Giovanni Maria Rossi:** Writing – review & editing. **Peter Stenvinkel:** Writing – review & editing. **Enrico Fiaccadori:** Conceptualization, Writing – review & editing, Funding acquisition. **Bengt Lindholm:** Conceptualization, Writing – review & editing, Supervision.

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