



## Global leadership initiative on malnutrition criteria for undernutrition diagnosis in hospitalized patients: a validation study

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### ABSTRACT

**Introduction:** Undernutrition presents high prevalence and burden in hospital environments. The Global Leadership Initiative on Malnutrition criteria were proposed to standardize the diagnosis of undernutrition.

**Objectives:** To determine the concurrent validity of Global Leadership Initiative on Malnutrition criteria and its predictive validity through the association with hospital length of stay in a sample of hospitalized adults and older adults.

**Methodology:** Prospective observational study in a sample of inpatients admitted to a University Hospital in Porto. The Nutritional Risk Screening 2002 was applied for undernutrition screening and the Patient-Generated Subjective Global Assessment for undernutrition diagnosis. Concurrent validity between Global Leadership Initiative on Malnutrition and Patient-Generated Subjective Global Assessment was assessed by agreement, Cohen's kappa, sensitivity, and specificity. Predictive validity was evaluated through the independent association between Global Leadership Initiative on Malnutrition criteria and length of stay using Cox proportional regression.

**Results:** The sample comprised 430 inpatients (18–90 years old, 54.0% men). According to Global Leadership Initiative on Malnutrition, 222 (51.6%) were not undernourished, 86 (20.0%) were moderately undernourished, and 122 (28.4%) were severely undernourished. Compared with Patient-Generated Subjective Global Assessment, Global Leadership Initiative on Malnutrition showed a sensitivity of 70.1% and specificity of 79.4%; agreement was 58.4% with kappa=0.484. Global Leadership Initiative on Malnutrition-defined undernutrition decreased the probability of discharge to the usual residence: Hazard Ratio=0.564 (95% Confidence Intervals: 0.431–0.738) for moderate undernutrition and 0.639 (0.505–0.809) for severe undernutrition.

**Contributions:** Conceptualization: RSG, ASS and TFA; Data curation: RSG and ASS; Formal Analysis: FST and RSG; Funding acquisition: RSG and TFA; Investigation: RSG and ASS; Methodology: FST, RSG and ASS; Project administration: RSG, ASS and TFA; Resources: Not applicable; Software: Not applicable; Supervision: RSG and ASS; Validation: RSG and ASS; Writing – original draft: FST; Writing – review & editing: RSG, ASS and TFA.

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**Conclusion:** Global Leadership Initiative on Malnutrition showed moderate agreement with Patient-Generated Subjective Global Assessment and satisfactory specificity. Moderate and severe undernutrition were associated with a lower probability of discharge to the usual residence and, consequently, with longer length of stay. Global Leadership Initiative on Malnutrition criteria can be used in clinical practice to diagnose undernutrition in hospitalized patients.

## INFORMAÇÃO DO ARTIGO

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## RESUMO

**Introdução:** A prevalência e o impacto negativo da desnutrição em ambiente hospitalar são elevados. Os critérios da *Global Leadership Initiative on Malnutrition* foram desenvolvidos para uniformizar o diagnóstico da desnutrição.

**Objetivos:** Avaliar a validade concorrente dos critérios *Global Leadership Initiative on Malnutrition* e a sua validade preditiva através da associação com o tempo de internamento em adultos e idosos hospitalizados.

**Metodologia:** Estudo observacional prospectivo realizado num Hospital Universitário do Porto. O *Nutritional Risk Screening 2002* foi utilizado para o rastreio nutricional e o Patient-Generated Subjective Global Assessment como método de referência para o diagnóstico da desnutrição. A validade concorrente entre o *Global Leadership Initiative on Malnutrition* e o Patient-Generated Subjective Global Assessment foi avaliada através da concordância, Kappa de Cohen, sensibilidade e especificidade. A validade preditiva foi analisada pela associação entre os critérios *Global Leadership Initiative on Malnutrition* e o tempo de internamento, utilizando regressão proporcional de Cox.

**Resultados:** Foram incluídos 430 doentes internados (18-90 anos; 54,0% do sexo masculino). Segundo os critérios *Global Leadership Initiative on Malnutrition*, 51,6% não apresentavam desnutrição, 20,0% apresentavam desnutrição moderada e 28,4% desnutrição grave. O *Global Leadership Initiative on Malnutrition* apresentou sensibilidade de 70,1%, especificidade de 79,4%, concordância de 58,4% e Kappa=0,484. A desnutrição moderada (Hazard Ratio=0,564; Intervalos de Confiança a 95%: 0,431-0,738) e grave (0,639; 0,505-0,809) associaram-se a menor probabilidade de alta para a residência habitual.

**Conclusão:** Os critérios *Global Leadership Initiative on Malnutrition* apresentaram concordância moderada com o Patient-Generated Subjective Global Assessment e especificidade satisfatória. A desnutrição moderada e grave identificada pelo *Global Leadership Initiative on Malnutrition* associou-se a maior tempo de internamento, apoiando a sua utilização na prática clínica para o diagnóstico nutricional em doentes hospitalizados.

## Introduction

Malnutrition is any condition that interferes with the balance of nutrients, either due to excess or deficiency.<sup>1</sup> When the deficiency is due to the catabolism of protein-energy reserves or other nutrients, as a result of illness or ageing, this is referred to as disease-related undernutrition.<sup>2</sup>

Disease-related undernutrition in adult patients who have been hospitalized is a syndrome associated with substantially increased morbidity, disability, short-term and long-term mortality, impaired recovery from illness, increased hospital length of stay (LOS) and cost of care.<sup>3</sup> Disease-related undernutrition is a cause of concern in hospital settings, due to its high prevalence and the impact of this condition on treatment results.<sup>4,5</sup> A late intervention is associated with worse clinical outcomes.<sup>6,7</sup>

The prevalence of undernutrition in hospitalized patients varies between 10%-60% in developed countries and this broad range can be due to the lack of information in healthcare teams' daily routines and demands and also due to the age of patients, comorbidities, and different screening and diagnostic tools used.<sup>8</sup>

To standardise diagnostic criteria, with the aim of promoting the dissemination and use of consensus criteria at a global level, and in the search for the adoption of these criteria by the World Health Organization (WHO) and International Classification of Diseases (ICD),<sup>9</sup> the Global Leadership Initiative on Malnutrition (GLIM) launched a consensus in 2018.<sup>10</sup>

This consensus established criteria for the diagnosis of undernutrition in adults in clinical settings. The GLIM defines a set of phenotypic and etiological criteria for diagnosing undernutrition and assessing its severity. According to

GLIM, the phenotypic criteria include unintentional weight loss, low body mass index and reduced muscle mass. The etiological criteria include reduced food intake or assimilation and burden of disease/inflammatory condition. At least one phenotypic criterion and one etiological criterion must be present for the diagnosis of undernutrition, and its severity is assessed based on the phenotypic criteria.<sup>8</sup>

Similar to any new instrument and because it is based on consensus, the GLIM criteria require validation, and several studies have already been carried out in this regard.<sup>4,10-21</sup> The predictive validity has been assessed through the association of undernutrition evaluated with GLIM with clinical results, quality of life after hospital discharge, readmission time after hospital discharge, mortality and LOS. Concurrent validity of GLIM has been assessed mostly using the Patient-Generated Subjective Global Assessment (PG-SGA) as the reference method.

Despite the extensive validation conducted since its publication, and the existing systematic reviews on the validity of GLIM, which generally demonstrate good results,<sup>21-23</sup> most previous studies were carried out in patients with specific pathologies, such as cancer, inflammatory bowel disease, elective gastrointestinal surgery, critically ill patients, or older adults.<sup>12-19</sup>

Thus, more information on the concurrent and predictive validity of GLIM is needed in a varied sample of hospitalised adults and older adults.

The present study aims to determine the concurrent validity of GLIM and its predictive validity, through the association with LOS, in a sample of hospitalized adults and older adults.

## Methodology

### Study design

A prospective observational study was carried out in a University Hospital in Porto, with hospitalized patients, whose sample was selected between July 2011 and December 2014.

The selection of participants occurred through daily consultation of the list of hospitalized patients and those who met the inclusion criteria were invited to participate in the study. Data collection occurred within the first 72 hours of hospitalization.

Eligibility criteria were:  $\geq 18$  years of age; caucasian; expected length of stay  $> 24$  hours; conscious, cooperative and able to provide written informed consent.

Patients with critical illness and admitted to intensive care units, pregnant women, individuals in isolation, admitted for procedures involving absolute bed rest (e.g. biopsies), in which the study could place them clinically at risk and those with hemodynamic instability at the time of assessment were excluded from the study. Thus, patients in angiology and vascular surgery; cardiology; digestive, non-digestive and hepatobiliary surgeries; endocrinology; gastroenterology; internal medicine; nephrology; orthopaedics; otolaryngology; and urology wards were recruited for this study. The concurrent validity of the GLIM was assessed using the PG-SGA<sup>20</sup> which is considered a reference for the diagnosis of

undernutrition. Predictive validity was studied through the independent association of the GLIM criteria with LOS.<sup>6</sup>

### Ethical declaration

The research was carried out in accordance with the guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of Centro Hospitalar do Porto. All study participants signed an informed consent form.

### Data collection

Sex, date of birth, clinical history and diagnoses, date of admission and discharge from hospital, destination of discharge (home, another ward, another hospital, discharge due to medical indication or death), serum concentrations of albumin and C-Reactive Protein (CRP) were obtained from the medical record.

All remaining data were collected using a structured questionnaire: education ( $\leq 4$  years;  $\geq 5$  years); marital status (married/civil union; divorced/widowed/single); occupation (no professional activity / professional activity). The Katz Index was used to assess functional activity in the last month<sup>21</sup> and the Charlson index was used to assess disease severity, using the discharge diagnoses in the patient's medical record. This index considers the number and severity of comorbidities, each scored from 0 to 6.<sup>22</sup>

The Nutritional Risk Screening 2002 (NRS-2002) was used for nutritional screening, using the first four questions from the "initial screening", according to European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines.<sup>23,24</sup> Besides nutritional screening, PG-SGA<sup>20</sup> and GLIM criteria were applied to patients who were identified as being at nutritional risk.<sup>6</sup>

Anthropometric measurements were taken by two trained nutritionists and included weight, standing height, triceps skinfold thickness, adductor pollicis of the non-dominant hand (APNDH) and mid-upper arm circumference (MUAC).<sup>25</sup> Body weight (kg)<sup>25</sup> was measured with a calibrated portable beam scale with 0.5 kg resolution, with the individuals wearing light pyjamas. Standing height (cm) and mid-upper arm circumference were measured with a metal measuring tape (Rosscraft® Innovations Incorporated, Surrey, Canada) with 0.1 cm resolution. A headboard was also used for measuring height. To measure triceps skinfold and APNDH, the Harpenden® Skinfold Caliper was used.

For bedbound patients, those presenting limitations to their ability to stand or presenting visible kyphosis, hand length, obtained using a small bone calliper with a 0.1 cm resolution (Kennon Instruments, Vignola, Italy),<sup>25</sup> was used as a surrogate of height ( $n=298$ ).<sup>26</sup> When it was impossible to measure hand length, height was estimated from half-span ( $n=2$ ),<sup>27</sup> measured with the metal tape measure from Rosscraft® Innovations Incorporated.

Dry body weight registered in the clinical file or, when unavailable, referred by the patient ( $n = 13$ ) was used for participants on dialytic therapies. When it was not possible to weigh a patient, body weight predicted from height and mid-upper arm circumference<sup>28</sup> was used ( $n = 156$ ). The Jamar Plus+Digital Hand Dynamometer (Sammons Preston) was used to measure handgrip strength (HGS).<sup>29</sup>

Whole-body resistance (ohm) and reactance (ohm) were measured by single frequency tetrapolar bioelectrical impedance analysis (BIA), with equipment from Biodinamics, Model 450 (Biodinamics Corporation, Shoreline, WA) with 0.1  $\Omega$  resolution. BIA was conducted with subjects in supine position, with upper and lower limbs apart so as not to have contact with the torso.<sup>30</sup> Electrodes were placed on the non-dominant side except for the patients with atrophy, hemiplegia, metal prostheses or implants on the non-dominant side, for whom the dominant side was used.<sup>30</sup>

Body mass index (BMI) was calculated as [weight (kg)/height<sup>2</sup> (m)] and participants were grouped in the following BMI classes: <18.5 and  $\geq 18.5$  kg/m<sup>2</sup>, <20 and  $\geq 20$  kg/m<sup>2</sup> (if age < 70 years) or <22 and  $\geq 22$  kg/m<sup>2</sup> (if age >70 y)<sup>31</sup>. Fat-free mass was calculated using the equation:  $[-4.104 + (0.518 \text{ height}^2/\text{resistance}) + (0.231 \times \text{weight}) + (0.13 \times \text{reactance}) + (4.229 \times \text{sex})]$ , resistance and reactance were obtained with BIA, sex = 0 for women, sex = 1 for men<sup>32</sup>. Fat-free mass index (FFMI) was calculated as [fat-free mass (kg)/height<sup>2</sup> (m)]. Participants were grouped into two FFMI categories, <15 and <17 kg/m<sup>2</sup> or  $\geq 15$  and  $\geq 17$  kg/m<sup>2</sup>, for women and men, respectively.<sup>33</sup>

The intra and inter-observer technical error for standing height, body weight, mid-upper arm circumference, half-span and hand length measurements were obtained in 17 and 18 individuals, respectively. The intra-observer error varied between 0.2% and 0.6% whereas the inter-observer error varied between 0 and 1.4%, errors acceptable for trained anthropometrics.<sup>34</sup>

Physical examination included the search for three elements: loss of subcutaneous fat, muscle wasting, presence of edema/ascites, and participants were grouped in three categories: no change, mild / moderate depletion, and severe depletion.<sup>20</sup>

#### *Statistical analysis*

For assessing the nature of variables distribution, the Kolmogorov and Smirnov test was used. Accordingly, continuous variables were expressed as mean and standard deviation (SD) or as median and interquartile range (IQR), and categorical variables were expressed as absolute (n) and relative frequencies (%).

Participants were compared for several sociodemographic, clinical and nutritional characteristics according to GLIM categories, without undernutrition, moderate undernutrition and severe undernutrition, using the Anova test for normality distributed variables, the Kruskal-Wallis test for variables with distribution different from normal, and Chi-square test for categorical variables.

Due to the small number of people with moderate and severe dependence, Katz Index was evaluated in two categories, independence and dependence for activities of daily living.

To investigate the concurrent validity of the GLIM criteria, sensitivity, specificity, positive and negative predictive values were determined, using the PG-SGA as the reference method. In order to conduct these analyses, for each tool, participants with moderate and severe undernutrition, were merged into one category. Agreement between the

GLIM criteria and PG-SGA was calculated, as well as the weighted Cohen's Kappa coefficient.

For predictive validity, the Kaplan-Meier method and Cox regression were used to evaluate the probability of being discharged home, according to GLIM criteria categories (without undernutrition, moderate undernutrition and severe undernutrition). For both analysis, length of stay was censored at 30 days, since 97% of the sample was in this range, and discharge to home was defined as the event of interest.

Cox proportional hazards regression models were used to respectively determine the unadjusted and adjusted hazard ratios (HR) and corresponding confidence intervals (95% CI); age [ $\leq 64$  years (reference) vs.  $\geq 65$  years] and Katz Index [independence (reference) vs. moderate and severe dependence] were used in the adjusted model.

Statistical significance considered  $p < 0.05$ . Data analysis was done with the Software Package for 28.0.1.0 (142) SPSS, inc. Chicago, IL.

## **Results**

During the period of data collection, 1053 patients were invited to participate and 804 entered the study. NRS-2002 initial screening could not be completed for 285 subjects, 217 were not nutritionally at-risk and 551 were at-risk. Additionally, 121 of the at-risk participants had missing data for variables essential for answering present study purposes and thus, this study final sample is composed of 430 hospitalized patients, mostly male ( $n=232$ , 54.0%) and aged between 18 and 90 years old. According to the PG-SGA criteria, 189 (44.0%) were not undernourished, 108 (25.1%) were moderately undernourished and 133 (30.9%) were severely undernourished. According to the GLIM criteria, 222 (51.6%) were not undernourished, 86 (20.0%) were moderately undernourished and 122 (28.4%) were severely undernourished.

Sociodemographic variables, according to GLIM nutritional status categories are presented in Table 1. A higher proportion of patients aged  $\geq 65$  years were found to be moderately or severely undernourished (Table 1).

**Table 1.** Sociodemographic characterization of 430 Portuguese inpatients participating in a prospective observational study according to GLIM nutritional status.

|                              |                          | Without<br>undernutrition<br>n = 222 | Moderate<br>undernutrition<br>n = 86 | Severe<br>undernutrition<br>n = 122 | p                  |
|------------------------------|--------------------------|--------------------------------------|--------------------------------------|-------------------------------------|--------------------|
| Sex                          |                          |                                      |                                      |                                     |                    |
|                              | Female                   | 96 (48.5)                            | 38 (49.2)                            | 64 (52.3)                           | 0.242 <sup>a</sup> |
|                              | Male                     | 126 (54.3)                           | 48 (50.7)                            | 58 (45.0)                           |                    |
| Age (years)                  |                          |                                      |                                      |                                     |                    |
|                              | ≤64                      | 161 (55.9)                           | 56 (64.2)                            | 71 (57.4)                           | 0.024 <sup>a</sup> |
|                              | ≥ 65                     | 61 (43.0)                            | 30 (31.1)                            | 51 (35.9)                           |                    |
| Education (years)            |                          |                                      |                                      |                                     |                    |
|                              | ≤ 4                      | 95 (51.9)                            | 41 (22.4)                            | 47 (25.7)                           | 0.419 <sup>a</sup> |
|                              | ≥ 5                      | 127 (51.4)                           | 45 (18.2)                            | 75 (39.4)                           |                    |
| Marital Status               |                          |                                      |                                      |                                     |                    |
|                              | Married/civil union      | 148 (54.6)                           | 55 (20.3)                            | 68 (25.1)                           | 0.130 <sup>a</sup> |
|                              | Divorced/widowed/single  | 74 (46.5)                            | 31 (19.5)                            | 54 (34.0)                           |                    |
| Occupation                   |                          |                                      |                                      |                                     |                    |
|                              | No professional activity | 146 (49.3)                           | 62 (20.9)                            | 88 (29.7)                           | 0.365 <sup>a</sup> |
|                              | Professional activity    | 76 (56.7)                            | 24 (17.9)                            | 34 (25.4)                           |                    |
| Median (interquartile range) |                          |                                      |                                      |                                     |                    |
| Age (years)                  |                          | 56 (20)                              | 59 (22)                              | 58 (27)                             | 0.130 <sup>b</sup> |

<sup>a</sup>Chi-squared test; <sup>b</sup>Kruskal-Wallis test.

In Table 2, inflammatory, clinical, anthropometric and functional parameters associated with undernutrition were analysed. Patients with severe undernutrition had a lower albumin value compared to participants in the other two categories. The results showed that being undernourished according to GLIM resulted in longer hospital stay, compared to those who were not undernourished. Undernourished men and women had significantly lower mean values for HGS, triceps skinfold thickness, MUAC, APNDH, when compared to those without undernutrition. It is also shown that the largest proportion of dependent patients were severely undernourished (46.2%). Through the physical examination, it was found that the highest proportion of participants with severe depletion were severely undernourished, according to the GLIM criteria (52.3%).

**Table 2.** Nutritional status assessment parameters associated with undernutrition of 430 Portuguese inpatients, in a prospective observational study, according to GLIM nutritional status.

|                                          |   | Without<br>undernutrition<br>n = 222 | Moderate<br>undernutrition<br>n = 86 | Severe<br>undernutrition<br>n = 122 | p                   |
|------------------------------------------|---|--------------------------------------|--------------------------------------|-------------------------------------|---------------------|
| Mean (standard deviation)                |   |                                      |                                      |                                     |                     |
| Albumin (g/l)                            | n | 289                                  | 33 (6.3)                             | 33 (5.3)                            | 0.022 <sup>a</sup>  |
| C reactive – Protein (g/l)               | n | 289                                  | 33 (7.1)                             | 33 (6.2)                            | 0.302 <sup>a</sup>  |
| Charlson Index                           | n | 430                                  | 18 (2.0)                             | 1.9 (2.1)                           | 0.545 <sup>a</sup>  |
| LOS <sup>a</sup> (days)                  | n | 430                                  | 7.4 (5.3)                            | 11.3 (8.0)                          | <0.001 <sup>a</sup> |
| n (%)                                    |   |                                      |                                      |                                     |                     |
| Katz index                               |   |                                      |                                      |                                     |                     |
| Independent                              | n | 206 (92.8)                           | 74 (86.0)                            | 98 (80.3)                           | <0.001 <sup>a</sup> |
| Dependent                                | n | 16 (7.2)                             | 12 (14.0)                            | 24 (19.7)                           |                     |
| Physical examination                     |   |                                      |                                      |                                     |                     |
| No change                                | n | 165 (98.7)                           | 54 (99.2)                            | 62 (52.2)                           | <0.001 <sup>a</sup> |
| Mild to moderate depletion               | n | 43 (24.2)                            | 23 (42.6)                            | 36 (30.3)                           |                     |
| Severe depletion                         | n | 14 (8.1)                             | 7 (12.9)                             | 25 (20.5)                           |                     |
| Mean (standard deviation)                |   |                                      |                                      |                                     |                     |
| Handgrip strength (kg)                   |   |                                      |                                      |                                     |                     |
| Female                                   | n | 198                                  | 18.6 (6.7)                           | 14.9 (6.4)                          | <0.001 <sup>a</sup> |
| Male                                     | n | 232                                  | 33.5 (9.4)                           | 28.1 (8.7)                          | 0.001 <sup>a</sup>  |
| Triceps skinfold thickness (mm)          |   |                                      |                                      |                                     |                     |
| Female                                   | n | 198                                  | 24.6 (8.0)                           | 21.2 (6.6)                          | <0.001 <sup>a</sup> |
| Male                                     | n | 232                                  | 11.9 (5.3)                           | 10.3 (6.3)                          | 0.020 <sup>a</sup>  |
| Mid upper arm circumference (cm)         |   |                                      |                                      |                                     |                     |
| Female                                   | n | 197                                  | 30.2 (3.8)                           | 28.1 (3.9)                          | <0.001 <sup>a</sup> |
| Male                                     | n | 231                                  | 29.2 (3.0)                           | 27.7 (4.0)                          | <0.001 <sup>a</sup> |
| Adductor pollicis non-dominant hand (mm) |   |                                      |                                      |                                     |                     |
| Female                                   | n | 183                                  | 21.1 (4.2)                           | 19.7 (3.4)                          | <0.001 <sup>a</sup> |
| Male                                     | n | 246                                  | 23.0 (4.3)                           | 22.2 (4.2)                          | 0.003 <sup>a</sup>  |

<sup>a</sup>LOS: length of stay; <sup>a</sup>Anova test; <sup>b</sup>Chi-squared test.

The agreement between the GLIM criteria and PG-SGA was 58.4%, and Kappa Coefficient (k) was 0.464 (0.404-0.567),  $p < 0.001$  (Table 3).

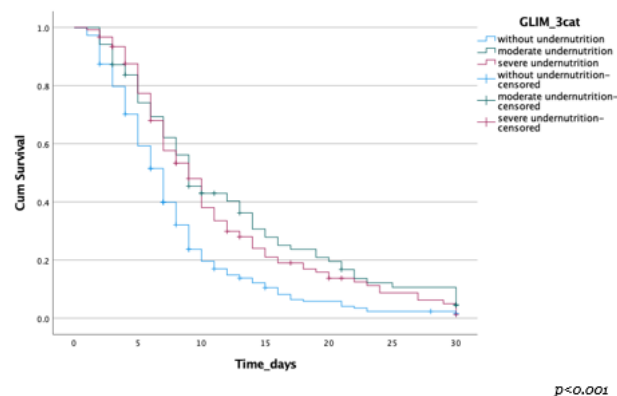
**Table 3.** Concurrent validity of GLIM criteria for undernutrition identification on the basis of undernutrition classification by Patient-Generated Subjective Global Assessment.

|                      |                   |
|----------------------|-------------------|
| Kappa                | 0.484 (p < 0.001) |
| Agreement (%)        | 58.4              |
| Sensitivity (%)      | 70.1              |
| Specificity (%)      | 79.4              |
| PPV (%) <sup>a</sup> | 81.2              |
| NPV (%) <sup>b</sup> | 67.2              |

<sup>a</sup>PPV= Positive Predictive Value;

<sup>b</sup>NPV = Negative Predictive Value

In comparison with the PG-SGA, GLIM criteria showed a sensitivity of 70.1%, a specificity of 79.4%. Positive and negative predictive values were 81.2% and 67.2%, respectively. The probability of being discharged home over time, according to the GLIM criteria, was tested by Kaplan-Meier curves, which showed that being undernourished increases hospital LOS (Figure 1).



**Figure 1.** Kaplan-Meier curves for being discharge-free over time for 430 Portuguese inpatients participating in a prospective observational study, according to GLIM criteria. (Higher values of being discharge-free over time represent a lower probability of hospital discharge; in-hospital deaths, transfers and discharge against medical advice were censored at the time of those events; length of hospital stay was censored at 30 days.)

According to the Cox regression models, presenting moderate and severe undernutrition according to GLIM was associated with a lower probability of being discharged home, in both the crude and adjusted models (Table 4).

**Table 4.** Hazard Ratios (HR) and corresponding confidence intervals (95% CI) for being discharged home according to GLIM criteria, for 430 inpatients participating in a prospective observational study.

|                         | Model 1 <sup>a</sup><br>Crude HR (95% CI) | Model 2 <sup>b</sup><br>Adjusted HR (95% CI) |
|-------------------------|-------------------------------------------|----------------------------------------------|
| Without undernutrition  | 1                                         | 1                                            |
| Moderate undernutrition | 0.564 (0.431 – 0.738)                     | 0.569 (0.435 – 0.745)                        |
| Severe undernutrition   | 0.639 (0.505 – 0.809)                     | 0.656 (0.516 – 0.833)                        |

Model 1: crude Cox proportional regression models.

Model 2: adjustment for Katz index (dichotomized: independence (reference) vs. moderate and severe dependence) and age (dichotomized, ≤64 years (reference) vs. ≥65 years).

## DISCUSSION

This study has shown that the GLIM Criteria, when compared to the PG-SGA as the reference method, has good specificity. Also, being moderately and severely undernourished according to the GLIM was associated with a longer LOS, as undernutrition by GLIM independently reduced the likelihood of being discharged home.

Although the sensitivity value obtained (70.1%) is lower than the recommended for validation, >80%, the specificity value found (79.4%) is very close to this recommended value.<sup>6</sup> The positive predictive value and negative predictive value were 81.2% and 67.2%, respectively. According to ESPEN, in a paper related to diagnostic criteria for undernutrition: "screening must be sensitive, while diagnosis must be specific"<sup>31</sup>. Also considering that a high positive predictive value results in assertively treating true patients,<sup>13</sup> the present study results contribute to the evidence regarding the validity of GLIM for the diagnosis of undernutrition.

As there is no gold standard for diagnosing undernutrition, there is a possibility that many patients will not be considered eligible to receive a diagnosis of undernutrition. The PG-SGA is considered a "semi-gold" standard and for this reason it was used to establish concurrent validity, after screening the participants, using the NRS-2002.<sup>4</sup>

In other studies, involving hospitalized patients who were diagnosed with undernutrition by the GLIM criteria, using the PG-SGA as the reference method, the prevalence of undernutrition varied between 10% and 80%. This variation can be explained by whether nutritional screening is done, which screening tool is used, and the individual and clinical characteristics of the participants. The methods used to assess the phenotypic criteria, namely how was fat free mass assessed, and the methods used to assess etiological criteria, namely inflammation, may also interfere with the results.<sup>10,11,16,17,35-38</sup>

In a systematic review using 66 studies conducted among adult critically ill patients, GLIM showed a specificity of 81.2% (95% CI: 74.1-86.1%) and a sensitivity of 86.7% (95% CI: 80.1%-90.9%).<sup>39</sup> In another systematic review that included 13 studies in older adults, results were similar: GLIM criteria demonstrated a pooled sensitivity of 79% (95% CI: 69-86%) and specificity of 88% (95% CI: 81-93%).<sup>40</sup>

Among 405 gastric cancer patients, and using PG-SGA as the reference method, values of Kappa, sensitivity, specificity, and positive and negative predictive value for GLIM criteria were, respectively: 0.463, 67.9 %, 87.3 %, 92.9 %, and 52.8 %.<sup>41</sup> In a study conducted with patients with esophageal cancer, when compared to PG-SGA, GLIM revealed a kappa value of 0.519 ( $p<0.001$ ), sensitivity equal to 79.5% and specificity equal to 80.5%.<sup>42</sup> In another study of 601 hospitalized patients, agreement between PG-SGA and GLIM criteria was 41.6%, with kappa=0.589 ( $p<0.001$ ), sensitivity=86.6% and specificity=81.6%.<sup>10</sup> In a study carried out in Norway and using once more PG-SGA as reference, agreement determined by the kappa value was 0.49 (0.38-0.60), sensitivity = 63% specificity = 90%.<sup>14</sup> An Australian study of 246 patients undergoing outpatient

treatment for cancer found, for GLIM, a sensitivity of 76% and specificity of 73%, with kappa=0.323. In this study, nutritional screening was done using the PG-SGA short-form.<sup>43</sup>

It is important to note that in the present study, sensitivity and specificity values obtained were lower than most of the other studies mentioned. However, results are not fully comparable to all cited studies, since screening was not carried out in some.<sup>10,42</sup> Moreover, our study included patients admitted to various medical and surgical wards, with a variety of clinical diagnoses, which may have accounted for the lower concurrent validity of GLIM criteria.

Regarding agreement with the PG-SGA, kappa was lower than the recommended value, which should be >0.8 for validation. Notwithstanding this there is a moderate agreement ( $k=0.484$ ) with the reference method. This result, although similar to those described in the literature,<sup>41</sup> can be justified by the criteria used to calculate Kappa, with the three categories of the PG-SGA and GLIM criteria (no undernutrition, moderate undernutrition and severe undernutrition). The classification into moderate and severe undernutrition can be influenced by the different methods used to assess muscle mass. In fact, more patients were classified as moderately and as severely undernourished by PG-SGA when compared to GLIM.

The PG-SGA uses weight loss and subjective criteria generated by the patient or the professional. Although the physical examination is an important indicator of undernutrition when assessing muscle depletion, it is based on the professional's judgement and not on cut-off points and objective data.<sup>18,20,44</sup>

In this study, FFMI was used to assess loss of muscle mass. The FFMI cut-off points are those recommended by the GLIM consensus for assessing low muscle mass, <15 and <17 kg/m<sup>2</sup>, for women and men, respectively.<sup>45</sup> The ideal FFMI cut-off points for identifying undernutrition have not yet been defined and it is recognized by GLIM panel of experts that more studies are needed to define these cut-off points.

Kaplan-Meier and Cox analysis revealed that undernutrition according to the GLIM Criteria was associated with longer LOS. Cox regression models were adjusted for the potential confounding variables, age and Katz index, and small changes in HR and respective 95% CI were observed between crude (unadjusted) and adjusted Cox proportional hazard models. These results show that the association between undernutrition identified by the GLIM criteria and LOS was not weakened by the adjustment. Many studies have been carried out to analyse the ability of the GLIM Criteria to predict negative outcomes such as postoperative complications, time between hospital discharge and readmission, LOS, and mortality.<sup>10,16-18,37,38,46</sup> However, there is a lack of studies that have analysed the association between undernutrition according to the GLIM criteria and LOS using survival analysis, with discharge to usual residence as the event of interest. This gap is particularly evident in large heterogeneous samples, such as the one used in this study.

Hospital LOS was truncated at 30 days and was arbitrarily chosen. In our study, only 14 patients (3.3%) remained

hospitalized for more than 30 days, and so this procedure probably did not affect the study results.

The present study has some limitations that must be considered when interpreting the results: FFMI was used to assess loss of muscle mass. Although recommended by the GLIM consensus, no evidence show if a FFMI <15 and <17 kg/m<sup>2</sup>, for women and men respectively, is indicative of moderate or severe low muscle mass,<sup>45</sup> which can lead to some degree of misclassification.

In fact, the lack of definition of cut-off points for muscle mass reduction, categorising it as moderate or severe, is a limitation that could compromise the results, since phenotypic variables are needed to classify the degree of undernutrition as moderate or severe, and require these muscle mass parameters to establish the result. Therefore, more studies are needed to define the FFMI cut-off points and better establish the concurrent validity of the GLIM criteria.

This study has also several strengths. Undernutrition in hospitalized patients has long been linked to worse outcomes for patients, including increased LOS.<sup>11,17,36,47</sup> The statistical analysis used allowed to treat LOS as a continuous variable, and it was possible to censor the data. In this way, it was possible to include hospitalized patients who would otherwise have been excluded from the data analysis. In addition, the characteristics of the sample are another strength of the study, since a large and representative number of inpatients were included, aged between 18 and 90, with various pathologies and diagnoses, from different medical and surgical wards.

## Conclusion

GLIM demonstrated moderate agreement with the reference tool PG-SGA. GLIM also showed satisfactory specificity. This study's findings also indicate that being classified as undernourished according to the GLIM criteria – both moderately and severely – reduces the likelihood of being discharged home or to the usual residence, and therefore undernutrition diagnoses with GLIM is associated with a longer LOS. The GLIM criteria can thus be applied in clinical practice to diagnose undernutrition in hospitalized patients.

The data used were collected by the authors and are available from the corresponding author upon reasonable request.

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