The New European Society for Clinical Nutrition and Metabolism Definition of Malnutrition: Application for Nutrition Assessment and Prediction of Morbimortality in an Emergency Service

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Abstract
Background: Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) provided novel consensus criteria for malnutrition diagnosis. This study aimed to evaluate the applicability of this instrument in combination with different nutrition screening tools (1) to identify malnutrition and (2) to predict morbidity and mortality in hospitalized patients. Materials and Methods: Observational prospective study in 750 adults admitted to the emergency service of a tertiary public hospital. Subjective Global Assessment (SGA—reference method) and the new ESPEN criteria were used to assess nutrition status of patients, who were initially screened for nutrition risk using 4 different tools. Outcome measures included length of hospital stay, occurrence of infection, and incidence of death during hospitalization, analyzed by logistic regression. Results: There was a lack of agreement between the SGA and ESPEN definition of malnutrition, regardless of the nutrition screening tool applied previously ($\kappa = -0.050$ to 0.09). However, when Malnutrition Screening Tool and Nutritional Risk Screening–2002 (NRS-2002) were used as the screening tool, malnourished patients according to ESPEN criteria showed higher probability of infection (relative risk [RR], 1.54; 95% confidence interval [CI], 1.02–2.31 and RR, 2.06; 95% CI, 1.37–3.10, respectively), and when the NRS-2002 was used, the risk for death was 2.7 times higher (hazard ratio, 2.69; 95% CI, 1.07–6.81) in malnourished patients than in well-nourished patients. Conclusion: Although the new ESPEN criteria had a poor diagnostic value, it seems to be a prognostic tool among hospitalized patients, especially when used in combination with the NRS-2002. (JPEN J Parenter Enteral Nutr. 2018;42:550–556)

Keywords
malnutrition; diagnosis; nutrition assessment; emergency service, hospital; prognosis

Clinical Relevancy Statement
Hospital malnutrition is a major cause of increased morbidity and mortality, leading to hospital readmissions and higher healthcare costs. There is no international consensus on a single “best tool” for nutrition status diagnosis. The new European Society for Clinical Nutrition and Metabolism (ESPEN) criteria for malnutrition diagnosis did not perform well in identifying patients with malnutrition, considering the Subjective Global Assessment as the reference method, in the current study. On the other hand, it was a good prognostic tool among hospitalized patients,
especially when used in combination with the Nutritional Risk Screening–2002 (NRS-2002), because it was positively associated with infection and mortality during the hospitalization. Considering that it is an easy and quick tool, the new ESPEN criteria of malnutrition could be incorporated in clinical practice to identify patients with poor prognosis linked to nutrition status.

Introduction

Malnutrition due to disease can be defined as a state resulting from lack of uptake or intake of nutrition, leading to altered body composition, diminished physical and mental function, and impaired clinical outcome. Hospital malnutrition is a major cause of increased morbidity and mortality, leading to hospital readmissions and higher healthcare costs. Estimates of the prevalence of in-hospital malnutrition vary from 13%–88% depending on the patient population, disease severity, and the criteria used for its diagnosis.

The assessment of nutrition status is the first step to nutrition assistance in hospitalized patients. Although there are several methods available for nutrition assessment, there is no international consensus on a single “best tool” for nutrition status diagnosis. Subjective Global Assessment (SGA) is considered a good method to perform in adults, while the Mini Nutritional Assessment (MNA) is regarded as the best choice for elderly patients. However, before the diagnosis of malnutrition, patients at risk of malnutrition should be identified by well-established criteria using a validated nutrition screening tool. The Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening–2002 (NRS-2002), Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Screening Tool (MST), and MNA are nutrition risk screening tools validated for hospitalized patients.

In an attempt to define malnutrition in all settings, the American Society for Parenteral and Enteral Nutrition (ASPEN) proposed a standardized set of diagnostic characteristics to identify and document malnutrition in routine clinical practice, based on the etiology of the disease. However, in ASPEN recommendations, malnutrition should be classified on the basis of several clinical characteristics, including energy intake, weight loss, body fat loss, muscle mass loss, edema, and reduced grip strength in the context of an acute illness or injury, chronic illness, or social/environmental circumstances. Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) also provided novel diagnostic consensus criteria for malnutrition. The intention was to provide criteria that were independent of etiologic mechanisms and could be used for all patients in all clinical settings. ESPEN recommends the use of 3 objective variables that most accurately reflect malnutrition: weight loss combined with reduced body mass index (BMI) (<18.5 kg/m²) or low fat-free mass index (FFMI), according to sex and age of patients. A multicentric study involving geriatric patients with diabetes mellitus during hospitalization applied the new ESPEN definition of malnutrition and identified 6.73% of malnourished individuals. Furthermore, malnutrition lengthened the hospital stay, increased 2.7 times the odds of dying in the hospital, and decreased to one-third the odds of being discharged home, suggesting that the new ESPEN definition is a reliable tool to predict clinical outcomes in older hospitalized patients with diabetes. In another study conducted in 4 populations, the prevalence of malnutrition according to ESPEN criteria was 14% in acutely ill middle-aged patients, 6% in geriatric outpatients, 0.5% in healthy old individuals, and 0% in healthy young individuals.

As far as we know, few studies have applied the new ESPEN definition of malnutrition in specific populations. Therefore, the current study aimed to evaluate the applicability of the new ESPEN diagnostic criteria for malnutrition to identify nutrition depletion and to predict morbidity and mortality in a heterogeneous sample of hospitalized patients.

Materials and Methods

This observational prospective study was carried out with patients admitted to the emergency service of a tertiary public hospital in Porto Alegre (Rio Grande do Sul, Brazil). The protocol was approved by the Ethical Committee of the hospital (number 360.639), and all patients gave their written informed consent before data collection. The sample was randomly selected from all patients admitted to the emergency service within 48 hours of hospitalization. The inclusion criteria were patients aged ≥18 years who were conscious and able to move. The sample did not include pregnant women or those who had given birth less than a year before; patients with limb amputation; patients who were unable to talk, confused, or bedridden; or those whose measurements could not be obtained.

Data were collected at the patients’ bedside by 3 previously trained researchers, who administered a specific questionnaire and anthropometric measurements. Hospital admission date, reason for admission, and medical history were obtained from electronic medical records. Patients wore as little clothing as possible and no shoes when anthropometric measurements were carried out. Body weight was measured with a portable, properly calibrated digital scale (Plenna; São Paulo, São Paulo, Brazil), with precision of 0.1 kg and total capacity of 150 kg. Height was measured using a 2-m-long stadiometer (Bodymeter 206, Seca; Cotia, São Paulo, Brazil) at the nearest of 0.1 cm, with patients standing barefoot, with their back straight, arms hanging down and head straight, facing forward. Body weight was recorded in kilograms and height in meters.
Identification of malnutrition in our study group was performed in 2 steps. First, validated screening tools—MUST,10 NRS-2002,11 SNAQ,12 and MST13—were used to identify patients at risk of malnutrition. The choice of these 4 screening tools among the many other mentioned in the literature6 can be explained by being validated, quick, and easy to apply for nutrition risk screening at hospital admission in emergency services for all hospitalized patients. The variables and cutoff points of each screening tool are shown in Table 1. In the second stage, nutrition status of patients was assessed by SGA and ESPEN criteria.9 All patients completed the SGA and were classified as healthy (A), mildly to moderately malnourished (B), or severely malnourished (C).7 In our study, patients classified as B or C were considered malnourished. Also, considering the ESPEN diagnosis criteria, individuals considered at risk of malnutrition were classified as malnourished if they met at least 1 of the 2 criteria5:

1. BMI <18.5 kg/m²
2. Unintentional weight loss >5% of body weight during the past 3 months in combination with reduced BMI (<20 kg/m² in patients younger than 70 years or <22 kg/m² in those older than 70 years)

Values of FFMI were not measured because the present study is an analysis of secondary data collected with the primary aim to compare different tools for nutrition screening, and none of the tools studied used FFMI as a variable. For the same reason, data of weight loss >10% over any time were not available to this study.

Outcome measures were length of hospital stay (LOS, in days), occurrence of infection, and incidence of death during hospitalization, which were obtained from patients’ medical records. A LOS equal to or higher than 16 days was considered a long LOS.19

The sample size was estimated considering the prevalence of malnutrition in hospitalized patients in Brazil (48.0%) and the incidence of death according to the presence (12.4%) or absence (4.7%) of this condition.20 For sample size calculation, we considered a type I error of 5% and type II error of 80%. In addition, the sample size was inflated by 20% to account for potential loss of follow-up. Based on these assumptions, a sample size of 480 patients was required (http://www.openepi.com/Menu/OE_Menu.htm).

The χ² test was used for comparisons of qualitative variables and the Student t test for comparisons of quantitative variables. The former were presented as relative frequency and the latter as mean ± standard deviation. The κ coefficient was used to test the degree of agreement between the 2 methods of nutrition assessment in diagnosing malnutrition diagnosis; κ varies from 0–1: a value <0.2 indicates poor agreement, 0.2–0.4 fair agreement, 0.4–0.6 moderate agreement, 0.6–0.8 substantial agreement, and >0.8 almost perfect agreement.21 Receiver operating characteristic (ROC) curve was constructed to evaluate the performance of the new ESPEN diagnostic criteria for malnutrition to identify malnourished patients in the study population, considering the SGA as the reference method. The area under the curve (AUC), the 95% confidence interval (CI), and the sensitivity and specificity were also determined. The greater the AUC, the greater the discriminatory power of the new ESPEN definition of malnutrition.

Relative risk (RR) and corresponding 95% CIs were determined by Poisson regression with robust variance considering the presence of infection during hospitalization or very long LOS (>16 d) as dependent variables and malnutrition as the independent variable. The influence of nutrition status on the probability of death was calculated using the Cox regression analysis. All analyses were adjusted for sex and stress of disease.

Statistical analyses were performed in SPSS 20.0 (SPSS, Inc, an IBM Company, Chicago, IL), and P values <.05 were considered significant.

### Results

The current study included 750 patients admitted to the emergency service of a public hospital. Patients were aged 53.6 ± 15.5 years (36.0% older than 60 years), 54.4% were females, and 86.2% were of white ethnicity. Twenty-one percent of patients had some gastrointestinal disorder (21.3%), followed by cancer (19.7%), cardiovascular disease (11.3%), renal disorder (8.5%), neurologic disease (7.8%), or others (31.4%).

The LOS was 9.0 (3.0–19.0) days, and the length of stay at the emergency department was 3.0 (2.0–5.0) days. Infection

<table>
<thead>
<tr>
<th>Feature</th>
<th>NRS-2002</th>
<th>MUST</th>
<th>MST</th>
<th>SNAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight loss</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Food/energy intake</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nutrition supplements</td>
<td></td>
<td></td>
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<tr>
<td>Severity of disease</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Acute disease effect</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification of nutrition risk (adapted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No nutrition risk</td>
<td>&lt;3 points</td>
<td>0</td>
<td>&lt;2 points</td>
<td>&lt;2 points</td>
</tr>
<tr>
<td>Nutrition risk</td>
<td>≥3 points</td>
<td>≥1 point</td>
<td>≥2 points</td>
<td>≥2 points</td>
</tr>
</tbody>
</table>

MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS-2002, Nutritional Risk Screening–2002; SNAQ, Short Nutrition Assessment Questionnaire.
detected among those at risk of malnutrition identified by MUST, SNAQ, and MST. Compared with patients at risk of malnutrition according to new ESPEN diagnosis was higher (20.5%) in this subgroup. However, the prevalence of malnutrition according to MUST, MST, SNAQ, and NRS-2002 did not differ between men and women.

A trend toward higher prevalence of malnutrition was detected between women and men according to ESPEN criteria ($P = 0.066$), and according to SGA, the prevalence of malnutrition did not differ among men and women.

Table 3 shows the frequency of patients at risk of malnutrition according to MUST, MST, SNAQ, and NRS-2002 and, among these, the prevalence of malnutrition according to new ESPEN criteria. A lower number of patients (29.3%) was classified as at risk of malnutrition by using the NRS-2002; however, the prevalence of malnutrition according to new ESPEN diagnosis was higher (20.5%) in this subgroup compared with patients at risk of malnutrition according to MUST, SNAQ, and MST.

The highest prevalence of malnutrition ($n = 45$) was detected among those at risk of malnutrition identified by the NRS-2002, and in 34 (75.5%), BMI <18.5 kg/m$^2$ was the diagnosis criterion. Weight loss >5% combined with BMI <20 kg/m$^2$ was the diagnostic criterion for malnutrition in 6 (13.3%) patients, and weight loss >5% combined with BMI <22 kg/m$^2$ identified 5 (11.2%) patients older than 70 years as malnourished. Malnourished patients according to BMI <18.5 kg/m$^2$ did not differ from malnourished patients according to the criteria of BMI <20 kg/m$^2$ plus weight loss >5% in the past 3 months according mean age (53.46 ± 16.82 vs 62.44 ± 17.96 y; $P = .226$) and frequency of males (61.8% vs 62.5%; $P = .09$). Other features were not compared due to the small sample size of malnourished patients.

The $\kappa$ coefficient demonstrated lack of agreement between SGA and the new ESPEN definition of malnutrition, regardless of the nutrition screening tool used previously (NRS-2002: $\kappa = 0.02$, $P = .816$; MUST: $\kappa = -0.05$, $P = .09$; SNAQ: $\kappa = 0.06$, $P = .291$; and MST: $\kappa = 0.07$, $P = .205$). ROC curve analysis did not show good accuracy of the new ESPEN consensus considering SGA as the reference method, independently of the nutrition screening tool (NRS-2002: AUC = 0.507 [95% CI, 0.426–0.588]; MUST: AUC = 0.503 [95% CI, 0.408–0.545]; SNAQ: AUC = 0.511 [95% CI, 0.446–0.608]; MST: AUC = 0.530 [95% CI, 0.454–0.606]). The accuracy detected was <65%, with low sensitivity, independently of the nutrition screening tool previously applied: The respective accuracy, sensitivity, and specificity was 60%, 21%, and 80% for NRS-2002; 56%, 3%, and 93% for MUST; 64%, 40%, and 86% for SNAQ; and 64%, 19%, and 87% for MST.

In addition, the ability of ESPEN diagnostic criteria of malnutrition to predict clinical outcomes was assessed considering the different tools of nutrition screening applied in the first step of malnutrition diagnosis. As shown in Table 4, malnutrition according to ESPEN definition was not associated with a very long LOS, independently of the screening nutrition tool applied. On the other hand, when NRS-2002 and MST were applied, malnourished patients...
Discussion

The prevalence of malnutrition according to the new ESPEN consensus for malnutrition diagnosis varied from 5.4%–20.5% depending on the nutrition screening tool previously applied. The ESPEN criteria did not perform well in identifying malnutrition in hospitalized patients, considering the SGA as the reference method, regardless of the nutrition screening tool used. On the other hand, malnutrition identified by the ESPEN criteria was able to predict increased risk of infection when applied following the MST or NRS-2002 and mortality when applied following the NRS-2002. Our results suggest that this new tool is a better prognostic predictor when applied in the emergency room and is more accurate when used in combination with the NRS-2002.

The prevalence of patients at nutrition risk (29.3%) according to the NRS-2002 was very similar to that found in another prospective study conducted in Brazil, which reported that 27.9% of 705 adult patients admitted to a public university hospital were at nutrition risk according to the same nutrition screening tool. In another study involving 1146 Greek patients, 27.9% and 9.1% of the hospitalized patients were found to be at moderate/high risk of malnutrition according to the NRS-2002 and MUST, respectively. This study analyzed the clinical value of these malnutrition screening tools in light of the new ESPEN definition for malnutrition. The authors concluded that the MUST is more efficient in screening malnourished patients, since it presented a better agreement with the ESPEN criteria ($\kappa = 0.777, P < .001$) compared with the NRS-2002 ($\kappa = 0.256, P < .001$). However, it is important to emphasize that the authors evaluated the agreement between 1 tool for malnutrition diagnosis and 2 tools for nutrition screening, and it is important note that nutrition assessment is different from nutrition screening. The difference in the prevalence of nutrition risk in the current study may be explained by the particularities of the tools. The different cutoff points of BMI in the NRS-2002 and MUST can explain the highest prevalence of nutrition risk according to the MUST (lowest BMI cutoff point) and the lowest prevalence of nutrition risk according to the NRS-2002 (highest BMI cutoff point). In addition, the 2 tools differently analyze weight loss. A similar prevalence of nutrition risk according to the MST and SNAQ was observed, and it can be attributed to the similarity of the questions that compose these tools.

In the present study, the prevalence of hospital malnutrition (according to ESPEN diagnosis criteria) was lower (20.5%) than that reported in the literature (20%–60%) but higher than that detected by the ESPEN criteria in a sample of 1014 elderly diabetic hospitalized patients (6.7%) previously evaluated for nutrition risk by the MNA. In the study conducted by Rojer et al in 4 different populations who were screened for nutrition risk by the SNAQ, the highest prevalence of malnutrition (14%) was found among acutely ill, middle-aged patients. It is possible that the choice of the screening tool used to identify patients at risk of malnutrition contributes to differences in the prevalence of malnutrition among the studies. Indeed, after the SNAQ and MUST, we observed a prevalence of malnutrition of 15.3% and 5.4% in our study group, respectively.

The new ESPEN diagnostic criteria for malnutrition did not show good accuracy as SGA was used as the reference method. Also, weak agreement between both methods was observed, regardless of the nutrition screening tool applied. Although the SGA is traditionally used as a reference method in validation studies of nutrition assessment tools, it may not be considered a gold standard for

Table 4. Prognostic Data of the New European Society for Clinical Nutrition and Metabolism Definition of Malnutrition According to Nutrition Screening Tools Previously Applied to Identify Patients at Risk of Malnutrition.α

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LOS &gt; 16 Days</th>
<th>Infection</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)b</td>
<td>RR (95% CI)b</td>
<td>HR (95% CI)c</td>
</tr>
<tr>
<td>NRS-2002</td>
<td>1.23 (0.65–2.56)</td>
<td>2.16 (1.18–3.94)</td>
<td>2.69 (1.07–6.81)</td>
</tr>
<tr>
<td>MUST</td>
<td>2.85 (0.93–8.72)</td>
<td>1.54 (0.51–4.63)</td>
<td>1.62 (0.32–8.19)</td>
</tr>
<tr>
<td>SNAQ</td>
<td>1.29 (0.65–2.56)</td>
<td>2.06 (0.96–4.45)</td>
<td>1.90 (0.65–5.55)</td>
</tr>
<tr>
<td>MST</td>
<td>1.30 (0.63–2.71)</td>
<td>2.12 (1.02–4.40)</td>
<td>1.53 (0.54–4.32)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; LOS, length of hospital stay; MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS-2002, Nutritional Risk Screening–2002; RR, relative risk; SNAQ, Short Nutrition Assessment Questionnaire.

αAll data were adjusted for age and stress of disease; presence of malnutrition was considered an independent variable.

βPoisson regression with robust variance.

cCox regression analyses.
malnutrition diagnosis, and its weak correlation with the ESPEN definition of malnutrition may limit the potential use of the new ESPEN consensus. Validity of the SGA was demonstrated by correlation of the clinical classification with objective measurement of nutrition status and with 3 measures of hospital morbidity—incidence of infections, use of antibiotics, and LOS—in a study performed by Baker et al.25 According to a systematic review conducted by van Bokhorst-de van der Schueren et al.6 due to the poorly chosen reference methods (prealbumin and NRS-2002) adopted in the studies that applied the SGA to assess patients’ nutrition status, it is difficult to say whether the SGA is a tool with good construct validity.

In light of the absence of a gold standard for nutrition assessment, adopting clinical outcomes as references usually has been performed to validate new methods. In this study, malnutrition identified by the ESPEN criteria was able to predict increased risk of infection in patients previously identified as at risk of malnutrition by the NRS-2002 and MST (malnourished patients had twice the risk of infection in comparison with well-nourished patients). However, when the NRS-2002 was applied as a nutrition screening tool, a significant association between malnutrition and mortality was observed only among patients identified as at risk of malnutrition by the NRS-2002 (risk of death was 2.7 times higher in malnourished patients than in well-nourished patients). These results agree with another study that used the new ESPEN criteria, in which malnutrition significantly increased the odds of dying during the hospital stay (odds ratio, 2.74; 95% CI, 1.02–7.40; \( P = .046 \)) and decreased to one-third the odds of being discharged home (odds ratio, 0.35; 95% CI, 0.20–0.62; \( P < .0001 \)).17 Taken together, the new ESPEN criteria represent a valid, accurate method to predict worse clinical outcomes related to malnutrition in hospitalized patients, although its accuracy depends on the nutrition screening tool initially applied.

Early identification of malnutrition in the hospital setting is important, considering that this condition has a negative impact on the cost of hospitalization; LOS; hospital readmission within 15, 90, and 180 days; and 1-, 2-, and 3-year mortality.4 Furthermore, a recent cross-sectional study conducted in a sample of 359 older adults of a geriatric outpatient clinic demonstrated that malnourished patients (MNA was applied for the nutrition diagnosis) have greater risk of structural brain changes. Underlying mechanisms explaining this association are still under investigation.26

A limitation of the current study is the lack of FFMI data, which may have underestimated the prevalence of malnutrition, despite the high correlation between BMI and body fat accumulation.27 Nevertheless, considering that two-thirds of our patients were classified as malnourished according to BMI (<18.5 kg/m²), we believe that the prevalence of malnutrition would not be significantly different if FFMI data were available. Furthermore, the optimal FFMI cutoffs for malnutrition identification need to be explored more and should be adapted to specific populations, considering that the cutoffs of FFMI proposed by ESPEN malnutrition criteria are arbitrary.11 We also did not consider weight loss >10% independent of time because these data were not available in our study, as well as in the multicentric study by Sanz-Paris et al.17 who evaluated the application of a new ESPEN diagnosis in geriatric patients with diabetes during hospitalization. However, we believe that this variable could not present a high sensitivity to identify malnourished patients considering that the deleterious effects of weight loss are probably dependent on timing since the severity of weight loss is classified according to time.28 Moreover, combining BMI with weight loss seems to be a better prognostic indicator, as demonstrated in a study conducted with patients with recent cancer.29 However, this issue should be better explored by other studies. Another limitation is that since our sample included only patients who were conscious and able to move, our results cannot be extrapolated to all hospitalized patients. However, this suggests a limitation of the new ESPEN criteria for a malnutrition definition, for it requires data of patients’ usual weight, actual weight, and height.

The main strength of our study is the large sample size, encompassing a wide range of ages and diseases. Furthermore, the study was conducted in an emergency service of a public hospital and highlights its importance as the first place where nutrition assistance of hospitalized patients should be started. Also, we used 4 screening nutrition tools to identify patients at risk of malnutrition. However, since we did not include a nutrition screening tool specifically for older people, such as MNA, we believe that it should be explored in further studies.

Conclusions

The new ESPEN criteria for malnutrition diagnosis identified malnutrition in 20.5% of patients admitted to an emergency service of a public hospital and demonstrated good accuracy to predict infection when the NRS-2002 and MST were used for nutrition risk screening and mortality when the NRS-2002 was applied. Further studies are needed to test the applicability of the new ESPEN criteria for diagnosis of malnutrition and their accuracy to predict other clinical outcomes.

Acknowledgments

We thank Luciane Figueira, Paula Becker, and Débora Raupp, who collected the data.

Statement of Authorship

F. M. Silva designed the study and analyzed the data; and F. M. Silva and J. da Silva Fink wrote the manuscript. All authors critically revised the manuscript, agree to be fully accountable.
for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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