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Diferentes métodos de diagnóstico da sarcopenia e sua associação com o estado nutricional e a sobrevida de pacientes com câncer avançado em cuidados paliativos.

Rio de Janeiro/RJ
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Trabalho de conclusão de curso em forma de artigo científico apresentado ao Instituto Nacional de Câncer José Alencar Gomes da Silva como requisito parcial para a conclusão do (a) Residência Multiprofissional.

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Title: Different methods for diagnostic of sarcopenia and its association with nutritional status and survival in patients with advanced cancer in palliative care.

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RESUMO

Objetivo: Investigar a associação da sarcopenia, obtida de acordo com diferentes métodos de avaliação da massa muscular, com o estado nutricional e a sobrevida. ***Métodos***: estudo observacional e prospectivo que envolveu 334 pacientes, sendo a sarcopenia definida pela redução concomitante da massa muscular e da força. A massa muscular foi avaliada por meio de 3 diferentes métodos, a saber: a área muscular do braço (AMB), a circunferência da panturrilha (CP) e a massa muscular esquelética apendicular (MMEA), descrita por Baumgartner (1998) e ajustada pela altura (IMMEA). A força foi determinada por meio do uso de um dinamômetro de preensão manual. A sobrevida foi determinada pelo tempo em dias contados da data da avaliação até o óbito/censura (90 dias). As curvas de Kaplan-Meier foram construídas para a análise da sobrevida e a associação entre a sarcopenia e a sobrevida foi avaliada pelo modelo de regressão de Cox. ***Resultados:*** A prevalência da sarcopenia variou de 27% a 65% de acordo com o método utilizado para avaliar a massa muscular. A desnutrição avaliada por diferentes parâmetros foi significativamente mais frequente em pacientes com sarcopenia. Os pacientes considerados sarcopênicos pela AMB (43 versus 67 dias, p <0,001), pela CP (44 versus 77 dias, p <0,001) e o IMMEA (48 versus 75 dias, p <0,001) apresentaram sobrevida significativamente inferior àqueles pacientes não sarcopênicos. A sarcopenia avaliada segundo a AMB (HR, 1,57; IC95%, 1,12-2,18) e a CP (HR, 2,00; IC95%, 1,45-2,76) configurou maior risco de mortalidade em 90 dias. ***Conclusão*****:** A sarcopenia diagnosticada pela AMB e a CP foi capaz de prever a mortalidade, sendo que a CP foi o melhor método prognóstico da sobrevida para esse grupo de pacientes oncológicos.

Palavras-chave: Sarcopenia; Estado nutricional; Câncer avançado; Cuidados paliativos; Sobrevida.

ABSTRACT

Aim: To investigate the association of sarcopenia, according to distinct muscle mass measurement methods, with nutritional status and overall survival (OS). ***Methods*:** This observational and prospective study, including 334 patients, defined sarcopenia as reduced muscle mass and strength. Muscle mass was evaluated adopting 3 different methods, mid-upper arm muscle area (MUAMA), calf circumference (CC) and appendicular skeletal muscle mass (ASMI) described by Baumgartner (1998) and adjusted for height. Strength was defined using a handgrip dynamometer and OS was established based on a 90 days follow-up after inclusion date. Kaplan-Meier curves were conducted for survival analyzes and the association between sarcopenia and OS was evaluated by Cox regression model. **Results:** Prevalence of sarcopenia varied from 27-65% according to the method used to evaluate muscle mass. Malnutrition assessed by different parameters was significantly more frequent in patients with sarcopenia. Patients considered sarcopenic by MUAMA (43 *versus* 67 days, $p<0.001$), CC (44 *versus* 77 days, $p<0.001$) and ASMI (48 *versus* 75 days, $p<0.001$) had significantly lower OS compared to non-sarcopenic patients. Sarcopenia evaluated by MUAMA (HR, 1.57; 95% CI, 1.12-2.18) and CC (HR, 2.00; 95% CI, 1.45-2.76) showed a higher risk of mortality. **Conclusion:** Sarcopenia diagnosed by MUAMA and CC could predict mortality and CC proved to be the best prognostic method for estimating OS in patients with advanced cancer in palliative care.

Keywords: Sarcopenia; Nutritional status; Advanced cancer; Palliative care; Survival.

1. Introduction

The term sarcopenia is derived from the Greek words sarx (flesh) and penia (poverty) [1]. The international consensus in sarcopenia defines it as a syndrome characterized by concomitant and generalized loss of skeletal muscle mass and strength [1,2,3,4]. Although sarcopenia is primarily a condition of the elderly individuals, it may also be associated with chronic diseases, including cancer [1].

Evidence of muscle loss and strength reduction exists for most cancer types and stages. However, these conditions are more evident in advanced phases of the disease and become significant in terms of functional disability, loss of autonomy and decreased quality of life [1,5,6,7]. Studies have shown that the presence of sarcopenia has been associated with adverse outcomes including decreased overall survival (OS) [8,9,10].

Current guidelines discuss the use of multiple measurement techniques and cut-points to diagnose sarcopenia. There are several methods available to assess depletion of skeletal muscle mass, such as, computed tomography (CT), magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA), anthropometric measures and bioelectrical impedance (BIA) [5,7,11].

Although the CT, MRI and DXA methods are considered gold standard, they are expensive, require skilled labor and some of them expose patients to radiation, which may render some of them unmanageable in the clinical setting. On the other hand, anthropometric measures are classified as low cost, noninvasive and easy to apply during routine clinical practice [12].

Despite the associations between sarcopenia and various significant health outcomes, there has been very limited research comparing the associations between nutritional status, survival and sarcopenia defined by anthropometric measurements. Therefore, the aim of the present study was to evaluate the association between sarcopenia, diagnosed by different

muscle mass measurement techniques, with nutritional status and overall survival (OS) in patients with advanced cancer under palliative care.

2. Methods

2.1 Patients

This study presents the preliminary results from an observational consecutive cohort study conducted in the Palliative Care Unit at the National Cancer Institute José Alencar Gomes da Silva (INCA), Rio de Janeiro, Brazil. A total of 334 advanced cancer patients were recruited from March 2016 to July 2017. Muscle mass, strength and nutritional status were measured and evaluated by trained nutritionists at the first visit for outpatients and within the first 48 hours of the first hospitalization for inpatients. Cancer type, stage of the disease, previous oncologic treatment, comorbidities and the date of death were obtained from medical records.

Patients were included according to the following eligible criteria: age ≥ 20 years old, ability to answer the necessary information and/or accompanied by someone capable of it, and Karnofsky Performance Status (KPS) ≥30%. This study received ethical approval from the Research Ethics Committees of INCA (Protocol number 1.407.458 of 2016) and all patients signed an informed consent term before joining the study.

2.2 Measurement instruments

Anthropometry

Measurements of weight and height were made with subjects wearing light clothing and without shoes. Weight was obtained using a calibrated portable Wiso Digital scale (150 kg capacity). For those patients who were unable to stand, it was used an in-bed scale system - Stryker, model Go Bed II. Weight loss history in the past 6 months was also collected. We considered a weight loss greater than or equal to 5% as clinically significant, consistent with malnourished state or at risk of malnutrition.

Height was measured using a tape stadiometer on the wall. However, when not possible, it had to be estimated using the knee height, which was measured with the knee and ankle joints flexed at 90°, using a measuring tape or an anthropometer. The estimated height was calculated through the Chumlea *et al.* [13] formulas. Body mass index (BMI) was calculated as body weight (kg) divided by the height^2 (m).

Muscle mass

Three measures were used to assess muscle mass:

- *Appendicular skeletal muscle mass (ASM, kg):* it was determined using the prediction equation described by Baumgartner *et al*. [14], which uses body weight, height, hip circumference and handgrip strength (HGS). The ASM index (ASMI) was measured using the following formula: ASM/height^2 [2].
- *Mid-upper arm muscle area (MUAMA, cm²):* it was obtained through the equation proposed by Heymsfield *et al.* [15], which depends on sex and uses arm circumference and triceps skinfold thickness.
- *Calf circumference (CC, cm):* it was assessed with the patient seated, knees and ankles 90^o flexed and the largest circumference was measured using inextensible tape. Values were defined as the nearest 0.1 cm [16].

Muscle Strength

Muscle strength was assessed by HGS using Jamar® hydraulic hand dynamometer (Baseline, Fabrication Enterprises, Inc, Elmsord, NY, USA). Each participant was instructed to comfortably arrange the instrument in his/her hand, and in sequence apply as much effort as possible with the dominant hand, while sitting with the elbow flexed at 90°. Three trials were performed with a 1 minute rest interval period. The first trial was discarded functioning as a warm up and the higher HGS value of the other two trials was recorded for the study.

Sarcopenia criteria

Sarcopenia was defined as a reduction of muscle mass and strength, concomitantly. Low muscle mass was characterized when: 1) ASMI <7.26 kg/m^2 for male and < 5.45 kg/m^2 for female [2]; 2) MUAMA <32 cm^2 for male and <18 cm^2 for female [11]; 3) CC ≤34 cm for male and ≤33 cm for female [17]. Low muscle strength was defined by HGS <30 kg for male and <20 kg for female [2].

Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF)

Nutritional status was evaluated according to PG-SGA SF, available by Ottery in Pt.Goblal.org, after its use permission. This tool consists of the first part of the PG-SGA, detecting issues on: weight change (maximum score of 5), food intake (maximum score of 4), symptoms (maximum score of 24) and functional capacity (maximum score of 3). Patients were categorized as malnourished if PG-SGA SF score ≥9.

2.3. Laboratory assessments

On the study enrollment day, a single intravenous blood sample was drawn for the analysis of serum levels of albumin and C-reactive protein (CRP). Low serum albumin was diagnosed as a plasma concentration <3,5 g/dL and high CRP with values ≥10mg/dl.

2.4 Survival

Patient OS was defined by the time interval, in days, between the baseline date of the study and the date of death (of any cause). Patients who remained alive after 90 days were censured.

2.5 Statistical analysis

We processed statistical analysis using the SPSS software version 21.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov test was performed to assess distribution symmetry. Descriptive statistics [count/frequency (%), means ± standard deviation (SD), or median and

interquartile ranges (IQR), as appropriate] were used to describe patient characteristics and prevalence of sarcopenia.

Differences in nutritional status between patients with and without sarcopenia based on different muscle measurements were evaluated using Chi^2 test for categorical variables, and independent t-test for continuous variables.

Kaplan-Meier method was used to illustrate survival curves and the long-rank test to compare OS according to the presence of sarcopenia (by ASMI, MUAMA and CC, respectively). Additionally, the Cox proportional hazard model was used to assess hazard ratios (HRs) and confidence interval (CI) of prognostic factors. Adjustments were made in multiple Cox regression analysis for age ≥ 60, female gender, gastrointestinal tract tumor, KPS 30-40%, CRP >10mg/L and PG-SGA SF score ≥9. Statistical significance was set at p <0.05.

3. Results

A total of 334 patients with advanced cancer were included in this study. The majority were female (54.8%) with an average age of 63 (interquartile range; IQR 55; 72). **Table 1** describes the overall characteristics of patients, including nutritional status and laboratory markers.

At the end of the follow-up, 127 (38.0%) patients were alive. The OS median was of 60 (IQR: 30-131) days for the entire group.

According to ASMI, MUANA and CC, low muscle mass was present in 89,9%, 32,3% and 68,3% of patients, respectively. Low muscle strength was prevalent in 70.4% of the sample. The prevalence of sarcopenia varied from 27% to 65% according to the diagnostic method.

The presence of malnutrition, diagnosed through different parameters (weight loss ≥5% in 6 months, serum albumin <3,5 g/dL and PG-SGA SF score ≥9), was significantly higher in patients with sarcopenia compared with patients without this condition, for the three muscle

mass measurements, except for MUAMA, in which the presence of malnutrition by PG-SGA SF, weight loss and serum albumin was higher among non-sarcopenic individuals. Furthermore, BMI average was significantly lower between sarcopenic patients compared to non-sarcopenic patients for all muscle mass parameters (**Table 2**).

The survival curves are in **Figure 1**. Patients considered sarcopenic by MUAMA (43 *versus* 67 days, p<0.001), CC (44 *versus* 77 days, p<0.001) and ASMI (48 *versus* 75 days, p<0.001) had significantly lower OS compared to non-sarcopenic group. In addition, significantly lower survival curves (not shown in the figure) were also observed for the groups with low HGS (median OS 49 *vs* 77 days; p<0.001).

In the Cox proportional hazard models (**Table 3**), the univariate analysis showed a higher hazard risk for mortality in the groups with sarcopenia, for the three different measurements, but in multivariate adjusted analysis, only sarcopenia by MUAMA (HR, 1.57; 95% CI, 1.12-2.18) and CC (HR, 2.00; 95% CI, 1.45-2.76) remained significant.

4. Discussion

The main aim of this study was to investigate the correlation of low muscle mass and strength combined (true sarcopenia), defined by different methods of muscle mass assessment, with nutritional status and overall survival (OS). Three different muscle mass measurement techniques were used, namely, CC, MUAMA and ASMI. These methods were selected because they are reproducible and easily incorporated in the clinical routine.

It is important to highlight that patients with sarcopenia classified by the three different methods to asses muscle mass had lower survival curves compared with their respective groups. Nevertheless, higher mortality ratios in the 90 days follow-up period were observed for low CC and low MUAMA, but not for low ASMI. The results suggest that two of the three methods

considered in this study can predict a 90 days follow-up mortality in patients with advanced cancer.

Our primary hypothesis is that the proportion of subjects classified as sarcopenic was overestimated when defined by ASMI, since Baumgartner's prediction equation takes into account the HGS and the fact that 70.4% of the sample was classified as dynapenic. Thus, non-sarcopenic individuals were possibly misclassified as sarcopenic according to this method. Besides that, although Baumgartner's prediction equation has been extensively used to estimate muscle mass in adults and has been validated for this application in older subjects, additional studies are needed to validate the use of this method in advanced cancer patients.

Some studies that investigated the relationship between sarcopenia and survival in advanced cancer patients corroborate our findings. In a study with patients receiving neoadjuvant treatment for locally advanced esophageal cancer, those with sarcopenia showed significantly decreased long-term survival compared to non-sarcopenic group [8]. Also in agreement with our study, Fukushima *et al.* [9], analyzing 88 patients with advanced urothelial carcinoma, showed that sarcopenia was a significant and independent predictor of shorter OS. It is important to note that although these studies were published recently, they classified sarcopenia simply by low skeletal muscle mass, which would be better designated as muscle atrophy [11].

Related studies that evaluated the association between survival and sarcopenia defined it as the concurrent loss of muscle mass and strength, occurring in patients with cancer but not in the advanced stage of the disease. For example, Huang *et al*. [22] in a prospective study of elderly patients who underwent curative gastrectomy for gastric cancer showed that sarcopenia, with muscle mass evaluated by CT, was an independent risk factor for 1-year mortality. Likewise, sarcopenia with muscle mass determined by ASM assessed using multi-frequency

bioelectrical impedance was a significant predictor of OS in patients with esophageal cancer who underwent esophagectomy [10].

Regarding anthropometric measurements, we did not find studies assessing the relationship between survival and sarcopenia using these methods with cancer patients. Nevertheless, Tartari *et al.* [23] evaluated MUAMA as a potential prognostic factor in patients with stage IV non-small cell lung cancer and found significant lower OS for those categorized as having depleted muscle mass. Additionally, Bourdel-Marchasson *et al.* [24] identified that calf circumference <31cm was found to be associated with 1-year mortality in a prospective cohort including 606 elderly patients with cancer (> 70 years old).

Concerning nutritional status, patients with sarcopenia, more frequently, presented malnutrition assessed by PG-SGA SF, weight loss, BMI and serum albumin than its respective groups. Corroborating these findings, Zhou *et al*. [25] performed a prospective study with patients with gastric cancer and also found that sarcopenia was associated with a lower BMI and lower serum albumin, as well as lower hemoglobin values and higher nutritional risk screening 2002 scores. Similarly, Kim *et al.* [26] evaluated patients with small cell lung cancer and demonstrated that sarcopenia determined by routine chest CT scan was significantly associated with lower BMI, serum albumin level, and weight. Therefore, with these results, we suggest that the condition of sarcopenia was able to differentiate the nutritional status of patients.

The limitation of this study was that the use of accurate methods such as CT and DXA were not used to determine muscle mass, not allowing a more accurate and comprehensive assessment of sarcopenia. The strength of the present study, on other hand, is the low-cost and user-friendly muscle mass measuring techniques applied as diagnostic criteria for sarcopenia. These methods are required for screening, particularly in developing countries, since the use of gold-standard methods are financially unfeasible at a large scale.

5. Conclusion

The results of the present study show that sarcopenia diagnosed by MUAMA and CC can predict mortality and CC is the best prognostic method to estimate OS in advanced cancer patients.

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7. Tables and figures

Table 1. Characteristics of the advanced cancer patients treated at a Palliative Care Unit in the city of Rio de Janeiro, Brazil (n= 334).

Variables	
Age (years)[a]	63 (55; 72)
Age ≥60 years[b]	208 (62.3%)
Female gender[b]	183 (54.8%)
Types of tumor[b]	
GI tract	104 (31.1%)
Ginecologic	58 (17.4%)
Head and neck	43 (12.9%)
Lung	37 (11.1%)
Breast	29 (8.7%)
Others	63 (18.9%)
Distant metastasis[b]	222 (66.5%)
Comorbidities[b]	
SAH	87 (26.0%)
DM	32 (9.6%)
KPS (30-40%)[b]	115 (34.4%)
PG-SGA SF (global score)[a]	14 (8; 19)
PG-SGA (SF ≥9 points)[b]	255 (74.6%)
BMI (kg/m²)[c]	22.1 (±5.2)
BMI (<20kg/m²)[b]	129 (38.6%)
Albumin (g/dL)[a]	3.4 (2.9; 3.9)
Reduced muscle mass[b]	
ASMI (Kg/m^2)	287 (89.9%)
MUAMA (cm^2)	108 (32.3%)
CC (cm)	228 (68.3%)
Reduced HGS[b]	235 (70.4%)

Note: n= number of observations; %= frequency; GI = gastrointestinal; SAH= systemic arterial hypertension; DM= diabetes mellitus; KPS= Karnofsky Performance Status; PG-SGA SF= Patient-Generated Subjective Global Assessment Short Form; BMI= body mass index; ASMI = appendicular skeletal muscle mass index; MUAMA= mid-upper arm muscle area; CC= calf circumference; HGS = handgrip strength.

[a]Median/interquartile ranges (p25-p75).

[b]Number of observation/frequency

[c]Mean/standard deviation

Table 2. Differences in nutritional characteristics between sarcopenia groups defined by different muscle measurements in advanced cancer patients treated at a Palliative Care Unit in the city of Rio de Janeiro, Brazil (n= 334).

	ASMI			MUAMA			CC		
Variables	**Sarcopenia (n=219)**	**No sarcopenia (n=115)**	**p value**	**Sarcopenia (n=90)**	**No sarcopenia (n=244)**	**p value**	**Sarcopenia (n=177)**	**No sarcopenia (n=157)**	**p value**
PG-SGA SF ≥9 points[a]	182 (54.5%)	66 (19.8%)	**<0.001**	78 (23.4%)	170 (50,9%)	**0.001**	147 (44.0%)	101 (30.2%)	**<0.001**
WL ≥5% in 6 months[a]	142 (60.9%)	63 (27.0%)	**0.016**	67 (28.8%)	138 (59.2%)	**0.034**	119 (51.1%)	86 (36.9%)	**0.009**
BMI (kg/m²)[b]	20.8 (±4.4)	24.6 (±5.8)	**0.004**	18.0 (±3.0)	23.6 (±5.0)	**<0.001**	19.7 (±3.6)	24.8 (±5.4)	**<0.001**
Albumin <3,5 g/dL[a]	140 (41.9%)	37 (11.1%)	**<0.001**	66 (19.8%)	111 (33.2%)	**<0.001**	117 (35.0%)	60 (18.0%)	**<0.001**

Note: ASMI = appendicular skeletal muscle mass index; MUAMA= mid-upper arm muscle area; CC= calf circumference; PG-SGA SF= Patient-Generated Subjective Global Assessment Short Form; WL= weight loss; BMI= body mass index.

[a]Number of observation/frequency; chi_2. 111 (33.2%)

[b]Mean/standard deviation; independent t-test.

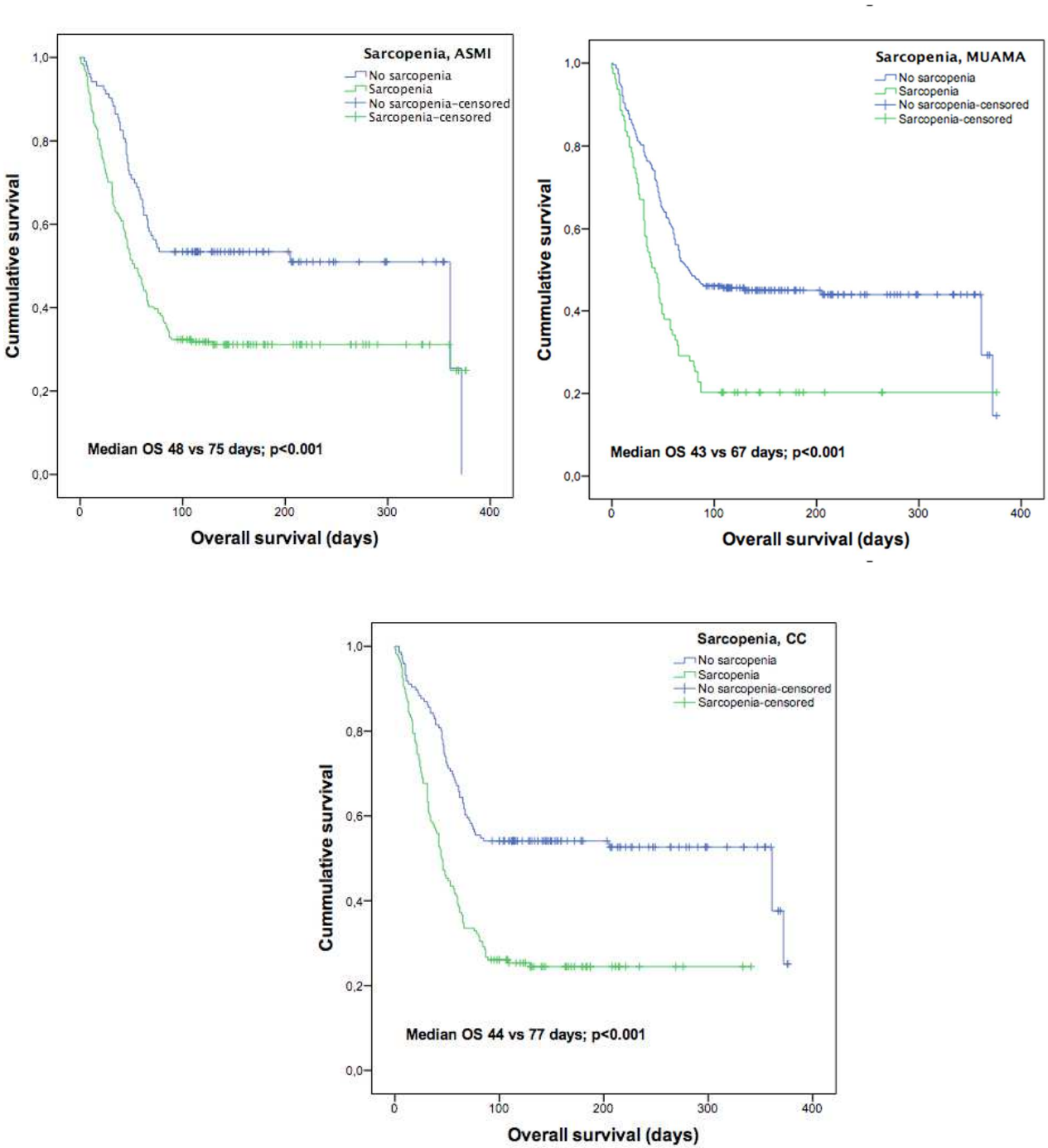

Figure 1. Comparison of survival curves among patients with sarcopenia and no sarcopenia by appendicular skeletal muscle mass, mid-upper arm muscle area and calf circumference, n=334.

Note: ASMI = appendicular skeletal muscle mass index; MUAMA= mid-upper arm muscle area; CC= calf circumference; OS= overall survival.

p-valor refers to log-rank test.

Table 3. Multiple Cox regression analysis of the association between sarcopenia with different muscle measurements and survival in advanced patients treated at a Palliative Care Unit in the city of Rio de Janeiro-Brazil (n=334).

	Univariate		**Multivariate**	
	HR (95% CI)	*p*-value	HR (95% CI)*	*p*-value
Sarcopenia, ASMI	1.97 (1.44; 2.69)	<0.001	1.34 (0.94; 1.92)	0.060
Sarcopenia, MUAMA	1.93 (1.45; 2.58)	<0.001	1.57 (1.12; 2.18)	0.007
Sarcopenia, CC	2.18 (1.64; 2.91)	<0.001	2.00 (1.45; 2.76)	<0.001

Note: ASMI = appendicular skeletal muscle mass index; MUAMA= mid-upper arm muscle area; CC= calf circumference; HR= hazard ratio; CI = confidence interval.

*Adjusted for age ≥60 years, female gender, gastrointestinal tract tumor, Karnofsky Performance Status 30-40%, C-reactive protein >10mg/L and Patient-Generated Subjective Global Assessment Short Form score ≥9.