



Published in final edited form as:

JPEN J Parenter Enteral Nutr. 2014 September ; 38(7): 873–879. doi:10.1177/0148607113500308.

The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using subjective global assessment and computed tomography

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Statement of Authorship: PMS designed, conceived and carried out the study, conducted the research and data analyses, and drafted the manuscript. SJP, KT and SGP assisted with the design and coordination of the study and conducted the research and data analyses. AP, FA, and JS conducted the research. CAB supervised the study, participated in its design and assisted in the drafting the manuscript.

Conflict of interest: The authors have no conflicts of interest to disclose.

Introduction

Patients admitted to the ICU have long been considered “high risk” for nutritional morbidity, resulting from preadmission alterations of the underlying disease process, general disease progression and consequential treatments following ICU admission. The illness-associated hypercatabolism that occurs in this population is associated with rapid deteriorations in nutritional status.¹ However, classifying malnutrition in the ICU is exceptionally challenging for a variety of reasons. Often investigators and clinicians employ the application of acute phase proteins. These are now considered invalid biomarkers of nutritional status during illness.² Further, MV and sedation impede efforts to solicit weight and intake history, and physical assessment findings are frequently obscured by fluid retention. SGA is a widely utilized nutritional assessment instrument developed by Baker *et al*³ 25 years ago. It is considered the “gold standard” for bedside nutrition assessment⁴ and includes several components of the medical history (weight change, dietary intake, gastrointestinal [GI] symptoms, functional capacity) and two components of a brief physical examination (eg, signs of fat loss and muscle wasting, alterations in fluid balance).^{5,6} (Figure 1) It relies on a collective clinical judgment rather than specific biochemical or objective markers to categorize nutritional status, and has been shown to predict complications.⁷ Inherent in the SGA categories are the recognition that reductions in nutrient intake lead to the adverse the body composition changes which characterize malnutrition (i.e. loss of lean body mass [LBM] and adipose tissue). The use of SGA has been demonstrated to be reliable in ICU populations,⁸ however its ability to correctly classify critically ill patients with severe muscle wasting has not been explored. The high prevalence of obesity in contemporary ICU populations may impede detection of severe wasting and cause misclassification of nutritional status in a significant proportion of these individuals.

The growth of imaging diagnostics reflects unique opportunities to advance our abilities to assess human body composition in the ICU setting. The ICU is an environment where enteral and parenteral nutrition therapies receive priority and are the focus of considerable research attention. Efforts within the last decade have highlighted the successful utilization of archived computerized tomography (CT) images to quantify lean and adipose tissue compartments in various oncology populations.^{9,10} Results from cancer cohort studies have demonstrated negative associations between sarcopenia, or low levels of skeletal muscle mass, and important clinical outcomes (eg, survival, chemotherapy toxicities).^{11,12} While DXA and CT are considered precise methods to assess body composition, the use of DXA in critically ill populations is impractical. Additionally, CT utilization in noncancer populations for body composition assessment is limited by high radiation doses, financial burden and lack of general availability and accessibility. However, patients in the ICU setting frequently undergo CT imaging for diagnostic purposes, reflecting novel prospects to extend previous nutrition assessment efforts. Therefore, the goals of this study were: 1) to examine the prevalence of sarcopenia in this population, 2) to determine if patients with sarcopenia were detected by SGA categorization and 3) to describe why these misclassifications occurred. We postulated that all patients categorized as normal nourished by SGA would not be sarcopenic.

Methods

Study design and patient population

Data were prospectively collected over 12 a month period on patients with acute lung injury under consideration for a larger randomized controlled feeding trial. To be included in the present cross-sectional study, the following eligibility criteria were required: admission to the surgical or the medical ICU, respiratory failure requiring MV, a nutrition status evaluation at admission to the ICU by a Registered Dietitian, and a diagnostic CT scan of the abdomen and/or pelvis during hospitalization. Because SGA measures short-term nutrition impact symptoms in the previous two weeks, these analyses were restricted to include only patients with SGA categorizations completed within 2 weeks of CT imaging. The ethical conduct of this study was approved by the appropriate Institutional Review Boards.

Demographic and medical information

Demographic and medical information including sex, race/ethnicity, age, date of hospital admission, date of ICU admission, hospital discharge, ICU discharge, ICU diagnosis, clinical variables related to APACHE II calculations, anthropometrics and hospital disposition were collected from the electronic medical record (EMR). Measured and/or self-reported heights were abstracted from the EMR and ICU admission weights obtained prior to fluid resuscitation were used to calculate BMI as follows: weight (kg)/ height (m)².

Nutritional status

Within 24 hours of ICU admission, patients were classified as normally nourished, moderately malnourished or severely malnourished using SGA. SGA classifications were completed by trained, experienced ICU RDs as a routine component of the admission ICU nutrition assessment recorded within the electronic medical record.

Body composition

The use of CT images has emerged as a precise methodology for measuring human body composition.^{9,13,14} Quantitative CT image analysis distinguishes different tissues with specific attenuation characteristics, such as density and chemical composition. CT images are comprised of three-dimensional arrays of voxels, which express volume. Each voxel is assigned an x-ray attenuation value that is expressed on a standardized linear scale of Hounsfield units (HU). Using this scale, air is assigned a value of -1000 HU and water is assigned a value 0 HU. Specific tissues are quantified based on pre-established thresholds of HU (Figure 2).

A single transverse CT slice located at the mid-point of the third lumbar (L3) region, the standard anatomical landmark, was isolated by a radiologist blind to study outcomes. Skeletal muscles located within the L3 region were identified and demarcated to include the psoas, paraspinal muscles (erector spinae, quadrates lumborum) and the abdominal wall muscles (transverses abdominus, external and internal obliques, rectus abdominus.) Voxels were classified as being muscle based on their anatomic location and having a HU value consistent with skeletal muscle between -29 and +150. Images were analyzed by two

individuals using Mimics software (version 14, Materialise, Leuven, Belgium). The mean values for the measurements were utilized and any two measures with a coefficient of variation >5% were reanalyzed. For additional quality assurance purposes, 15 images were also subsequently analyzed by a third individual to be sure all measures had a coefficient of variation <5%.

Cross-sectional area (cm²) was computed for each of these muscles by summing tissue voxels and multiplying by the voxel surface area. The muscle cross sectional area at the L3 level was used because it is linearly related to whole-body muscle mass in cancer and non-cancer populations.¹³⁻¹⁵ Estimates of whole-body lean mass (kg) were calculated from the regression equation of Mourtzakis et al¹⁶ as follows: 0.30 X [skeletal muscle at L3 region using CT (cm²)] + 6.06 (r=0.94; p<0.001). These values were then normalized for stature (L3 skeletal muscle index, cm²/m²). The international definition of sarcopenia includes the presence of both, low muscle mass and low muscle function,¹⁷ however, our study design precluded inclusion of these measures. Based on similar methodologies that have been validated and linked with impaired outcomes by Prado et al, sarcopenia was defined as: L3 skeletal muscle index < 38.5 cm²/m² for women and < 52.4 cm²/m² for men.¹⁸ Sarcopenic obesity was defined as L3 values lower than the sex-specific cut-points for sarcopenia in individuals with a BMI > 30 kg/m².

Statistical Analyses

Descriptive statistics were conducted to compare baseline measures and differences between groups, using two-sample T tests for continuous variables and Pearson, Chi square and Fisher's exact test for categorical variables. Linear regression was used to examine differences between body composition variables, controlling for age. Data are expressed as means, medians, standard deviations (SD) and frequencies and a p value of 0.05 was used to denote statistical significance. Patients were dichotomized as normally nourished vs. malnourished, collapsing moderate and severely malnourished into one nutritionally compromised group for more meaningful comparisons. Patients categorized as normal nourished by SGA that were sarcopenic using sex-specific CT cut-points were considered misclassified. The prevalence of sarcopenia was examined using 3 different time points, rationalizing that the longer time between SGA rankings and CT imaging may increase the propensity for misclassification. Therefore, misclassification was assessed for CT imaging conducted within 14, 10 and 7 days of SGA categorization. Sarcopenia may or may not be present in patients classified as moderately malnourished. This lack of mutual exclusivity between categories prohibited misclassification detection in these individuals. (See Figure 3 for a depiction of this concept.) Only one patient was ranked as severely malnourished; therefore agreement with sarcopenia categorizations was not possible. All analyses were performed using SAS (version 9.2, 1998, SAS Institute, Cary, NC.)

Results

A total of 301 patients requiring MV were screened within the 12 month study time frame; 236 patients did not require CT imaging or had images excluding the L3 region; 4 images were of poor quality and 5 images were >14 days of SGA assessment. In total, 56 patients

met all the eligibility and inclusion criteria. Overall, the prevalence of moderate (n=25) or severe (n=1) malnutrition was 46%. Clinical characteristics of those classified as normal nourished vs. malnourished are presented in Table 1. Malnourished patients had a significantly higher frequency of gastrointestinal-related diagnoses (p=0.04), and normal nourished patients had significantly greater admission body weight (p=0.02). Overall BMI was significantly higher for the normally nourished (p=0.02), however, both groups, on average, met the international classification for overweight at ICU admission.¹⁹ The prevalence of malnutrition was 100% (n=2/2) in underweight (BMI < 18.5), 43% (n=6/14) in normal weight (BMI 18.6–24.9), 57% (n=12/21) in overweight (BMI 25.0–29.9) and 32% (n=6/19) in obese (BMI > 30) participants. Upon discharge, normally nourished participants more commonly required skilled nursing or rehabilitation services (p=0.02), whereas malnourished participants had a significantly higher prevalence of death or hospice requirements (p=0.008).

Table 2 compares differences in body composition measures and sarcopenia at various time points between SGA completed at ICU admission and diagnostic CT imaging. Both measures were completed within 14 days of each other in 56 patients (Group 1), within 10 days of each other for 48 patients (Group 2) and within 7 days of each other in 36 patients (Group 3). Controlling for age, no significant differences were noted for patients classified as normal nourished vs. malnourished by SGA for lumbar muscle cross-sectional, whole-body lean mass or skeletal muscle index in any group. Overall, sarcopenia was prevalent in 60% (n=34/56) of patients in Group 1, 60% (n=29/48) of patients in Group 2, and 56% (n=20/36) of patients in Group 3. The prevalence of sarcopenic obesity was also consistent across groups with 24% (n=8/34) in Group 1, 24% (n=7/29) in Group 2 and 25% (n=5/20) in Group 3.

Misclassifications (ie, ranked as normal nourished and sarcopenic) were observed in 60% of patients (n=18/30) in Group 1, 58% (n=14/24) in Group 2 and in 50% (n=7/14) in Group 3. For exploratory purposes, participants with CT imaging and SGA within 3 days (n=25) were analyzed. This subgroup also demonstrated that 63% (n=5/8) of patients were misclassified. Overall, this signifies generally poor abilities of SGA to detect severe muscle wasting regardless of the time between imaging and nutrition assessment. In Group 1, misclassified individuals were predominantly male (78%, n=14/18), minority (78%, n=14/18), overweight (33%, n=6/18) or obese (33%, n=6/18). Similar relationships were noted in those misclassified in Group 2 (71% male, n=10/14; 79% minority, n=11/14; 29% overweight, n=4/14 or 36% obese n=5/14) and in Group 3 (57% male, n=4/7; 71% minority, n=5/7; 29% overweight, n=2/7 or 43% obese, n=3/7.)

Discussion

This study found that sarcopenia was highly prevalent in patients with respiratory failure. More importantly, we found that sarcopenia occurred in the majority of individuals classified as normally nourished utilizing SGA completed by experienced, trained clinicians. Sarcopenia was originally described by Evans and Campbell as an age-related loss of muscle mass²⁰ and is associated with increased physical disability, falls, fractures and frailty.^{21,22} Definitions and diagnostic criteria have now been operationalized by the European Working

Group on Sarcopenia in Older People for clinical practice and research studies.¹⁷ Based on this consensus report, it is reasonable to assume that sarcopenia, specifically secondary sarcopenia, is not consistent with a normal SGA nutrition classification. To this end, Tandon et al. used L3 images to examine the prevalence of sarcopenia and its associations with SGA rankings of nutritional status in patients listed for liver transplantation. Of the 140 patients with available SGA information, sarcopenia was identified in 40% (n=17/42) of the patients ranked as normal nourished and in 30% (n=21/71) of patients with a BMI ≥ 25 kg/m².²³ In our study, sarcopenia was identified in 50–60% of patients ranked as normal nourished and the overwhelming majority of the misclassified participants were overweight or obese. These results are not altogether surprising since SGA was developed by Baker et al nearly 30 years ago³ when the prevalence of obesity (BMI ≥ 30 kg/m²) was only 18%²⁴ and clinical assessments of malnutrition at that time primarily entailed detection of obvious and overt signs of muscle and fat wasting. Considering that the majority of the US population is now overweight or obese,²⁵ our findings and those of Tandon et al underscore the limitations of SGA in contemporary populations and support the need for alternate methods for detecting malnutrition and severe muscle wasting in acutely ill individuals.

Overall ~25% of participants who were sarcopenic were also obese. A recent review by Prado et al describes the potential multiplicative effects of excess fat mass couple with depleted muscle mass on clinical outcomes.²⁶ The authors postulate that *fat mass* represents the degree of fat infiltration, tissue disorganization, mechanical stress, limited respiratory function, altered metabolic and neuro-hormonal signaling. Alternatively, *fat free mass* reflects metabolic flexibility, optimal ventilation-perfusion coupling, endocrine and autocrine sensitivity, and maintenance of fluid/electrolyte balance.²⁶ The influence of sarcopenic obesity on outcomes in critically ill populations is not known; however meta-analyses have found that being overweight or obese confers a survival advantage in the ICU.^{27,28} Adipose tissue of patients with protracted critical illness have been reported to undergo morphologic alterations characterized by increased newly differentiated, small adipocytes with infiltration of M2 macrophages. This heightens their ability to take up greater amounts of circulating glucose and triglycerides.²⁹ The authors speculate these changes may enable the adipose depots to act as a storage facility for toxic metabolites, which in turn contributes to the improved survival of obese, critically ill patients. Currently it is unknown if lack of muscle mass together with excess adiposity in persons with critical illness culminates into a ‘worst case scenario’ or if it is beneficial compared to those who are sarcopenic and not obese. Until these complex relationships are elucidated, more simplistically, we offer that identifying individuals with sarcopenia provides a quantifiable method to classify obese individuals as malnourished. This is a phenomenon that investigators and clinicians have struggled with amidst the growing obesity epidemic.

Finally, this study found that sarcopenia was overall more prevalent among male participants (n=25/34), reflecting similar gender disparities reported in other studies using CT image based methodologies.^{18,23,30} It can be hypothesized that women would be more likely to lose fat mass rather than muscle mass because of greater baseline adipose depots compared to men. However, reductions in testosterone concentrations resulting from illness may lead to a down-regulation in the rate of muscle protein synthesis. Specifically, critical

illness is associated with various endocrine dysfunctions and male patients in the ICU have depleted levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate- two testosterone precursors.³¹ Thus, the biological plausibility of gender differences for muscle loss exists, lending support for a higher prevalence of sarcopenia among men in this study.

Collectively, these findings should be interpreted with caution, as several limitations warrant consideration. First, the cross-sectional nature of this investigation should be used to generate further hypotheses, not to establish causality or temporality. In this particular population, we cannot decipher if the declines in skeletal muscle mass occurred prior to critical illness or if the critical illness resulted in sarcopenia. Second, these results are only generalizable to patients in the ICU who require MV, undergo CT imaging and have protracted stays. Clearly, there is great variability in the severity of illness among patients admitted to the ICU and this can also differ by type of ICU (eg, neurology, cardiac care, trauma, etc.) Third, there is heterogeneity regarding sarcopenia cut-points, depending on the body composition methodology (eg, bioelectrical impedance, waist circumference, DXA).²⁶ This has likely been minimized in our study, however, since we prioritized using a sex-specific definition of sarcopenia that was established using CT imaging. Fourth, while established and accepted, an inherent limitation is these analyses is the use of a single-slice cross-sectional image to reflect whole body measures of lean mass. This assumes a linear relationship between these components which may vary between individuals. Fifth, we extrapolated sarcopenia definitions established for patients with advanced cancer. We speculate that the physiologic stress is likely higher for patients with critical illness and as a result, our estimates of sarcopenia may be artificially lowered. Finally, for simplicity we specifically focused on one body composition compartment (skeletal muscle mass) due to lack of availability of published cut-points for other body composition depots. Perhaps other components, such as subcutaneous or visceral fat reserves, in conjunction with skeletal mass, could have offered additional insights.

Conclusions

While this study was relatively small, it is the first to utilize a precise methodology for body composition assessment to assess the applicability of SGA in an ICU population. The results offer prevalence estimates for sarcopenia and sarcopenic obesity in a population not yet reported and corroborate data from previous studies showing that malnutrition is common in critically ill patients requiring MV. The novelty of this work highlights concerns regarding the validity of SGA; a tool developed prior to the obesity epidemic when physical findings of malnutrition were more apparent for clinicians. We recognize that CT imaging for body composition assessment requires considerable training, software and expertise. However, future work should prioritize validity studies using body composition, in conjunction with nutrition impact symptoms in hopes of enhancing and modernizing SGA, our “gold standard” bedside assessment tool.

Acknowledgments

Funding Source: Support for this study was provided by the National Cancer Institute, Cancer Education and Career Development Program #R25CA057699-18 and the National Heart Lung and Blood Institute #R01 HL093142-02.

Abbreviations

SGA	subjective global assessment
CT	computed tomography
ICU	intensive care unit
MV	mechanical ventilation
DXA	dual energy x-ray absorptiometry
BMI	body mass index
L3	third lumbar
HU	Hounsfield unit

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Clinical Relevancy

Using computed tomography imaging, sarcopenia, a condition characterized by low muscle mass, was found to be highly prevalent in the majority of critically ill patients in this study. Although ICU admission nutritional status was categorized by clinicians trained and experienced in using SGA, the majority of patients classified as normal nourished were sarcopenic, regardless if the assessment was completed within 14, 10 or 7 days of CT imaging. Misclassifications (ie, normal nourished and sarcopenic) were more frequent in men, minorities and the overweight or obese. Although SGA is considered a “gold standard” bedside assessment tool, these results support its inability to accurately detect severe muscle wasting in critically ill populations and the need to advance these methodologies in contemporary hospitalized populations.

History	<p>1. Weight change</p> <ul style="list-style-type: none"> ○ In the past 2 weeks, weight has: Increased / Decreased / Not changed ○ Overall decrease was _____ kg over the past 6 month <p>2. Dietary Intake (relative to usual intake): No change Borderline/Poor Unable to eat</p> <p>3. GI symptoms (>2 weeks): None Nausea Vomiting Diarrhea Anorexia</p> <p>4. Functional capacity: No change ↓ ADL Bed ridden</p> <p>5. Metabolic stress : No stress Low/Mod stress High stress</p>
Physical exam	<p>(for each trait specify normal⁰, mild¹, moderate² or severe³)</p> <p>_____ Triceps and chest subcutaneous fat _____ Quadriceps and deltoid muscle</p> <p>_____ Ankle edema _____ Sacral edema</p> <p>_____ Ascites</p>
SGA RANKING	<p>A= Normal/Well Nourished</p> <p>B= Moderate/ Suspected of being malnourished</p> <p>C=Severely Malnourished</p>

Figure 1. Features of the Subjective Global Assessment used in the intensive care unit¹

¹ Based on Detsky et al⁴

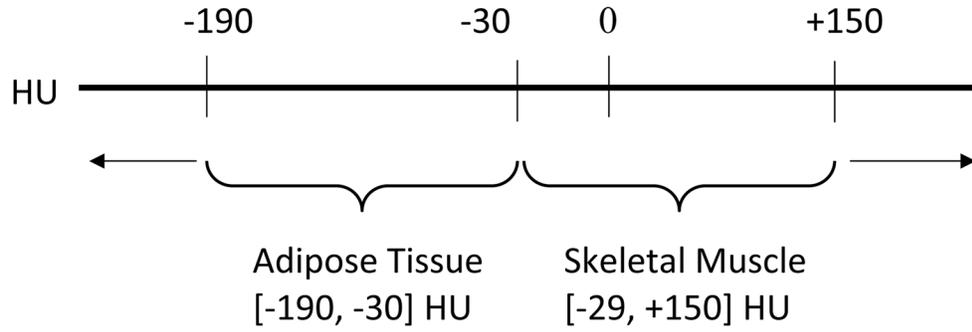


Figure 2.

Definition and ranges for Hounsfield units used for tissue quantification

The Hounsfield scale is a quantitative scale for describing radiodensity and used in the application of computed axial tomography. It reflects the linear transformation of the attenuation coefficient measurement in which the radiodensity of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU) and the radiodensity of air STP is defined as -1000 HU. HU values range from -29 to +150 for skeletal muscle and -190 to -30 for adipose tissue. Based on Prado et al.⁹

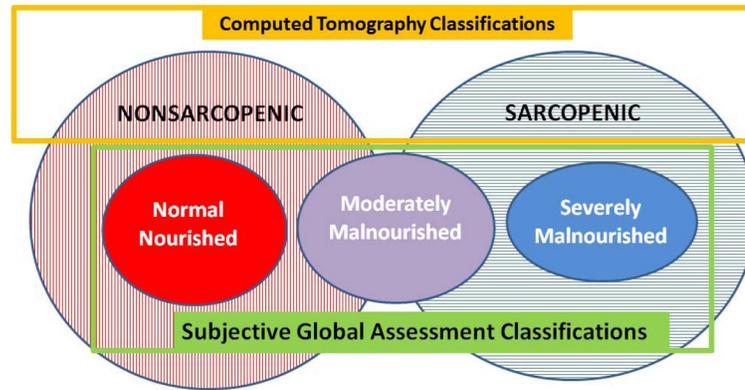


Figure 3. Conceptual model of exclusivity and overlap between body composition using computed tomography and nutritional status classified by subjective global assessment

Table 1

Clinical characteristics stratified by nutritional status for eligible patients (n=56)

Variable	Normally nourished (N=30)	Malnourished ^I (N=26)	P-value
Age			
(mean ± SD)	58.5 ± 14.6	60.0 ± 17.0	0.73
Sex			
Female	12 (40%)	12 (46%)	0.64
Male	18 (60%)	14 (54%)	
Race/Ethnicity			
White	9 (30%)	13 (50%)	0.12
Black	14 (47%)	8 (31%)	0.22
Other	7 (23%)	5 (19%)	0.75
Admission body weight			
(mean ± SD)	86.3 ± 17.0	75.0 ± 16.5	0.02
Body Mass Index			
(mean ± SD)	29.6 ± 6.3	26.7 ± 4.8	0.02
(range)	20.3 – 44.8	16.3 – 34.9	
Underweight (BMI < 18.5)			
N (%)	0 (0%)	2 (8%)	0.21
Normal weight (BMI 18.5–25.0)			
N (%)	8 (27%)	6 (23%)	0.76
Overweight (BMI 25.1–29.9)			
N (%)	9 (30%)	12 (46%)	0.07
Obese^a(BMI ≥ 30.0)			
N (%)	13 (43%)	6 (23%)	0.33
ICU diagnosis-			
Infection/Sepsis	14 (46%)	6 (23%)	0.07
Gastrointestinal related	6 (20%)	12 (46%)	0.04
Cancer related	5 (17%)	7 (27%)	0.35
Other	5 (17%)	1 (4%)	0.20
APACHE II Score			
(mean ± SD)	25 ± 9	27 ± 6	0.45
Hospital length of stay²			
(mean ± SD)	42.4 ± 30.0	39.8 ± 27.0	0.93
ICU length of stay²			
(mean ± SD)	29.1 ± 26.7	29.8 ± 25.9	0.63

Variable	Normally nourished (N=30)	Malnourished ¹ (N=26)	P-value
Discharge status			
Home	8 (27%)	5 (18%)	0.51
Skilled Nursing Facility	13 (43%)	4 (15%)	0.02
Hospice/Death	9 (30%)	17 (65%)	0.008

¹Patients classified as moderate (n= 25) and severe (n=1) were combined for more meaningful comparisons.

²Values were log transformed

Comparing body composition variables and sarcopenia prevalence when CT imaging is completed within +/- 14, 10 and 7 days of admission Subjective Global Assessment

Table 2

	Group 1 SGA and CT imaging +/- 14 days N=56			Group 2 SGA and CT imaging +/- 10 days ¹ N=48			Group 3 SGA and CT imaging +/- 7 days N=36		
	Normal N=30	Malnourished N=26	P value	Normal N=24	Malnourished N=24	P value	Normal n=14	Malnourished n=22	P value
Lumbar muscle cross-sectional area² (cm ²)	135.1 ± 32.8	120.8 ± 36.9	0.19	134.4 ± 35.9	123.1 ± 36.7	0.34	135.2 ± 41.4	122.9 ± 38.0	0.34
Estimated total lean body mass^{2,3} (kg)	46.6 ± 9.8	42.3 ± 11.1	0.19	46.4 ± 10.8	43.0 ± 11.0	0.34	46.6 ± 12.4	42.9 ± 11.4	0.34
Estimated skeletal muscle index^{2,4} (cm ² /m ²)	46.0 ± 9.7	43.4 ± 10.5	0.37	45.8 ± 10.7	43.6 ± 10.5	0.28	45.3 ± 10.7	43.4 ± 10.9	0.23
Sarcopenia⁵ N (%)	18 (60%)	16 (62%)	0.91	14 (58%)	15 (62%)	0.77	7 (50%)	13 (59%)	0.59

¹ Patients from Group 2 are included in Group 1 analyses and patients in Group 3 are included in Group 1 and 2 analyses.

² Adjusted for age

³ Calculated from regression equation from Mourtzakis et al (ref): whole-body lean mass (kg) = 0.30 X [(skeletal muscle at L3 region using CT (cm²)] + 6.06

⁴ Lean mass area at the L3 region divided by height (m²).

⁵ Defined as estimated skeletal muscle index < 38.5 cm²/m² for women and < 52.4 cm²/m² for men.