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Frailty and skeletal muscle in older adults with cancer☆

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ABSTRACT

Objective: Computerized tomography (CT) imaging is routine in oncologic care and can be used to measure muscle quantity and composition that may improve prognostic assessment of older patients. This study examines the association of single-slice CT-assessed muscle measurements with a frailty index in older adults with cancer.
Materials and Methods: Using the Carolina Senior Registry, we identified patients with CT imaging within 60 days ± of geriatric assessment (GA). A 36-item Carolina Frailty Index was calculated. Cross-sectional skeletal muscle area (SMA) and Skeletal Muscle Density (SMD) were analyzed from CT scan L3 lumbar segments. SMA and patient height (m^2) were used to calculate skeletal muscle index (SMI). Skeletal Muscle Gauge (SMG) was calculated by multiplying SMI × SMD.
Results: Of the 162 patients, mean age 73, 53% were robust, 27% pre-frail, and 21% frail. Significant differences were found between robust and frail patients for SMD (29.4 vs 24.1 HU, $p < 0.001$) and SMG (1188 vs 922 AU, $p = 0.003$), but not SMI (41.9 vs 39.5 cm^2/m^2, $p = 0.29$). After controlling for age and gender, for every 5 unit decrease in SMD, the prevalence ratio of frailty increased by 20% (PR = 1.20 [1.09, 1.32]) while the prevalence of frailty did not differ based on SMI.
Conclusions: Muscle mass (measured as SMI) was poorly associated with a GA-based frailty index. Muscle density, which reflects muscle lipid content, was more associated with frailty. Although frailty and loss of muscle mass are both age-related conditions that are predictive of adverse outcomes, our results suggest they are separate entities.

1. Introduction

Cancer is primarily a disease of older adults, with the majority of new cancer diagnoses and cancer deaths occurring in patients over the age of 65 [1]. By 2030, 70% of all new cancer diagnoses will occur in adults over 65 years of age [2]. The treatment of older adults with cancer is complicated by the heterogeneous aging process and is associated with a wide range in treatment tolerability. Frailty is a medical condition? status? with multiple causes and contributors that ultimately increase an individual's vulnerability for adverse outcomes such as increased dependency and/or death [3,4]. Many frail older adults lack the physiologic reserve to recover from surgical operations or from the acute toxicities of chemotherapy or radiation [5,6]. Several methods exist for defining frailty, yet frailty assessment is rarely employed in routine clinical practice and decision-making. Recent publications have highlighted the benefits of using a frailty index in older adults with cancer that categorizes patients as robust (or non-frail), pre-frail, and frail, and have shown it to be predictive of all-cause mortality, as well as increased severe chemotherapy toxicity and hospitalizations [7,8]. Developing more precise and easier methods to identify frail, at-risk older adults with cancer is a focus of ongoing research [9,10].

Low muscle mass, commonly termed sarcopenia within oncology, is highly prevalent in older adults, and has been associated with increased chemotherapy toxicity, surgical complications, and mortality [11–14]. Computerized tomography (CT) imaging, utilized in routine oncologic care for staging, disease monitoring, and surveillance, can also be used to assess muscle mass without significant resource allocation. Consistent methods for utilizing CT imaging to achieve practical and precise measurements of body composition have been developed [15,16]. CT-

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based body composition measures represent a nascent opportunity to improve the assessment of older patients and provide additional prognostic information, including the identification of frail, at-risk patients.

This study examines associations between single-slice, CT-assessed skeletal muscle measurements and a frailty index derived from a brief geriatric assessment. Our specific focus is on older adults diagnosed with cancer, in which treatment decisions require careful attention to prognosis and the potential for treatment toxicities. As both frailty and low muscle mass are highly prevalent age-related conditions that are associated with adverse outcomes, we sought to better understand their interrelationship.

2. Methods

2.1. Participants

The sample for this cross-sectional study was derived from the Carolina Senior Registry (CSR) (NCT01137825). The CSR was developed in 2009 as a clinic-based registry to collect geriatric assessment (GA) data on older adults (65+) with cancer. The CSR utilizes a well-validated GA tool designed specifically for use with older adults with cancer [17–19]. For a detailed description of the CSR, including recruiting procedures, sampling methods, and the performance of assessments, please see Williams et al. [19] Using electronic medical records, we identified CSR patients recruited through outpatient clinics of the North Carolina Cancer Hospital that had CT abdominal imaging within 60 days of completing the GA. This study was approved by the Institutional Review Board of the University of North Carolina (IRB #15-1524).

2.2. Frailty Index

The primary outcome in our study is frailty, as determined by the 36-item Carolina Frailty Index (CFI). This cancer-specific frailty index was created based on the principles of deficit accumulation and methodology reported by Searle et al. and uses 36 items from the GA [8,20,21]. The CFI includes multiple items pertaining to deficits in basic and instrumental activities of daily living, comorbidities, cognition, depression, and nutrition. Guerard et al. showed that the CFI was predictive of all-cause and cancer-specific mortality in older adults with cancer independent of cancer stage, cancer type, age, sex, and number of comorbidities [8]. A similarly constructed frailty index was also associated with increased grade 3/4 chemotherapy toxicity and hospitalizations in older adults undergoing chemotherapy [7]. A list of CFI variables is provided in Supplement 1. Each variable/deficit is rated between 0 and 1, where a higher score indicates greater frailty. A score is achieved by calculating the total number of deficits divided by the total number of variables assessed. For instance, if 8 deficits are identified in a patient of 36 possible deficits, then that person's frailty index is $8/36 = 0.22$. The CFI is a continuous variable with a range of 0–1 and categorized patients as robust (<0.2), pre-frail (0.2–0.35), or frail (>0.35) based on cumulative deficit counts. Patients were included in our final sample if they answered at least half [18] of the 36 CFI variables.

2.3. Body Composition Analysis

Abdominal CT images were acquired from the UNC Picture Archiving and Communication office. Using AGFA-Impax (version 6) radiological software (Mortsel, Belgium), transverse sections at the L3 vertebral level were identified and extracted for external analysis. Automated Body composition Analyzer using Computed tomography image Segmentation (ABACS) software was then used to analyze the L3 lumbar segments [15,22]. The software recognizes muscle tissue based on density thresholds between −29 and +150 Hounsfield Units (HU) and provides an unbiased estimation of the cross-sectional skeletal muscle area. The software also uses a priori information about the L3 muscle shape to avoid mislabeling parts of the neighboring organs that have HU values similar to those of muscle tissue. Images were then reviewed and corrected for accuracy and verified by two authors (GRW, SSS). The measured skeletal muscle area (SMA) was then normalized for height (in meters) to calculate a skeletal muscle index (SMI) (cm^2/m^2). Skeletal Muscle Density (SMD) was derived by averaging the HU of skeletal muscle of the cross-sectional image. The attenuation of skeletal muscle is a non-invasive radiological technique to indirectly assess muscle fat content, known as myosteatosis. The density of skeletal muscle is inversely related to muscle fat content [23]. Fig. 1 illustrates the visual differences of these various muscle measures. Images A and B show two patients with identical BMI but varying skeletal muscle quantity, with image B representing a patient with low muscle mass (low SMI). Images C and D represent two patients with similar BMI that primarily differ in terms of muscle density, as shown by the color variation.

To integrate both the quantity (SMI) and attenuation/quality (SMD), we calculated the Skeletal Muscle Gauge (SMG) by multiplying SMI × SMD. The actual units for SMG are (cm^2 tissue area × average HU)/(m^2 height); for simplicity we chose to represent them as arbitrary units (AU). This method was first introduced by Weinberg et al. and showed better correlation of SMG with aging than either SMD or SMI alone [24]. SMG has also been associated with toxicity and survival in patients with metastatic breast cancer receiving first-line taxane therapy [25].

2.4. Statistical Analysis

Descriptive statistics were used to characterize the baseline characteristics of the sample. Kruskall-Wallis and Wilcoxon non-parametric tests were used to compare distributions of skeletal muscle measures between frailty groups and gender. Pearson correlation coefficients were used to evaluate associations of continuous CFI with skeletal muscle measures. Prevalence ratios (PR) and 95% confidence interval (CI) for the prevalence of frailty were calculated using Poisson regression [26], with both unadjusted and adjusted (age, gender, BMI) PR

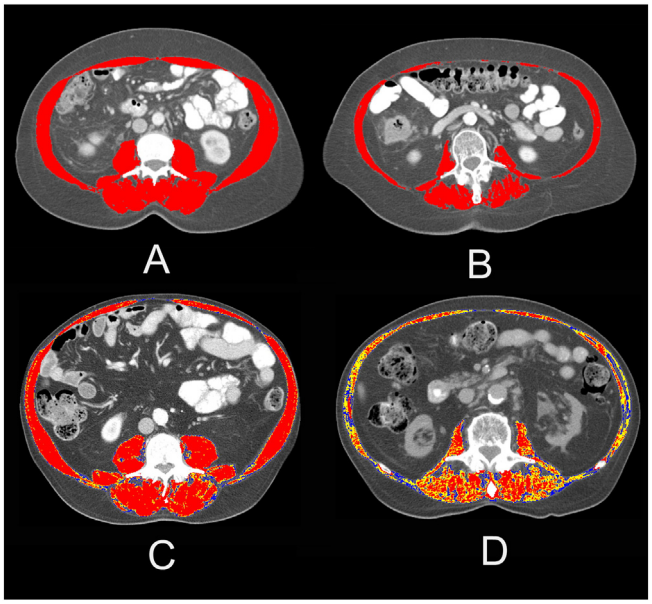

Fig. 1. Examples of representative abdominal computerized tomography (ct) images. Images A and B illustrate differences in skeletal muscle mass in patients with the same BMI (BMI = 25). For the top portion of the figure, the red area highlights the skeletal muscle area between −29 and +150 Hounsfield Units (HU). Images C and D represent two patients with contrasting values of muscle radiodensity. For the lower portion of the figure, the red area represents skeletal muscle within the normal range of radiodensity (+30 to +150 HU), the yellow represents +1 to +29 HU, and the blue represents 0 to −29 HU. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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