

“Influence of Body Composition Assessed by Computed Tomography on Mortality in Older Adults Undergoing Hematopoietic Stem Cell Transplantation”

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Abstract

Aim: The incidence of most hematologic malignancies increases with age. Hematopoietic stem cell transplantation (HSCT) provides a potentially life-prolonging or curative option for many patients in this scenario. Limited data is available on muscle mass and density assessed from CT-images on outcomes after HSCT. We aimed to evaluate the influence of body composition on morbidity and mortality in older adults undergoing (HSCT).

Methods: Retrospective longitudinal study conducted with 50 patients ≥ 60 years undergoing HSCT at Hospital Israelita Albert Einstein, São Paulo. Body composition was assessed by chest computed tomography and treatment related mortality, graft versus host disease, neutrophil grafting, and overall survival were analyzed.

Results: 148 HSCT patients were evaluated, 50 patients were eligible: 60% with autologous and 40% with allogeneic transplantation. Body mass index in patients was (female: 26.9 ± 4.7 kg/m²; 30.1 ± 4.9 kg/m²) - autologous and (female: 24.3 ± 5.15 kg/m²; male: 26.4 ± 2.0 kg/m²) - allogeneic. In autologous transplant group, we found a positive association between age and death risk with an increase of 63.5% in this risk ($p=0.006$) and also Karnofsky performance scale with decrease of 11.9% in death risk ($p<0.001$). A negative association between muscle radiodensity and death risk was observed in allogeneic transplantation patients with risk decrease of 20.1% ($p = 0.032$). We found a positive association between T4 muscle area and radiodensity with risk of acute graft versus host disease ($p=0.028$).

Conclusion: In population studied, body composition assessed by chest tomography showed the importance of radiodensity for better prognosis.

Introduction

Hematopoietic stem cell transplantation (HSCT) in older adults increases progression free and overall survival. Older adults are at high risk for diseases related to age and geriatric syndromes, which are generally associated with worse outcomes^{1,2}. However, the research is limited in the pre-transplant period.

Among geriatric comorbidities, one of the most important is sarcopenia, a syndrome of multifactorial etiology, which consists of loss of muscle mass, loss of strength, and decreased functional ability. It is present in approximately 50–90% of patients with cancer. It is associated with increases in chemotherapy toxicity, postoperative complications, and reduced overall survival. The coexistence between sarcopenia and frailty ranges from 50 to 70% of patients in this age group.³

The main imaging modalities used for detection of sarcopenia are dual-energy X-ray absorptiometry (DXA), bioimpedance, and abdominal computed tomography, all having limitations in the elderly

undergoing HSCT. ⁴

Chest computed tomography (CCT) is routinely performed in HSCT candidates with precise quantification of muscle mass and differentiation of muscle and adipose tissue. There is good correlation and differentiation between adipose tissue and whole body skeletal muscle mass^{4,5} In addition, the muscle radiodensity parameter, defined as mean radiation attenuation in Hounsfield units in the pectoral muscle area, correlates well with muscle quality. ⁶

The aim of this study was to identify whether the quantitative and qualitative data of muscle mass, obtained by evaluation of CCT, are associated with morbidity and mortality in older patients undergoing HSCT.

Materials And Methods

Patients

We retrospectively evaluated medical records from 148 older patients submitted to HSCT. Inclusion criteria were patients ages ≥ 60 years with a diagnosis of hematologic malignancy confirmed by pathological examination who were submitted to chest computed tomography in the period from 60 days before to 21 days after HSCT. All patients < 60 years-old and/or without CCT were excluded of this study.

This study was approved by the institutional review board as minimal risk study and the University of Alberta Health Research Ethics Board.

Clinical Data

All patients were evaluated for the following topics:

- Graft versus host disease (GVHD) only in allogeneic transplants;
- Neutrophil grafting, which corresponds to the time to neutrophil grafting (defined as the first of three consecutive days when neutrophils exceeded $0.5 \times 10^9/L$);
- Treatment related mortality (TRM), and death from any cause that has not been from progression of disease within 30 days after HSCT;
- Overall survival (OS), calculated from date of HSCT to date of death from any cause or until last outpatient follow-up.
- The strength assessment of the dominant upper limb was assessed by a validated and adjustable strength dynamometer (Hand grip). After 3 measurements and an average between them. This test was applied during the patient's oncogeriatric evaluation before HSCT, only starting in 2012, which justifies not all patients having undergone it.

Body composition

Body composition was assessed by analyzing the difference in radiation absorption of different body tissues. We used CCT image, taken 60 days before and 21 days after HSCT, stored in a PACS Vue Motion system (image file) using SliceOmatic® Software Version 5.0 software (TomoVision, Montreal, Quebec, Canada).^{5,7-9}

Classification of sarcopenia performed by measurements for skeletal muscle mass in the third lumbar vertebra (L3) is the most studied method. However, L3 slice has not been included in several clinical computer tomography (CT) protocols. Derstine et al., demonstrated while L3 remains the ideal location for skeletal muscle measurement, results indicate that (in order) L2, L4, L5, L1, T12, T11, and T10 are the preferred alternatives when L3 is unavailable.¹⁰

Therefore, we used CT cutting at the level of the fourth thoracic vertebra (T4) to analyze subcutaneous fatty tissue, muscle tissue of the major and minor pectoralis muscle, latissimus dorsi muscle, subscapularis muscle, intercostal muscle, infraspinatus muscle, greater rhomboid muscle, trapezius muscle, erector spinae muscle, and larger round muscle.¹¹ All images were analyzed by experienced examiner through double-checking at the University of Alberta, in Canada.

Quantification of muscle mass and subcutaneous adipose tissue were performed by adding cross-sectional areas (cm^2) calculated for each tissue and multiplying by the pixel surface area. Average muscle area was normalized to height in meters squared (m^2) and expressed in skeletal muscle index (SMI) (cm^2/m^2).^{12,13} Mean muscle radiodensity in Hounsfield units (HU) was reported for the entire muscle area in the fourth thoracic vertebra. (Figs. 1 and 2).

The amount of radiation absorbed by the tissue was measured in Hounsfield units (HU). The amount of X-ray energy absorbed by water is set to 0 HU. The bone percentage absorption coefficient is equivalent to 100 HU and for air is -1000 HU. Skeletal muscle is characterized by a range of -29 to 150 HU and subcutaneous adipose tissue by a range of -190 to -30 HU.⁹

Statistical analysis

Categorical variables were described by absolute frequencies and percentages. Quantitative variables were described by means and standard deviations (SD). To access variables related to overall survival or GVHD we used Cox proportional hazard models separately by type of transplant (Allogeneic or Autologous), in which models with body composition measures were controlled by sex and proportionality of risks were assessed with Schoenfeld residuals. Results were presented as hazard ratios, 95% confidence intervals and p-values. Analyses were performed with SPSS and R, with a significance level of 5%.

Results

Of the 148 patients evaluated, only 50 were included according to the eligibility criteria: 30 (60%) patients with autologous transplantation and 20 (40%) with allogeneic transplantation. Autologous transplant

patients had a mean age of 67.8 ± 13.6 years and 18 (60%) were men. Allogeneic transplant patients had a mean age of 67.9 ± 5.5 years and 13 (65%) were men. The predominant diagnosis in patients undergone allogeneic transplant was leukemia and lymphoma for patients undergoing autologous transplantation. Clinical follow-up time ranged from 0.3 to 95.1 months, with a median of 3.2 months in the allogeneic transplant group and 17.0 months in the autologous transplant group. The average KPS for allogeneic transplant patients was $85.0 \pm 13.6\%$ and $88.3 \pm 13.9\%$ for those undergoing autologous transplantation.

The mean body mass index (BMI) in female patients undergone autologous transplantation and allogeneic was $26.9 \pm 4.7 \text{ kg/m}^2$ and $24.3 \pm 5.1 \text{ kg/m}^2$, respectively. We found in the allogeneic transplant female group 28.6% of eutrophic and 28.6% of obesity, while 25.0% eutrophic and 41.7% obesity in the autologous transplant group. For male patients undergone autologous and allogeneic transplantation the mean BMI was $30.1 \pm 4.9 \text{ kg/m}^2$ and $26.4 \pm 2.0 \text{ kg/m}^2$, respectively. We found in the allogeneic transplant male group 76.9% of eutrophic and 15.4% of obesity, while 27.8% eutrophic and 66.7% obesity in the autologous transplant group., However, there was no significant association between BMI and other variables analyzed in this study.

Body assessment data are described in Table 1. No significant differences were observed between sexes.

In regards to events related to allogeneic transplantation, we observed acute GVHD in (40%) of patients: five (62.5%) grade II cases, one (12.5%) grade III case, and two (25%) grade IV cases. Neutrophil grafting occurred in 19 (95%) patients and did not occur in one (5%) patient.

Twenty-five (50%) patients in the sample died, of those 15 (60%) underwent allogeneic transplantation and 10 (40%) underwent autologous transplantation due to TRM for all age groups. At 1 year, the TRM was 20% for autologous transplantation and 35% for allogeneic.

A multiple model was adjusted to assess the radiodensity association and risk of death by controlling for the age of the patients, the KPS index and sex with an estimated risk decrease of 20.1% for each unit increased in radiodensity ($p = 0.032$), according to Table 2. No association was found with autologous transplantation.

In the autologous transplant group, in the multiple model we found a positive association between age and death risk with an increase of 63.5% in this risk for each year of age increased ($p = 0.006$), according to Table 3. We also found negative association with KPS scores, with an estimated decrease of 11.9% in the risk associated with an increase of 1% in the KPS ($p < 0.001$).

We found a positive association between T4 muscle area and radiodensity with risk of acute GVHD ($p = 0.028$). A multiple regression model, adjusted to assess the association of radiodensity and acute GVHD controlling for kinship degree and sex, shows evidence of a significant association with radiodensity with an addition of 25.7% in the risk of acute GVHD for each unit increased in radiodensity ($p = 0.029$), see Table 4.

Discussion

In this report, assessment of body composition by CCT in older patients undergone allogeneic transplantation showed that high muscle radiodensity was associated with higher risk of death persisting even after adjusting for age, KPS, and sex e greater risk of acute GVHD controlling for kinship degree and sex. While the age had a positive association with risk of death only in patients undergone autologous transplantation.

Hematologic malignancies are a group of diseases that are associated with aging. With the growth of the older population in Brazil, more candidates will be eligible for HSCT.⁽¹⁴⁾ This therapeutic modality has high morbidity and mortality, associated with a high incidence of acute and chronic complications.^{2,15,16} Our Onco-hematology service is accredited by the Foundation for the Accreditation of Cellular Therapy (FACT)⁽¹⁷⁾, performing a significant number of HSCT in older patients. All patients undergone oncogeriatric clinical evaluation before the procedure.^{18,19}

Age should not be used as an exclusion criterion in isolation as a limiting factor for transplantation once based on currently data, age alone is not the best predictor of toxicity and outcomes; rather, the comorbidities and functional status of the older patient are likely better predictors of toxicity than chronologic age in both the autologous and allogeneic setting. A comprehensive geriatric assessment (CGA) in older adults being considered for either an autologous and allogeneic transplant may identify additional problems or geriatric syndromes, which may not be detected during the standard pre-transplant evaluation.^{20,21} The measurement of skeletal muscle mass can be a tool of choice for evaluation of frailty.²²

In regard to outcomes by transplantation type, studies suggest that elderly patients undergone HSCT are at high risk for treatment-related mortality. Our death results related to TRM after one year were similar to those found in the literature. We observed a rate of 20% at 1 year for autologous transplantation, whereas in recent studies with the adoption of better supportive care and the advent of reduced-intensity conditioning, TRM rates for older patients of 4–12%. TRM rate of 35% for allogeneic in our study that in literature varying between 33% and 35%.²

Regarding BMI, our data showed few malnourished patients in pre-transplantation, as in other studies.²³ Although some studies have shown a positive association between BMI and overall survival, we did not find such an association. BMI alone does not properly evaluate lean mass and fat mass changes and does not reflect patients' body composition, which helps to explain conflicting literature results for HSCT outcomes in the elderly when only BMI or is considered.^{24,25}

Currently, the measurement of body composition by analysis of muscle area at the fourth thoracic vertebra level is not validated, although it has already been used in other studies. Future studies are still needed to determine the relationship between various cutoff points of the various vertebral levels and clinical outcomes.¹⁰

The use of abdominal CT scans is not routinely done for staging in HSCT, only CCT. CCT, besides being routinely performed in this group of patients, was used for assessment of muscle mass, since it has good correlation with total skeletal muscle mass.⁴

In allogeneic HSCT patients, our results demonstrated a significant association between T4 muscle area ($p = 0.015$) and radiodensity ($p = 0.028$) with chance of GVHD. Our body composition findings are conflicting with the literature. Kyle *et al.* demonstrated that changes in lean mass were significantly associated with GVHD. Chughtai *et al.* did not demonstrate a significant association between muscle area and acute GVHD. In allogeneic transplant pediatric patients with long-term survival, there was no such relationship, either.^{26,27} However, none of these studies evaluate the older adults or reported radiodensity. There is no evidence of association between radiodensity and risk of death in patients undergoing autologous HSCT. We also identified, in the allogeneic transplant group, an association between radiodensity and risk of death after controlling for age, sex, and KPS ($p = 0.032$), with a reduction in risk of death by 20.1%. In patients with melanoma, kidney cancer, colorectal cancer, and follicular lymphoma, lower muscle radiodensity is found when there are fewer muscle fibers and more fatty infiltration and is associated with worse survival. However, our study did not demonstrate this result.²⁸ We found no studies in the literature showing an association between radiodensity and GVHD. Our results showed a positive relationship between GVHD and radiodensity.

In evaluating BMI by categories, eutrophic patients who received allogeneic transplantation had a positive association with neutrophil recovery. Although there are studies showing earlier recovery in patients with high BMI in underweight patients, this finding occurred 3 days and 4 days later than in normal and overweight patients, respectively.²⁹

The influence of age on transplant outcomes remains a controversy. Until two decades ago, 60 years old was considered maximum age for autologous transplantation and 55 for allogeneic. After the introduction of reduced intensity conditioning regimens, age has been shown to have minimal influence on outcomes. Unlike other studies, among our patients, in which age ranged between 60 and 76 years with a median of 67 years, we found a significant association with mortality only in cases of autologous transplantation.³⁰

Our study findings suggest that there is no significant association between age, KPS, and risk of death in allogeneic HSCT, although these associations were significant in patients undergone autologous HSCT in either the simple or multiple models. One of the hypotheses to explain this result would be that patients submitted to allogeneic HSCT, in principle, have more severe underlying diseases and, as a result, have already undergone several treatment lines prior to transplantation. This finding suggests that the severity of the underlying disease has a greater impact than age and KPS on morbidity and mortality, as described in other studies.²⁵

Although older adults have been identified as being vulnerable to the side effects of cancer treatment, few studies have specifically incorporated health condition measurement metrics in addition to ECOG or

Karnofsky functional status to identify those at higher risk.^{1,19}

Albeit our sample has been the largest case series published, our small number of patients was a limiting factor for quantitative analysis with higher power, however the qualitative findings and study trends encouraged us to evaluate the results.

In future prospective studies, assessment of body composition by CCT should be performed early in the initial staging and during treatment to increase the sensitivity of our assessment of body composition and variation during treatment.

The risks and benefits of HSCT in older adults remain poorly defined in the transplant community. Our evidence that the use of chest CT as a body assessment tool in the pre-transplantation clinical routine is extremely relevant, as this exam is part of patient diagnosis and follow-up as a tool that could be explored to estimate morbidity and mortality of these patients.

Declarations

A) There is no funding that have supported this work.

B) The authors have declared that no competing interests exist.

C) The dataset underlying the findings in the manuscript (i.e. the values behind statistics, figures, and tables) to be freely available to other researcher.

D) Statement of authorship: Ludmila de Oliveira Muniz Koch, Andrea Z Pereira, and Reynaldo Jesus Garcia equally contributed to the conception and design of the research; Nelson Hamerschlak contributed to the design of the research; Adriano Tachibana, and Adham do Amaral e Castro contributed to the acquisition and analysis of the data; Elivane da Silva Victor contributed to analysis and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript agree to be fully accountable for ensuring the integrity and accuracy of the work, read and approved the final manuscript.

E) This study was approved by the our institutional review board as a minimal risk study and the University of Alberta Health Research Ethics Board and that it conforms to the provisions of the Declaration of Helsinki

F) c) There is no informed consent term since it is a retrospective study and the patient's anonymity has been preserved.

G) The author and co-authors grant the Publisher the sole and exclusive license of the full copyright in the Contribution, which license the Publisher hereby accepts.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

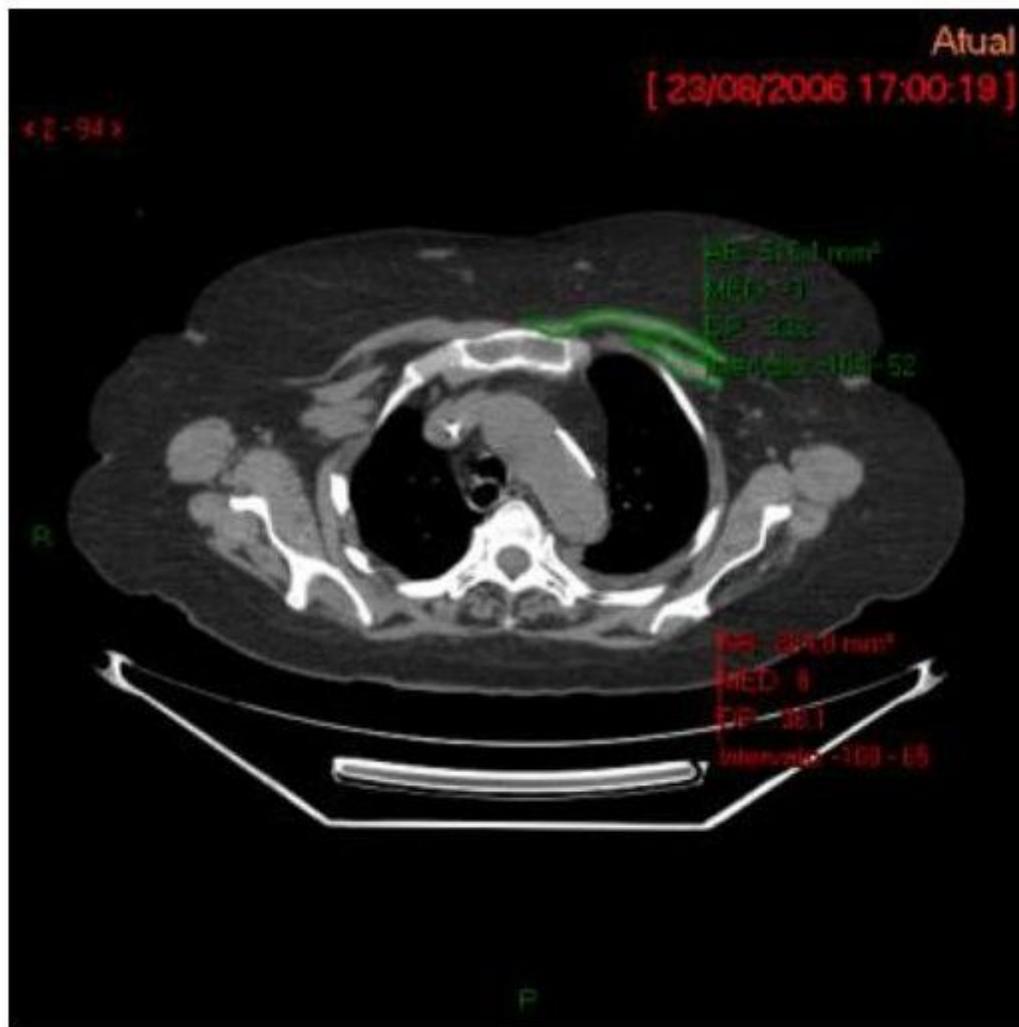


Figure 1

Image example of CT on T4 level axial plane used for pectoralis area measurements.

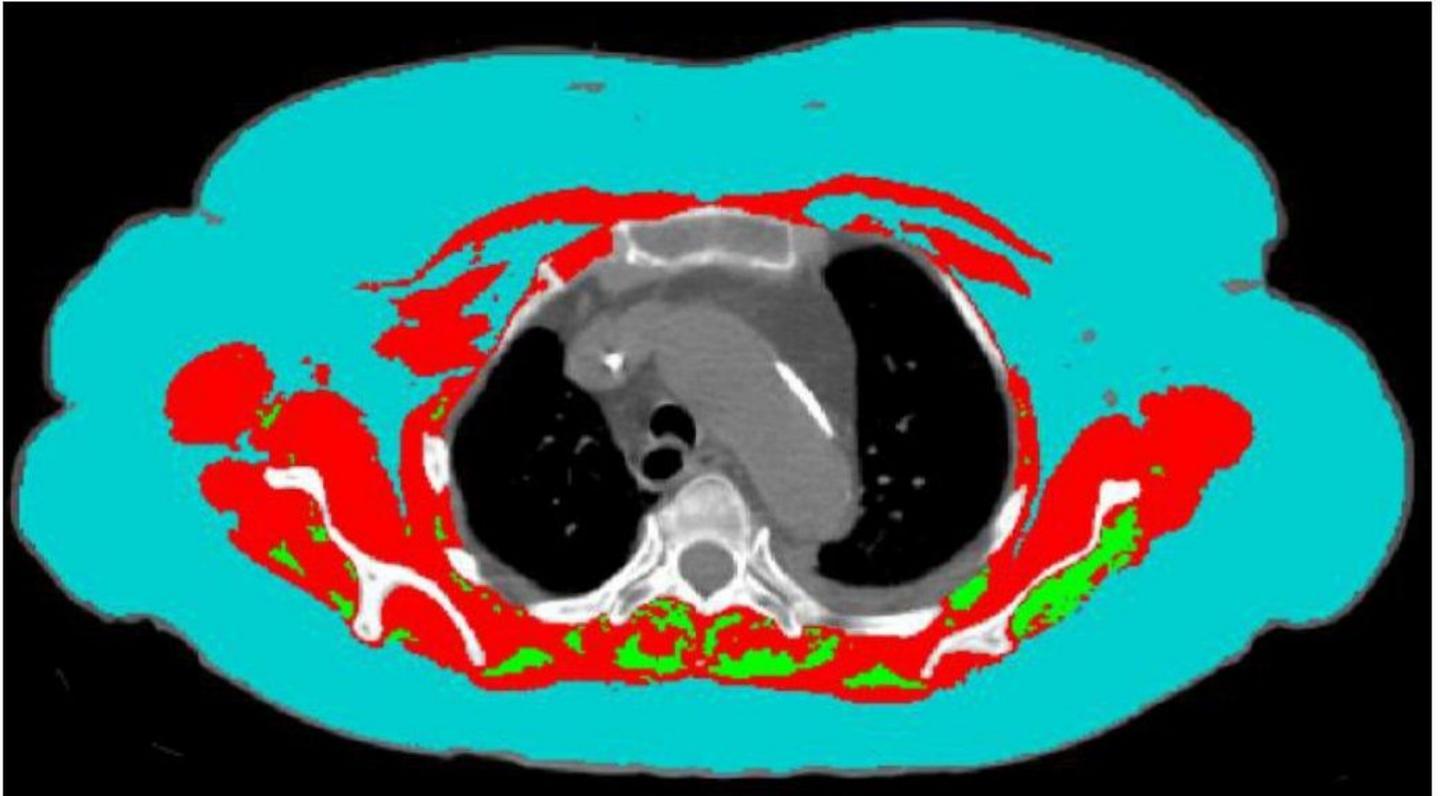


Figure 2

Image example of CT on T4 level axial plane, analyzed with sliceomatic®: the red color indicates the skeletal muscle; green indicates the intramuscular adipose tissue and blue the subcutaneous adipose tissue

Supplementary Files

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