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Journal

Skeletal Radiology, 53(3)

ISSN

0364-2348

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Publication Date

2024-03-01

DOI

10.1007/s00256-023-04438-w

Peer reviewed

HHS Public Access

Author manuscript

Skeletal Radiol. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

Skeletal Radiol. 2024 March ; 53(3): 515–524. doi:10.1007/s00256-023-04438-w.

Clinical, functional, and opportunistic CT metrics of sarcopenia at the point of imaging care: analysis of all-cause mortality

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Abstract

Purpose—This study examines clinical, functional, and CT metrics of sarcopenia and all-cause mortality in older adults undergoing outpatient imaging.

Methods—The study included outpatients ≥ 65 years of age undergoing CT or PET/CT at a tertiary care institution. Assessments included screening questionnaires for sarcopenia (SARC-F) and frailty (FRAIL scale), and measurements of grip strength and usual gait speed (6 m course). Skeletal muscle area (SMA), index (SMI, area/height^2) and density (SMD) were measured on CT at T12 and L3. A modified SMI was also examined (SMI-m, area/height). Mortality risk was studied with Cox proportional hazard analysis.

Results—The study included 416 patients; mean age 73.8 years [sd 6.2]; mean follow-up 2.9 years (sd 1.34). Abnormal grip, SARC-F, and FRAIL scale assessments were associated with higher mortality risk (HR [95%CI] = 2.0 [1.4–2.9], 1.6 [1.1–2.3], 2.0 [1.4–2.8]). Adjusting for age, higher L3-SMA, T12-SMA, T12-SMI and T12-SMI-m were associated with lower mortality risk (HR [95%CI] = 0.80 [0.65–0.90], 0.76 [0.64–0.90], 0.84 [0.70–1.00], and 0.80 [0.67–0.90], respectively). T12-SMD and L3-SMD were not predictive of mortality. After adjusting for abnormal grip strength and FRAIL scale assessments, T12-SMA and T12-SMI-m remained predictive of mortality risk (HR [95%CI] = 0.83 [0.70–1.00] and 0.80 [0.67–0.97], respectively).

Conclusion—CT areal metrics were weaker predictors of all-cause mortality than clinical and functional metrics of sarcopenia in our older patient cohort; a CT density metric (SMD) was not predictive. Of areal CT metrics, SMI (area/height^2) appeared to be less effective than non-normalized SMA or SMA normalized by height^1.

Keywords

Sarcopenia; Frailty; Muscle; CT; Opportunistic CT; Screening; Mortality

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Conflicts of interest The authors declare they have no conflicts of interest.

Introduction

Interest in sarcopenia has grown in parallel with wider recognition of the prognostic significance of sarcopenia in many clinical settings. Current definitions of sarcopenia are multidimensional, including markers of low muscle strength (dynapenia) and low physical performance, in addition to measures of reduced muscle mass (myopenia). Working definitions for sarcopenia have been developed by various groups. The recommendations from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) have achieved the widest use [1]. Presently, the various working definitions for sarcopenia exhibit poor classification agreement [2–5].

Despite variances in definitions, individual indices of sarcopenia have prognostic value [5]. A convenient, validated questionnaire exists to screen for sarcopenia, SARC-F [6]. The SARC-F alone has been shown to predict all-cause and cause-specific mortality risk [7, 8].

Frailty is a related but broader clinical syndrome than sarcopenia, encompassing phenotypes associated with biologic aging that place patients at risk for disability and poor health outcomes. Frailty is a construct that, like sarcopenia, encompasses strength and physical function, but also other dimensions including cognitive, psychological, and social factors [9]. A 5-item FRAIL scale is a simple and convenient screening tool for frailty that can capture essential elements of more comprehensive assessments for frailty [10, 11].

DXA is a convenient method to measure muscle mass in clinical and research settings. Appendicular lean mass (ALM) based on DXA, in particular, has been widely used in studies and working definitions of sarcopenia. Muscle metrics are also readily available on CT, commonly based on analysis of axial imaging at the L3 or T12 levels [12]. CT-derived skeletal muscle density (SMD), as a surrogate of myosteatosis, may reflect muscle quality [13]. Skeletal muscle area (SMA) measured on axial CT is another common muscle metric, often normalized to the square of patient height (area/height2), and referred to as the skeletal muscle index (SMI) [14]. CT muscle measures have been shown to predict mortality risk in patients after hip fracture [15], in patients with cancer [16], and in older adults [17].

Multi-dimensional screening for frailty and sarcopenia can be performed quickly and safely in the Radiology Department at the point of imaging care [18]. The feasibility of such data collection provides the opportunity to examine the relationship of various metrics of frailty and sarcopenia with patient outcomes. This study analyzes risk prediction for all-cause mortality by clinical, functional, and imaging metrics of sarcopenia, with special attention to CT muscle metrics, in a cohort of older adult patients encountered during outpatient imaging.

Methods

Patients

This study was approved by the Institutional Review Board and complied with the Health Insurance Portability and Accountability Act (HIPAA) guidelines. The study included consecutive patients aged 65 years and older who were enrolled before undergoing routine

outpatient CT or PET/CT examinations at a single institution, regardless of clinical indication. There were no exclusion criteria; neither race or ethnicity were considered in the enrollment process.

Clinical evaluation of patients included validated screening questionnaires for sarcopenia (SARC-F) [19] and frailty (FRAIL scale) [20]. Functional evaluation included assessments of grip strength and usual gait speed (6-m course). Grip strength was measured with a calibrated hand-held Jamar dynamometer by a single physician using validated techniques [21]. The functional evaluations were performed by one physician. Mortality was determined using the California Electronic Death Reporting System, which is a centralized database of death record information [22].

CT acquisition and image analysis

Patients were scanned on either a 128-row CT scanner (Somatom Definition AS +, Siemens Healthineers) or a 64-row PET/CT scanner (GE Discovery 690, GE HealthCare). Calibration of the CT scanners was completed daily using a quality assurance phantom to ensure consistency in measurements of tissue density, following specifications of the CT manufacturers and the American College of Radiology. Scans were performed at 120 or 140 kV and reconstructed using filtered back projection and standard body filter. Slice thickness varied depending on the type of study (chest, 2.5–5 mm; abdomen, 1.25–5 mm). 165 of the CT examinations were performed after administration of intravenous contrast (125 mL of iohexol containing 350 mg I/mL). In these cases, recorded muscle density was measured in the portal venous phase and corrected based on published estimates of normal muscle enhancement on contrast-enhanced CT [23].

Muscle segmentation was performed on axial CT images at the T12 level, and when available, at the L3 level, using OsiriX (v7.5.1, Pixmeo, Switzerland) as described previously [24]. SMA (in cm^2) was recorded at L3, and paraspinous muscle area was recorded at T12 (Fig. 1A, B). SMI (in cm^2/m^2) was computed as segmented muscle area divided by patient $height^2$ at T12 and L3 (T12-SMI and L3-SMI, respectively). SMD (in HU) was recorded as the mean CT density of segmented muscle regions at T12 and L3 (T12-SMD and L3-SMD, respectively). An additional CT measure was analyzed: a modified SMI (SMI-m, area/height, in cm^2/m). Muscle segmentations were performed by a musculoskeletal radiologist with four years of experience, with an audit of all images and segmentations by a second musculoskeletal radiologist with 25 years of experience.

Data analysis and statistics

Comparison of sex and metrics of sarcopenia was performed with t-tests and Kruskal–Wallis tests. Univariable survival analysis was performed for clinical, functional, and CT metrics, with dichotomization of patients based on prior published criteria. Specifically, cutoff values for abnormal grip strength were < 27 kg for men and < 16 kg for women [1], and the cutoff value for usual gait speed was < 0.8 m/sec [1]. Diagnostic cutpoints for abnormal CT muscle metrics were taken from healthy reference population studies [25, 26]: for T12-SMI, < 7.8 cm^2/m^2 for women and < 10.9 cm^2/m^2 for men; for L3-SMI, < 34.4 cm^2/m^2 for women and < 45.4 cm^2/m^2 for men; for T12-SMD < 31.3 HU for women and < 37.5 HU for men;

for L3-SMD, < 34.3 HU for women and < 38.5 HU for men. SMA and SMI-m were not analyzed as binary variables, due to the absence of accepted cutpoints for these CT metrics. Cutpoints for abnormal SARC-F and FRAIL scale assessments were scores > = 4 and > = 3, respectively. Patients classified as confirmed or severe sarcopenia based on the EWGSOP2 criteria were considered sarcopenic in the binary analysis, using T12-SMI as the metric of muscle mass.

Multi-variable Cox proportional hazard analysis of CT metrics was also performed, in models correcting for patient age and sex, and in models including non-CT metrics that were significant predictors in the univariable survival analysis. For multi-variable analysis, CT metrics were transformed to sex-specific Z scores. For generation of Kaplan–Meier curves, patients were dichotomized by CT metrics, with groups defined by sex-specific Z scores < −1 and > = −1. Confidence intervals for Kaplan–Meier curves were based on log transformed point estimates of the survival rate, using the Greenberg equation. Harrel C (concordance index) was computed to describe the relative discrimination of Cox proportional hazard models.

T12-SMA and L3-SMA were each analyzed separately using allometric models. In logarithmic form, the model used to derive empirical scaling factors for height was ln(SMA) = a*ln(ht) + b*ln(age) + ln(c) + d, where ‘a’ is the scaling factor of interest, ‘c’ is a proportionality constant, and d is an error term [27, 28]. Patient age, and the associated fitted scaling factor ‘b’ is included in this model, given the older age of our patient cohort, and the observed proportional decrease in muscle mass that occurs in older adults [29]. Interaction terms between sex and age or sex and height was examined in linear models including all subjects to test whether scaling factors for age and height differed significantly between men and women.

Statistical analysis was performed using R (R Core Team (2019), R Foundation for Statistical Computing, Vienna, Austria, version 3.4.4).

Results

The study included 416 adults (200 men, 216 women; mean age 73.8 years [sd, 6.2]; mean BMI 27.1 [sd, 5.9]). Of the study patients, 322 identified as non-Hispanic white, 32 as Asian or Pacific Islander, 14 as Black or African American, 30 as Hispanic, and 18 as “other”. The mean length of follow-up was 2.9 years (sd, 1.34 years). The mean time of death after CT evaluation was 1.50 years. The observed mortality rate during the study was 32.7% (136/416). 233 subjects had a chest or abdominal CT scan and 183 subjects had a PET/CT scan. After excluding CT images that were compromised by the presence of orthopedic hardware or metallic foreign bodies, CT measurements were performed at T12 and L3 levels in 408 and 320 subjects, respectively.

Baseline patient characteristics and metrics are summarized in Table 1. BMI was significantly higher in men. All CT muscle areal metrics, including those adjusted to height, were significantly higher in men, while CT muscle density metrics were not significantly different between men and women.

Sex-stratified frequency of abnormal clinical, functional and CT muscle metrics are summarized in Table 2. The frequency of abnormal SARC-F was significantly higher in women. The common CT metrics L3-SMD, T12-SMD, T12-SMI, but not L3-SMI, were abnormal significantly more frequently in men than women. Sarcopenia by EWGSOP2 criteria was substantially less common overall than diminished muscle quantity by CT metrics, but was also more common in men than women.

Survival analysis: clinical, functional metrics

Patient sex and BMI were not significantly associated with mortality risk in our study group, which was restricted to older patients (Table 3). Abnormal grip (HR = 2.0, 95% CI [1.4–2.9]), abnormal SARC-F (HR = 1.6, 95% CI [1.1–2.3]), and abnormal FRAIL scale (HR = 2.0, 95% CI [1.4–2.8]) assessments were associated with higher mortality risk, but abnormal gait assessment was not. Patients with either ‘confirmed’ or ‘severe’ sarcopenia, by EWGSOP2 designation, also had higher mortality risk (HR = 2.2, 95%CI [1.4–3.6]). Kaplan–Meier curves are shown for patients dichotomized by FRAIL scale and grip assessments (Fig. 2A, B).

In a multivariable Cox analysis including abnormal grip, SARC-F, FRAIL scale assessments, abnormal grip strength and FRAIL scale assessments remained significantly associated with higher mortality risk (HR = 1.61 and 1.94, 95% CI = [1.08–2.39] and [1.28–2.93] respectively), while abnormal SARC-F assessment was no longer significantly predictive.

Survival analysis: CT metrics

The results of Cox regression analysis of CT metrics, adjusted for age, are summarized in Table 4. T12-SMD was not associated with mortality risk, but T12-SMI, T12-SMI-m, and T12-SMA were associated with mortality risk (HR = 0.84, 0.80, 0.76, 95% CI [0.70–1.00], [0.67–0.90], [0.65–0.90], respectively). At L3, only L3-SMA was associated with mortality risk (HR = 0.80, 95% CI [0.65–0.90]). Kaplan–Meier curves are shown for patients dichotomized by Z scores for T12-SMD and T12-SMA (Fig. 2C, D).

The results of multivariable models including CT metrics which were predictive in univariable analysis, and abnormal grip and FRAIL scale assessments are summarized in Table 5. In these models, an abnormal FRAIL scale assessment was consistently predictive. Of the CT metrics, T12-SMA and T12-SMI-m remained independently predictive of mortality risk, after adjustment for abnormal FRAIL scale and grip assessments.

Allometric analysis of SMA

The results of allometric analysis for height scaling of SMA at T12 and L3 are summarized in Table 6. For men and women, SMA scaled to height with a power which was close to 1, and significantly less than 2 at both L3 and T12. Scaling factors for height did not differ significantly between men and women. SMA also significantly scaled negatively with age. The scaling factor for age was significantly more negative in men than women at T12 ($p < 0.05$); the sex difference in scaling factors for age at L3 was not statistically significant.

Discussion

A unified, consensus definition for sarcopenia is elusive, but may be facilitated by consideration of determinants of criterion validity [30, 31]. In our older adult, outpatient cohort, weak grip strength, abnormal SARC-F and FRAIL scale assessments were significantly predictive of all-cause mortality risk. EWGSOP2 combined categories of confirmed and severe sarcopenia were also highly associated with mortality risk. These findings are consistent with previous studies. The FRAIL scale has been associated with the risk of complications and short-term mortality after surgery [32], and is predictive of all-cause mortality in ambulatory, elderly adults [10]. SARC-F has been associated with all-cause mortality as well as cause-specific mortality in a multi-ethnic adult cohort [7]. Diminished grip strength and gait speed have each been associated with higher all-cause mortality in a large cohort of community dwelling adults [33].

In our study, sex and BMI were not associated with mortality risk. The apparent paradox that an elevated BMI may be associated with lower rather than higher all-cause mortality risk in the elderly has been well documented in large studies [34, 35]. Some but not all CT muscle metrics were associated with mortality risk, although clinical and functional evaluations appear to be more powerful predictors. On multi-variable analysis, some CT metrics (namely T12-SMA and T12-SMI-m) are independently associated with mortality risk even when adjusted for the most significant clinical and functional metrics. CT metrics of muscle quantity or quality, independent of clinical measures, have now been shown to have value in predicting morbidity and outcomes in a variety of clinical settings [36–41].

Our study results were notable in indicating that areal, as opposed to density CT metrics, were predictive of survival. This was true for all areal metrics at T12 (SMI, SMA, SMI-m), and for SMA at L3. This observation is particularly interesting given the prevalent use of SMD to summarize muscle health in studies of opportunistic CT [42]. Variable implications of areal versus density CT muscle measures have been reported in other study populations. A recent study in liver transplant recipients found that SMI, but not myosteatosis (a CT density-based metric) was associated with survival risk [43]. SMI but not SMD at L3 was predictive of overall survival in a cohort of breast cancer patients [44]. Abdominal muscle area, but not density measures, was associated with higher risk coronary artery calcium profiles in the large Multi-Ethnic Study of Atherosclerosis [45]. The correlation between metrics of myopenia and myosteatosis has been observed to be quite low ($R^2 = 0.021$), as reported in women with non metastatic breast cancer [46].

Technical factors may partially explain variances in reported conclusions about areal versus density-based CT muscle measures. Contrast administration and differences in CT kilovoltage [47] are known to influence muscle density to a greater degree than muscle areal measures. The evolution of muscle segmentation algorithms over time may also explain disparate conclusions about measured CT muscle density in different studies [12]. Increasingly muscle segmentation is automated and driven by deep learning models [41, 48]. As segmentation adheres more strictly to deep fascial and compartmental, rather than epimysial or fascicular boundaries, intermuscular and sub-epimyseal fat (perimuscular fat, or intermuscular adipose tissue [IMAT]) is more fully encompassed. Greater inclusion of IMAT

may minimally increase total muscle area, while substantially lowering density. IMAT itself, or IMAT%, can serve as an alternative, areal CT metric of myosteatosis [49], but this was not done in our study.

Opportunistic CT screening for sarcopenia is most often performed at the L3 level [12]. The differential predictive utility we observed between CT muscle measures at T12 versus L3 could simply reflect low study power. One prior study reported that paraspinal muscle measures at T12, but not L4, were predictive of mortality in older adults after hip fracture [15]. More recent studies that leverage the efficiency of automated segmentation tools summarize CT muscle metrics for larger anatomic regions spanning many contiguous axial images [50]. Single slice muscle areas at L3 and multi-slice muscle volume at T12-L5 have been shown to be highly correlated, and to be similarly predictive of survival in patients with colorectal cancer [50]. The incremental or differential utility of specific, regional versus more global muscle metrics awaits clarification by future studies.

Also interesting is our study finding that SMA was consistently predictive of survival, while SMI was only predictive at T12. After adjusting for abnormal FRAIL scale and grip strength assessments, only T12-SMI-m and T12-SMA remained independently predictive of survival risk. Our finding of a trend toward greater predictive utility of SMA and SMI-m is conceptually supported by allometric analyses, which estimates a power for height scaling of cross-sectional muscle area that is closer to one than two [51, 52]. Allometric analysis in our patients, particularly if adjusted for age, also supports a height scaling factor for SMA that is significantly closer to 1 than 2, both for men and women, and for muscle areas measured at T12 and L3.

Like body weight, global lean body components such as total body skeletal mass and fat-free mass do scale with height to a power of approximately 2 [52], based on analysis of data derived from whole body DXA and whole body MRI [53]. Scaling of DXA determined ALM by height^2, also appears appropriate, yielding an index that is independent of height [54]. Perhaps the observation that muscle area measured on a single axial CT slice could effectively estimate total body skeletal mass [55] prompted the adoption of a height scaling factor of 2 for muscle areas measured on single axial CT images. These predictive models, however, were also shown to be confounded by a residual height factor [56]. The use of SMI is nevertheless prevalent in investigations of sarcopenia.

Our study has important limitations that should be considered in interpreting the results. The patient population is not well defined, nor is it representative of the general population or a specific clinical cohort. We feel, however, that the study group is fairly representative of patients routinely referred for advanced imaging at a major, tertiary care medical center. While our study is focused on the mortality risk prediction of CT, clinical, and functional indicators of sarcopenia, the relative value of these metrics could vary in different, more specific, clinical subgroups of patients. Methods of muscle segmentation continue to evolve and are now largely automated, unsupervised, and driven by deep learning models, which may be proprietary. The results of this study may not be transferrable to CT metrics derived by other, newer muscle segmentation techniques.

In conclusion, our study confirms the prognostic value of opportunistic CT metrics of sarcopenia for all-cause mortality risk in older patients undergoing outpatient CT or PET/CT. CT metrics can supplement more powerful prognostic information provided by clinical or functional metrics of sarcopenia and frailty. In predicting all-cause mortality in our outpatient cohort, areal CT metrics offered greater utility than density-based CT metrics. In this context of mortality risk assessment, raw muscle area measured on a single axial CT slice, or muscle area normalized by height, yielded a more useful metric than SMI, the prevalent metric which normalizes muscle area by height^2. These observations warrant further examination in future studies on the clinical utility and predictive validity of CT metrics of sarcopenia.

Funding

The work was supported by the National Institutes of Health grants R61AT012187 and R01AR076088. This project was facilitated by the UC Davis Health Innovation Technology, Data Center of Excellence, and the assistance of Sharon Myers and Anna Liu.

References

1. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Writing group for the European working group on Sarcopenia in older people 2 (EWGSOP2), and the extended group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16–31. [PubMed: 30312372]
2. Yang L, Yao X, Shen J, et al. Comparison of revised EWGSOP criteria and four other diagnostic criteria of sarcopenia in Chinese community-dwelling elderly residents. Exp Gerontol. 2020;130:110798. [PubMed: 31816424]
3. Petermann-Rocha F, Balntzi V, Gray SR, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022;13(1):86–99. [PubMed: 34816624]
4. Mayhew AJ, Amog K, Phillips S, et al. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. Age Ageing. 2019;48(1):48–56. [PubMed: 30052707]
5. Westbury LD, Beaudart C, Bruyère O, et al. International musculoskeletal ageing network. Recent sarcopenia definitions-prevalence, agreement and mortality associations among men: Findings from population-based cohorts. J Cachexia Sarcopenia Muscle. 2023;14(1):565–75. [PubMed: 36604970]
6. Lu JL, Ding LY, Xu Q, et al. Screening accuracy of SARC-F for Sarcopenia in the elderly: A diagnostic meta-analysis. J Nutr Health Aging. 2021;25(2):172–82. [PubMed: 33491031]
7. Wu AH, Setiawan VW, Lim U, et al. Prognostic utility of self-reported sarcopenia (SARC-F) in the Multiethnic Cohort. J Cachexia Sarcopenia Muscle. 2022;13(2):987–1002. [PubMed: 35098697]
8. Ida S, Kaneko R, Imataka K, et al. Verification of the predictive validity for mortality of the SARC-F questionnaire based on a meta-analysis. Aging Clin Exp Res. 2021;33(4):835–42. [PubMed: 32451963]
9. Reijnierse EM, Trappenburg MC, Blauw GJ, et al. Common ground? The concordance of Sarcopenia and frailty definitions. J Am Med Dir Assoc. 2016;17(4):371.e7–12.
10. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. J Am Geriatr Soc. 2012;60(8):1478–86. [PubMed: 22861118]
11. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601–8. [PubMed: 22836700]
12. Amini B, Boyle SP, Boutin RD, Lenchik L. Approaches to assessment of muscle mass and myosteatosis on computed tomography: a systematic review. J Gerontol A Biol Sci Med Sci. 2019;74:1671–8. [PubMed: 30726878]

13. Goodpaster BH, Thaete FL, Kelley DE. Composition of skeletal muscle evaluated with computed tomography. Ann N Y Acad Sci. 2000;904:18–24. [PubMed: 10865705]
14. Walowski CO, Braun W, Maisch MJ, et al. Reference values for skeletal muscle mass - current concepts and methodological considerations. Nutrients. 2020;12(3):755. [PubMed: 32178373]
15. Boutin RD, Bamrungchart S, Bateni CP, et al. CT of patients with hip fracture: muscle size and attenuation help predict mortality. AJR Am J Roentgenol. 2017;208(6):W208–15. [PubMed: 28267356]
16. Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Pail-laud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. Clin Nutr. 2018;37(4):1101–13. [PubMed: 28734552]
17. Lenchik L, Lenoir KM, Tan J, Boutin RD, et al. Opportunistic measurement of skeletal muscle size and muscle attenuation on computed tomography predicts 1-year mortality in Medicare patients. J Gerontol A Biol Sci Med Sci. 2019;74(7):1063–9. [PubMed: 30124775]
18. Yao L, Petrosyan A, Fuangfa P, Lenchik L, Boutin RD. Diagnosing sarcopenia at the point of imaging care: analysis of clinical, functional, and opportunistic CT metrics. Skeletal Radiol. 2021;50(3):543–50. [PubMed: 32892227]
19. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7:28–36. [PubMed: 27066316]
20. Gleason LJ, Benton EA, Alvarez-Nebreda ML, Weaver MJ, Harris MB, Javedan H. FRAIL questionnaire screening tool and short-term outcomes in geriatric fracture patients. J Am Med Dir Assoc. 2017;18(12):1082–6. [PubMed: 28866353]
21. Hamilton GF, McDonald C, Chenier TC. Measurement of grip strength: validity and reliability of the sphygmomanometer and Jamar grip dynamometer. J Orthop Sports Phys Ther. 1992;16(5):215–9. [PubMed: 18796752]
22. Wang M Developing Novel Computational Approaches to Characterize and Predict Therapeutic Performances Using Real-World Data (Doctoral dissertation, UCSF). 2022. https://escholarship.org/uc/item/5wn4v2sk. Accessed 15 Jan 2023
23. Boutin RD, Kaptuch JM, Bateni CP, Chalfant JS, Yao L. Influence of IV contrast administration on CT measures of muscle and bone attenuation: Implications for Sarcopenia and osteoporosis evaluation. AJR Am J Roentgenol. 2016;207(5):1046–54. [PubMed: 27556335]
24. van Vugt JL, Levolger S, Gharbharan A, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. J Cachexia Sarcopenia Muscle. 2017;8(2):285–97. [PubMed: 27897414]
25. Derstine BA, Holcombe SA, Goulson RL, et al. Quantifying Sarcopenia reference values using lumbar and thoracic muscle areas in a healthy population. J Nutr Health Aging. 2017;21(10):180–5.
26. Derstine BA, Holcombe SA, Ross BE, Wang NC, Su GL, Wang SC. Skeletal muscle cutoff values for sarcopenia diagnosis using T10 to L5 measurements in a healthy US population. Sci Rep. 2018;8(1):11369. [PubMed: 30054580]
27. Heymsfield SB, Heo M, Thomas D, Pietrobelli A. Scaling of body composition to height: relevance to height-normalized indexes. Am J Clin Nutr. 2011;93(4):736–40. [PubMed: 21248190]
28. Heymsfield SB, Hwaung P, Ferreyro-Bravo F, Heo M, Thomas DM, Schuna JM Jr. Scaling of adult human bone and skeletal muscle mass to height in the US population. Am J Hum Biol. 2019;31(4):e23252. [PubMed: 31087593]
29. Magudia K, Bridge CP, Bay CP, et al. Population-Scale CT-based body composition analysis of a large outpatient population using deep learning to derive age-, sex-, and race-specific reference curves. Radiology. 2021;298(2):319–29. [PubMed: 33231527]
30. Mayhew AJ, Raina P. Sarcopenia: new definitions, same limitations. Age Ageing. 2019;48(5):613–4. [PubMed: 31297512]
31. Fernandes LV, Paiva AEG, Silva ACB, et al. Prevalence of sarcopenia according to EWGSOP1 and EWGSOP2 in older adults and their associations with unfavorable health outcomes: a systematic review. Aging Clin Exp Res. 2022;34(3):505–14. [PubMed: 34398438]

32. Gong S, Qian D, Riazi S, et al. Association between the FRAIL scale and postoperative complications in older surgical patients: a systematic review and meta-analysis. Anesth Analg. 2023;136(2):251–61. [PubMed: 36638509]
33. Petermann-Rocha F, Parra-Soto S, Cid V, et al. The association between walking pace and grip strength and all-cause mortality: A prospective analysis from the MAUCO cohort. Maturitas. 2023;168:37–43. [PubMed: 36442346]
34. Cheng FW, Gao X, Mitchell DC, et al. Body mass index and all-cause mortality among older adults. Obesity (Silver Spring). 2016;24(10):2232–9. [PubMed: 27570944]
35. Javed AA, Aljied R, Allison DJ, Anderson LN, Ma J, Raina P. Body mass index and all-cause mortality in older adults: A scoping review of observational studies. Obes Rev. 2020;21(8):e13035. 10.1111/obr.13035. [PubMed: 32319198]
36. Zumsteg DM, Chu CE, Midwinter MJ. Radiographic assessment of sarcopenia in the trauma setting: a systematic review. Trauma Surg Acute Care Open. 2020;5(1):e000414. [PubMed: 32201738]
37. Su H, Ruan J, Chen T, Lin E, Shi L. CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. Cancer Imaging. 2019;19(1):82. [PubMed: 31796090]
38. Nishimura JM, Ansari AZ, D'Souza DM, Moffatt-Bruce SD, Merritt RE, Kneuertz PJ. Computed tomography-assessed skeletal muscle mass as a predictor of outcomes in lung cancer surgery. Ann Thorac Surg. 2019;108(5):1555–64. [PubMed: 31228408]
39. Rossi F, Valdora F, Bignotti B, Torri L, Succio G, Tagliafico AS. Evaluation of body computed tomography-determined sarcopenia in breast cancer patients and clinical outcomes: A systematic review. Cancer Treat Res Commun. 2019;21:100154. [PubMed: 31220793]
40. Soud M, Alahdab F, Ho G, et al. Usefulness of skeletal muscle area detected by computed tomography to predict mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis study. Int J Cardiovasc Imaging. 2019;35(6):1141–7. [PubMed: 30915667]
41. Lenchik L, Barnard R, Boutin RD, et al. Automated muscle measurement on chest CT predicts all-cause mortality in older adults from the national lung screening trial. J Gerontol A Biol Sci Med Sci. 2021;76(2):277–85. [PubMed: 32504466]
42. Pickhardt PJ, Perez AA, Garrett JW, Graffy PM, Zea R, Summers RM. Fully automated deep learning tool for sarcopenia assessment on CT: L1 versus L3 vertebral level muscle measurements for opportunistic prediction of adverse clinical outcomes. AJR Am J Roentgenol. 2022;218(1):124–31. [PubMed: 34406056]
43. Shafaat O, Liu Y, Jackson KR, et al. Association between abdominal CT measurements of body composition before deceased donor liver transplant with posttransplant outcomes. Radiology. 2023;306(3):e212403. 10.1148/radiol.212403. [PubMed: 36283115]
44. Shachar SS, Deal AM, Weinberg M, et al. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving Taxane-based chemotherapy. Clin Cancer Res. 2017;23(3):658–65. [PubMed: 27489287]
45. Crawford MA, Criqui MH, Forbang N, Unkart JT, Allison MA, Larsen BA. Associations of abdominal muscle area and density with coronary artery calcium volume and density: The multi-ethnic study of atherosclerosis. Metabolism. 2020;107:154230. [PubMed: 32298722]
46. Weinberg MS, Shachar SS, Muss HB, et al. Beyond sarcopenia: Characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. Breast J. 2018;24(3):278–84. [PubMed: 29139618]
47. Lortie J, Gage G, Rush B, Heymsfield SB, Szczykutowicz TP, Kuchnia AJ. The effect of computed tomography parameters on sarcopenia and myosteatosis assessment: a scoping review. J Cachexia Sarcopenia Muscle. 2022;13(6):2807–19. [PubMed: 36065509]
48. Burns JE, Yao J, Chalhoub D, Chen JJ, Summers RM. A machine learning algorithm to estimate Sarcopenia on abdominal CT. Acad Radiol. 2020;27(3):311–20. [PubMed: 31126808]
49. Jing X, Tan L, Fu H, Yang L, Yang M. Associations of ADL disability with trunk muscle mass and muscle quality indicators measured by opportunistic chest computed tomography imaging among older inpatients. Front Med (Lausanne). 2021;28(8):743698.

50. Anyene I, Caan B, Williams GR, et al. Body composition from single versus multi-slice abdominal computed tomography: Concordance and associations with colorectal cancer survival. J Cachexia Sarcopenia Muscle. 2022;13(6):2974–84. [PubMed: 36052755]

51. Brown JC, Heymsfield SB, Caan BJ. Scaling of computed tomography body composition to height: relevance of height-normalized indices in patients with colorectal cancer. J Cachexia Sarcopenia Muscle. 2022;13(1):203–9. [PubMed: 34741439]

52. Heymsfield SB, Gallagher D, Mayer L, Beetsch J, Pietrobelli A. Scaling of human body composition to stature: new insights into body mass index. Am J Clin Nutr. 2007;86:82–91. [PubMed: 17616766]

53. Heymsfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S. Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol Endocrinol Metab. 2002;282(1):E132–8 [PubMed: 11739093]

54. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755–63. [PubMed: 9554417]

55. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 1985;2004(97):2333–8.

56. Schweitzer L, Geisler C, Pourhassan M, et al. Estimation of skeletal muscle mass and visceral adipose tissue volume by a single magnetic resonance imaging slice in healthy elderly adults. J Nutr. 2016;146(10):2143–8. [PubMed: 27581576]

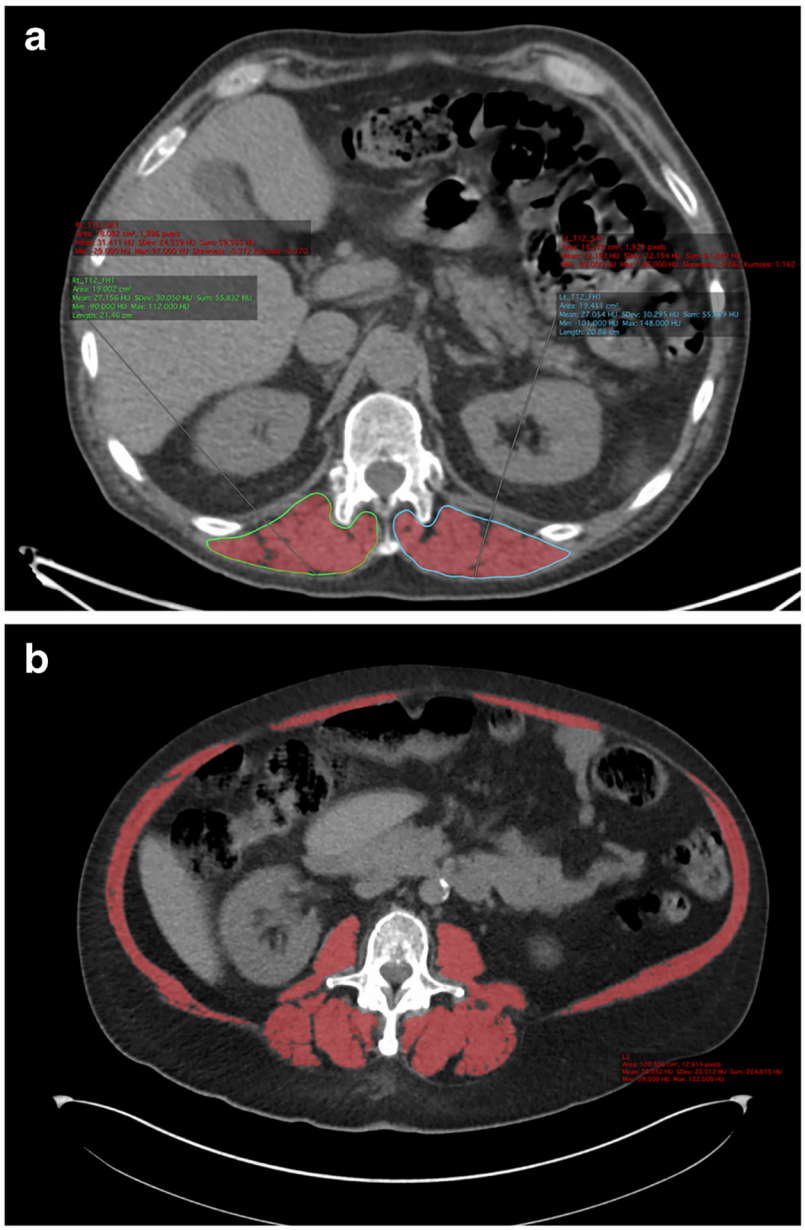

Fig. 1.

A Axial CT image at the T12 level, illustrating paraspinous muscle segmentation. The green and blue lines are manually drawn, and the shaded red regions within these lines represent the muscle segmentations generated by a region growing tool that selects pixels with density values between −29 and + 150 Hounsfield units within these boundaries. **B** Axial image at the L3 level illustrating segmented skeletal muscle regions, shaded in red, generated by the same supervised, threshold based region growing method shown in Fig. 1A

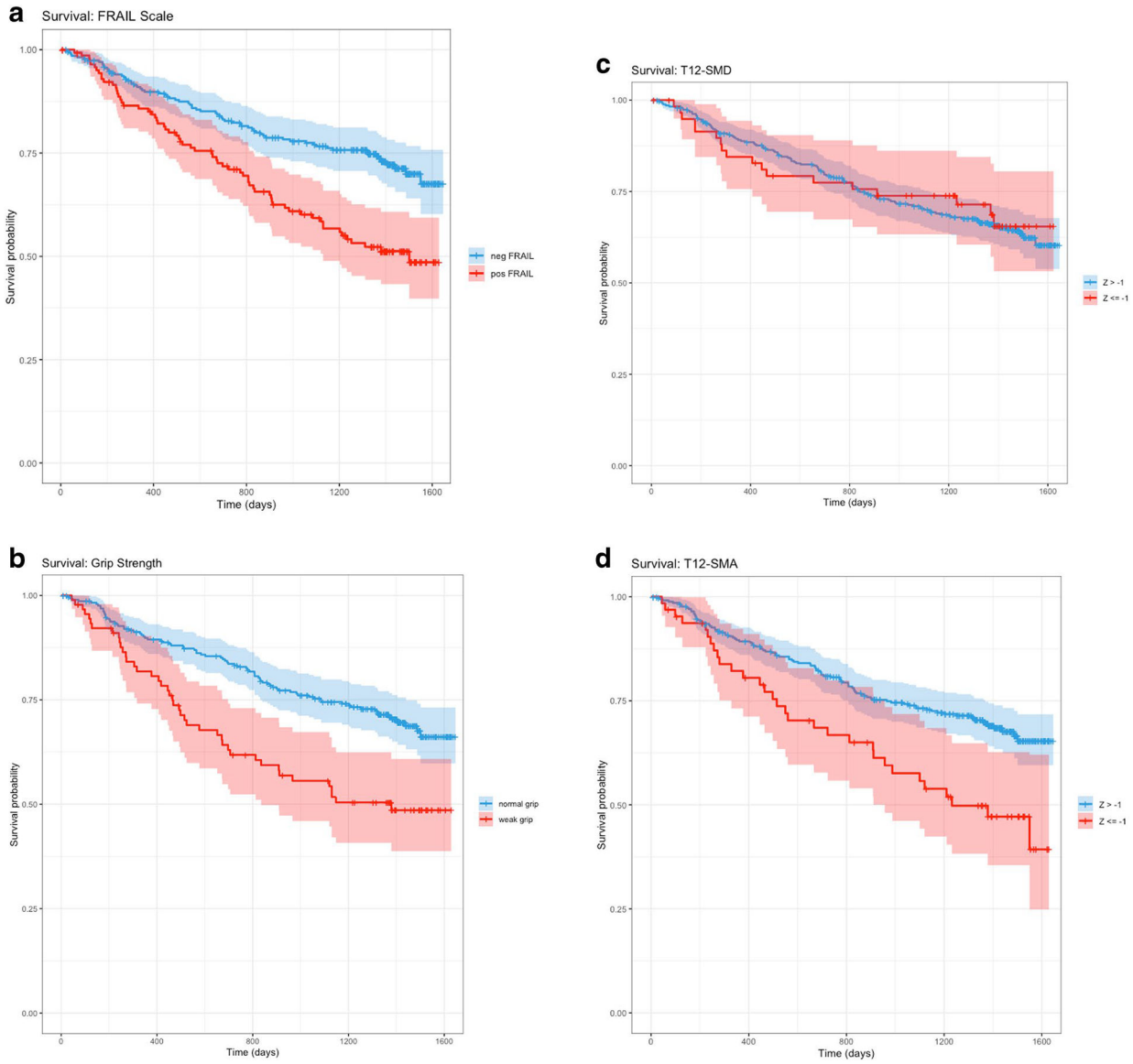

Fig. 2.

Kaplan–Meier curves showing patient survival stratified by: (**A**) normal (blue) versus abnormal (red) FRAIL scale assessment, (**B**) normal (blue) versus abnormal (red) grip strength, (**C**) T12-SMD, and (**D**) T12-SMA. The CT metrics (**C** and **D**) are dichotomized by sex-specific Z score < = −1 (red), and > −1 (blue). The colored regions highlight estimated 95% confidence bands for group survival rate

Table 1

Baseline patient characteristics, by patient sex

			Women			Men		
	units	***N***	**Mean**	**SD**	***N***	**Mean**	**SD**	***p***
Age	years	216	73.72	6.3	200	73.92	6.12	ns
BMI	kg/m^2	214	26.14	6.11	198	28.07	5.54	**
SARC-F	na	216	2.22	2.19	200	1.57	1.93	**
FRAIL Scale	na	216	2.09	1.41	200	1.75	1.51	**
Grip strength	kg	200	19.6	5.59	185	32.7	8.63	***
Gait speed	m/sec	173	1.05	0.23	171	1.1	0.21	*
L3-SMD	HU	170	30.98	10.86	150	32.72	9.2	ns
L3-SMI	cm^2/m^2	170	36.04	7.38	150	46.06	10.22	***
L3-SMA	cm^2	170	93.06	18.58	150	143.41	31.89	***
L3-SMI-m	cm^2/m	170	57.85	11.4	150	81.19	17.64	***
T12-SMD	HU	213	37	13.35	195	36.14	12.29	ns
T12-SMI	cm^2/m^2	213	9.22	2.2	195	10.96	2.92	***
T12-SMA	cm^2	213	23.79	5.41	195	34.1	9.23	***
T12-SMI-m	cm^2/m	213	14.79	3.33	195	19.31	5.11	***

Patient characteristics summarized by sex. CT areal muscle measures, including those normalized by patient height, were significantly higher in men than in women, while CT muscle density measures did not differ significantly between sexes. Abbreviations: BMI-body mass index; na-not applicable; SMA-skeletal muscle area; SMI-skeletal muscle index; SMD-skeletal muscle density, SMI-m-modified skeletal muscle index.

P values, *ns* not significant,

*' < 0.05;

**' < 0.01;

***' < 0.001

Table 2

Patient characteristics: frequency of abnormal baseline assessments

	Women			Men			
	N	**Abnormal**	**%**	***N***	**Abnormal**	**%**	***p***
FRAIL Scale	216	82	38.0%	200	62	31.0%	ns
SARC-F	216	58	26.9%	200	30	15.0%	**
Gait speed	173	25	14.5%	171	16	9.4%	ns
Grip strength	198	45	22.7%	184	45	24.5%	ns
Sarcopenia (EWGSOP2)	165	17	10.3%	110	27	24.5%	**
L3-SMD	170	109	64.1%	150	114	76.0%	*
L3-SMI	170	115	67.6%	150	114	76.0%	ns
T12-SMD	213	69	32.4%	195	104	53.3%	***
T12-SMI	213	51	23.9%	195	105	53.8%	***

Incidence of abnormal clinical, functional and CT muscle assessments, summarized by sex. Criteria for abnormal assessments based on published guidelines; abnormal EWGSOP2 classification here corresponds to categories of ‘confirmed’ or ‘severe’ sarcopenia (see Methods). An abnormal SARC-F assessment was more common in women than men, while an abnormal CT muscle assessment was more common in men than women, for 3 of 4 common CT muscle metrics.

P values, *ns* not significant,

*’< 0.05;

**’< 0.01;

***’< 0.001

Table 3

Survival analysis: clinical and functional metrics

	HR	95% CI	*p*	C
Age	1.00	(1–1.1)	*	0.54
Sex	1.20	(0.87–1.7)	ns	0.53
BMI	0.97	(0.94–1)	ns	0.55
Abnormal SARC-F	1.60	(1.1–2.3)	*	0.54
Abnormal FRAIL scale	2.00	(1.4–2.8)	****	0.58
Slow gait	1.10	(0.61–2)	ns	0.50
Weak grip	2.00	(1.4–2.9)	***	0.57
Sarcopenia (EWGSOP2)	2.20	(1.4–3.6)	***	0.56

Summary of univariable survival analysis of clinical features and metrics. Patients were classified as abnormal for the listed clinical and functional metrics based on published definitions (see Methods). Weak grip strength, abnormal FRAIL scale assessment, and EWGSOP2 categories of either ‘confirmed’ or ‘severe’ sarcopenia are most strongly associated with mortality risk. Abbreviations: HR-hazard ratio, CI-confidence interval, C-concordance index.

P values *ns* not significant;

*’< 0.05;

**’< 0.01;

***’< 0.001;

****’< 0.0001

Table 4

Survival analysis: CT metrics

Level	Metric	Unadjusted				Adjusted for Age			
		HR	**95% CI**	***p***	**C**	**HR**	**95% CI**	***p***	**C**
L3	SMD	0.91	(0.75–1.1)	ns	0.54	0.92	(0.76—1.12)	ns	0.54
	SMI	0.92	(0.76–1.1)	ns	0.54	0.94	(0.77—1.16)	ns	0.53
	SMI-m	0.85	(0.7–1)	ns	0.56	0.86	(0.70—1.06)	ns	0.55
	SMA	0.79	(0.65–0.96)	*	0.58	0.80	(0.65—0.98)	*	0.58
T12	SMD	0.91	(0.77–1.1)	ns	0.54	0.93	(0.78—1.11)	ns	0.55
	SMI	0.81	(0.68–0.97)	*	0.55	0.84	(0.70—1.00)	*	0.56
	SMI-m	0.77	(0.65–0.92)	***	0.57	0.80	(0.67—0.95)	*	0.57
	SMA	0.74	(0.62–0.88)	***	0.58	0.76	(0.64—0.92)	**	0.58

Summary of survival analysis of CT metrics, unadjusted, and adjusted for patient age. CT metrics were analyzed as sex-specific Z scores. SMD measures were not significantly predictive. All areal muscle measures at T12 were predictive of mortality risk; T12-SMA being the mostly significantly predictive. Of CT measures at L3, only L3-SMA was significantly predictive. Abbreviations: HR-hazard ratio; CI-confidence interval; C-concordance index; SMA-skeletal muscle area; SMI-skeletal muscle index; SMD-skeletal muscle density, SMI-m-modified skeletal muscle index.

P values, *ns* not significant;

*, < 0.05;

**, < 0.01;

***, < 0.001

Table 5

Multivariable survival analysis: CT metrics

CT Metric				Abnormal FRAIL Scale			Weak Grip			C
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	
T12-SMD	1.037	(0.86–1.25)	ns	1.915	(1.31–2.81)	***	1.622	(1.09–2.41)	*	0.62
T12-SMI	0.8614	(0.72–1.03)	ns	1.8993	(1.30–2.77)	***	1.5379	(1.03–2.30)	*	0.63
T12-SMI-m	0.805	(0.67–0.97)	*	1.909	(1.31–2.78)	***	1.4	(0.92–2.13)	ns	0.63
T12-SMA	0.8326	(0.70–1.00)	*	1.9045	(1.31–2.78)	***	1.4705	(0.98–2.22)	ns	0.63
L3-SMA	0.9297	(0.76–1.14)	ns	2.1299	(1.42–3.20)	***	1.4407	(0.91–2.28)	ns	0.63

Summary of multivariable models analyzing CT metrics as expressed by sex specific Z scores. Abnormal FRAIL scale assessment is the most strongly predictive of mortality risk, followed by abnormal Grip strength. Of significantly predictive CT metrics in univariable analysis, only T12-SMA shows independent predictive value for mortality risk after adjusting for abnormal FRAIL scale and grip strength assessments. Abbreviations: HR-hazard ratio; CI-confidence interval; C-concordance index; SMA-skeletal muscle area; SMI-skeletal muscle index; SMD-skeletal muscle density, SMI-m-modified skeletal muscle index.

P values, *ns* not significant;

*, < 0.05;

**, < 0.01;

***, < 0.001

Table 6

Allometric analysis of height scaling of muscle area

	Level	Height				Age		
		Scale Factor	SE	*p*	*p**	Scale Factor	SE	*p*
Men	L3	1.00	0.38	**	**	−0.89	0.22	****
	T12	1.04	0.38	**	**	−1.35	0.22	****
Women	L3	1.08	0.33	**	**	−0.59	0.18	**
	T12	0.63	0.31	*	****	−0.69	0.20	***

Summary of allometric regression analysis of muscle area scaling by patient height, adjusted for patient age, reported separately by patient sex and vertebral level. The adjustments for height and age are significant for men and women. At both L3 and T12, the scaling factor for height is significantly (p*) different than 2, the scale power used in SMI. Abbreviations: SE -standard error of regression; p—null hypothesis that scale factor = 0; *p**- null hypothesis that scale factor = 2.

P values, *ns* not significant;

*’< 0.05;

**’< 0.01;

***’< 0.001;

****’< 0.0001