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Research Article

Automated Muscle Measurement on Chest CT Predicts All-Cause Mortality in Older Adults From the National Lung Screening Trial

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Abstract

Background: Muscle metrics derived from computed tomography (CT) are associated with adverse health events in older persons, but obtaining these metrics using current methods is not practical for large datasets. We developed a fully automated method for muscle measurement on CT images. This study aimed to determine the relationship between muscle measurements on CT with survival in a large multicenter trial of older adults.

Method: The relationship between baseline paraspinous skeletal muscle area (SMA) and skeletal muscle density (SMD) and survival over 6 years was determined in 6,803 men and 4,558 women (baseline age: 60–69 years) in the National Lung Screening Trial (NLST). The automated machine learning pipeline selected appropriate CT series, chose a single image at T12, and segmented left paraspinous muscle, recording cross-sectional area and density. Associations between SMA and SMD with all-cause mortality were determined using sex-stratified Cox proportional hazards models, adjusted for age, race, height, weight, pack-years of smoking, and presence of diabetes, chronic lung disease, cardiovascular disease, and cancer at enrollment.

Results: After a mean 6.44 ± 1.06 years of follow-up, 635 (9.33%) men and 265 (5.81%) women died. In men, higher SMA and SMD were associated with a lower risk of all-cause mortality, in fully adjusted models. A one-unit standard deviation increase was associated with a hazard ratio (HR) = 0.85 (95% confidence interval [CI] = 0.79, 0.91; $p < .001$) for SMA and HR = 0.91 (95% CI = 0.84, 0.98; $p = .012$) for SMD. In women, the associations did not reach significance.

Conclusion: Higher paraspinous SMA and SMD, automatically derived from CT exams, were associated with better survival in a large multicenter cohort of community-dwelling older men.

Keywords: Sarcopenia, Myosteatosis, Mortality, Computed tomography, Machine learning

Maintenance of skeletal muscle quantity and quality is an essential component of physical health of older adults (1,2). For over two decades, noninvasive measurement of muscle mass in large observational studies was performed using dual x-ray absorptiometry (DXA) (3–12). DXA-derived appendicular lean mass has been associated with various biomarkers of aging in the Health Aging and Body Composition Study (5,7), Osteoporotic Fractures in Men Study (8,9), and National Health and Nutrition Examination Surveys

(NHANES) (10–12). However, recent data from the Sarcopenia Definitions and Outcomes Consortium (13) brought the value of DXA measurements of muscle in older adults into question, concluding that these were poor predictors of mobility disability.

In contrast to DXA, the use of computed tomography (CT) for measuring muscle has become more common in studies of older adults (14–26). However, most of the studies evaluating CT-derived muscle metrics and mortality in older adults have been convenience samples in hospitalized patients with higher comorbidities (14–26). In a recent pragmatic evaluation of community-dwelling Medicare recipients, Lenchik et al. (27) reported that higher CT-derived skeletal muscle index (SMI) and skeletal muscle density (SMD) were associated with improved overall survival even after adjusting for multiple comorbidities. However, this study and most others (26,27) used manual or semi-automated approaches for segmenting muscles on CT images, a process that is time-consuming and unrealistic for large research datasets and clinical practice.

Automated segmentation of medical images has benefited greatly from machine learning algorithms, promising to transform large-scale research and eventually improve patient care. In a recent systematic review, Lenchik et al. (28) reported on 408 studies of automated segmentation of CT or MR images. Most of these studies involved segmentations of the heart on CT images or the brain on MR images (28). Only a handful of studies used automated segmentation of skeletal muscle (28). More importantly, while some centers have already implemented automated pipelines for neuroimaging, such pipelines for musculoskeletal imaging have not previously been reported.

We developed the first automated pipeline for skeletal muscle measurement based on open-source machine learning methods (29,30). Our pipeline selects the appropriate chest CT series, chooses a single CT image at the level of T12 vertebra, and segments the left paraspinous muscle, recording the muscle cross-sectional area (a measure of muscle mass) and muscle density (a measure of myosteatosis).

The purpose of our study was to determine whether the automated measurement of paraspinous skeletal muscle area (SMA) and SMD on chest CT examinations can be used to predict survival in a large cohort of community-dwelling older adults evaluated at 33 different medical centers across the United States followed for over 6 years. We hypothesized that higher paraspinous SMA and SMD would be associated with improved survival.

Method

This retrospective cohort study was conducted on data from the National Lung Screening Trial (NLST). NLST is one of the largest datasets from which CT images and mortality data are publically available from the National Cancer Institute (31,32). The NLST enrolled 53,454 participants, aged 55–74 years, at 33 medical centers in the United States, from August 2002 to April 2004 (31). Subjects were randomly assigned to a chest CT scan arm (n = 26,722) or chest x-ray arm (n = 26,732) (31). Cancers and deaths were recorded through December 31, 2009 (31). Although lung cancer was the leading cause of death in the chest x-ray arm (n = 503), the reduction in lung cancer deaths in the CT arm (n = 427) resulted in cardiovascular disease becoming the leading cause of death for the CT arm (n = 486) and the entire study (n = 956) (32). For the current study, a subgroup of older participants (age 60–69 years at enrollment) in the CT arm was examined to increase the prevalence of low SMA and SMD. The oldest NLST subgroup (baseline age, 70 years and older) was used to develop and train the automated CT segmentation algorithm and was excluded. CT scans were acquired using scanners from all four major manufacturers (General Electric [n = 6,281], Siemens [n = 3,336], Philips [n = 1,115], Toshiba (n = 643]) using an unenhanced, ungated, low-dose CT protocol. CT acquisition parameters were: 120 kVp, 40–80 mAs (depending on patient size), 1.0–2.5 mm slice thickness, and soft tissue reconstruction algorithm.

Automated Muscle Measurements

Using open-source machine learning tools, we developed a fully automated pipeline for obtaining muscle measurements on chest CT exams. The pipeline uses three sequential processing stages (Figure 1). The first stage uses a random forest classifier to analyze metadata from the raw DICOM files to select and extract the appropriate CT series. The second stage uses a convolutional neural network to localize and extract the CT slices at the level of the T12 vertebra. The third stage applies another convolutional neural network to the CT image extracted during the second stage to segment the left paraspinous muscle and record SMA and SMD. The automated pipeline was developed, trained, and tested on a separate set of CT examinations from the current study. The training set comprised of 2,084 exams from an older subgroup of NLST (70 years and older at enrollment). Further details on the automated CT analysis methods are provided in the Supplementary Appendix.

Mortality

Mortality was provided by the National Cancer Institute. For participants confirmed as deceased, the length of follow-up was determined from the date of the initial study visit to date of death. For living participants, the length of follow-up was determined from the date of the initial study visit to December 31, 2009. More recent mortality data were not available from the National Cancer Institute. All covariates used in the current study were obtained from the National Cancer Institute.

Statistical Analysis

For participant characteristics and skeletal muscle measures, summary statistics by sex were determined as counts and percentages for categorical variables and as means and standard deviations for continuous variables. For non-normally distributed continuous variables, medians, first quartiles, and third quartiles were additionally determined. Two predictor variables of interest were considered:

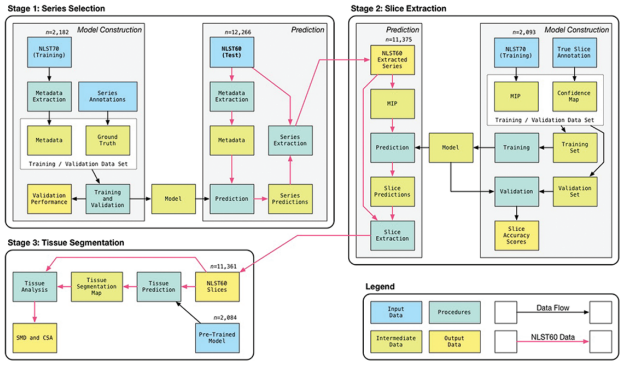

Figure 1. Diagram of the automated machine learning pipeline shows three stages used to derive muscle metrics from computed tomography (CT) images: (a) series selection, (b) slice extraction, and (c) tissue segmentation.

(a) baseline paraspinous SMA and (b) baseline paraspinous SMD. Unadjusted Cox proportional hazards models were used to evaluate the association between mortality and each characteristic.

The interactions between sex and CT-derived muscle metrics were determined. While interactions between sex and skeletal muscle index were significant (p = .017–.045), those between sex and SMA or SMD were not (p = .2–.3). However, because many prior clinical and experimental studies have shown sex differences in muscle metabolism and its effect on longevity, all of our analyses were stratified by sex (16,33–37).

The sex-specific standardized muscle measures were evaluated for relative importance. Kaplan–Meier survival curves were constructed to examine patterns of mortality for baseline SMA and SMD. The survival curves for each muscle measure were stratified as follows: standardized muscle measure ≤–1, between –1 and 1, and >1. To examine how the survival curves changed by considering the two muscle measures together, the survival curves were stratified into three categories: either standardized muscle measure ≤–1, both between –1 and 1, and either >1. The log-rank test was used to compare survival curves. Pairwise comparisons for the log-rank test were performed based on Tukey's studentized range test.

Cox proportional hazards models were used to examine the relationships between muscle metrics and all-cause mortality. Five models were used: (a) unadjusted; (b) adjusted for age, race, and pack-years of smoking; (c) adjusted for Model 2 plus height (3A) or weight (3B); (d) adjusted for Model 3 plus presence at enrollment of type 2 diabetes (T2D), chronic lung disease, cardiovascular disease, and cancer (4A adjusted for height, 4B adjusted for weight); and (e) adjusted for Model 4 plus the other muscle metric (ie, SMA or SMD) of interest (5A adjusted for height, 5B adjusted for weight).

To check the potential nonlinearity association between the muscle metrics and mortality, the square term and cubic term of muscle metrics were included in Models 4A and 4B. If the polynomial term was not significant, it was removed from the model.

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was set at $p < .025$ after Bonferroni correction for two primary muscle measures (ie, SMA and SMD).

Results

The NLST cohort of 6,803 men and 4,558 women was followed for 6.44 ± 1.06 years. Tables 1 and 2 present demographic characteristics, muscle metrics, and survival data in men and women. In men and women, compared to the survivor group, the deceased group

Table 1. Participant Characteristics at Baseline in 6,803 Men, Aged 60–69 Years, From the CT Arm of the National Lung Screening Trial

Characteristic	All (n = 6,803)	Survivors (n = 6,168)	Deceased (n = 635)	HR (95% CI)	p-Value
Age ± *SD* (y)	63.7 ± 2.8	63.6 ± 2.8	64.4 ± 2.9	1.10 (1.07, 1.13)	<.001
BMI ± *SD* (kg/m^2)	27.9 ± 4.5	27.9 ± 4.3	28.0 ± 5.4	1.00 (0.99, 1.02)	.711
Caucasian	6,237 (92.0)	5,661 (92.1)	576 (91.0)	0.87 (0.66, 1.14)	.309
Pack-years of smoking	61.7 ± 26.8	61.1 ± 26.6	67.6 ± 28.2	1.01 (1.01, 1.01)	<.001
	53 (43, 75)[a]	53 (42, 74)[a]	60 (46, 83)[a]		
Type 2 diabetes	812 (12.0)	699 (11.4)	113 (17.8)	1.64 (1.34, 2.02)	<.001
Chronic lung disease	1,656 (24.4)	1,454 (23.6)	202 (31.8)	1.48 (1.25, 1.75)	<.001
Cardiovascular disease	3,274 (48.1)	2,924 (47.4)	350 (55.1)	1.35 (1.15, 1.57)	.002
Cancer	134 (2.0)	119 (1.9)	15 (2.4)	1.20 (0.72, 2.01)	.477
Skeletal muscle area (cm^2)	16.0 ± 3.50	16.1 ± 3.48	15.3 ± 3.61	0.82 (0.76, 0.88)[b]	<.001
Skeletal muscle density (HU)	49.1 ± 7.0	49.2 ± 6.9	48.4 ± 7.6	0.90 (0.84, 0.98)[b]	.010

Notes: BMI = body mass index; CI = confidence interval; CT = computed tomography; HR = hazard ratio; HU = Hounsfield units. Mean ± *SD* for continuous variables; n (%) for categorical variables. *p-values* are calculated using the unadjusted Cox proportional hazards model.

[a]Median (first quartile, third quartile).

[b]HR per *SD*.

Table 2. Participant Characteristics at Baseline in 4,558 Women, Aged 60–69 Years, From the CT Arm of the National Lung Screening Trial

Characteristic	All (n = 4,558)	Survivors (n = 4,293)	Deceased (n = 265)	HR (95% CI)	p-Value
Age ± *SD* (y)	63.6 ± 2.8	63.5 ± 2.8	64.2 ± 2.7	1.08 (1.03, 1.13)	<.001
BMI ± *SD* (kg/m^2)	27.2 ± 5.4	27.2 ± 5.3	27.3 ± 6.9	1.00 (0.98, 1.03)	.703
Caucasian	4,193 (92.2)	3,956 (92.3)	237 (89.4)	0.69 (0.47, 1.03)	.066
Pack-years of smoking	52.7 ± 21.0	52.4 ± 20.9	57.2 ± 22.1	1.01 (1.00, 1.01)	<.001
	46 (39, 62)[a]	45 (39, 62)[a]	50 (43, 68)[a]		
Type 2 diabetes	373 (8.2)	338 (7.9)	35 (13.3)	1.79 (1.26, 2.56)	.001
Chronic lung disease	1,400 (30.7)	1,298 (30.2)	102 (38.5)	1.43 (1.12, 1.84)	.004
Cardiovascular disease	1,929 (42.3)	1,802 (42.0)	127 (47.9)	1.28 (1.01, 1.63)	.046
Cancer	364 (8.0)	333 (7.8)	31 (11.7)	1.54 (1.06, 2.24)	.024
Skeletal muscle area (cm^2)	11.9 ± 2.50	11.9 ± 2.49	11.8 ± 2.70	0.97 (0.86, 1.09)[b]	.564
Skeletal muscle density (HU)	42.7 ± 7.3	42.7 ± 7.3	42.6 ± 8.0	0.99 (0.88, 1.12)[b]	.843

Notes: BMI = body mass index; CI = confidence interval; CT = computed tomography; HR = hazard ratio; HU = Hounsfield units. Mean ± *SD* for continuous variables; n (%) for categorical variables. *p-values* are calculated using the unadjusted Cox proportional hazards model.

[a]Median (first quartile, third quartile).

[b]HR per *SD*.

Table 3. Association Between CT-Derived Baseline Paraspinous Skeletal Muscle Area and All-Cause Mortality in 6,803 Men and 4,558 Women, Aged 60–69 Years, From the CT Arm of the National Lung Screening Trial

Skeletal Muscle Area		HR per *SD* (95% CI)	*p*-Value
Men (*SD* = 3.50 cm^2)			
Model 1	Unadjusted	0.82 (0.76, 0.88)	<.001
Model 2	Adjusted for age, race, pack-years of smoking	0.85 (0.79, 0.92)	<.001
Model 3A	Adjusted for Model 2 and height	0.85 (0.78, 0.91)	<.001
Model 3B	Adjusted for Model 2 and weight	0.85 (0.79, 0.91)	<.001
Model 4A	Adjusted for Model 3A and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.85 (0.79, 0.91)	<.001
Model 4B	Adjusted for Model 3B and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.85 (0.79, 0.92)	<.001
Model 5A	Adjusted for Model 4A and skeletal muscle density	0.83 (0.77, 0.90)	<.001
Model 5B	Adjusted for 4B and skeletal muscle density	0.83 (0.77, 0.90)	<.001
Women (*SD* = 2.50 cm^2)			
Model 1	Unadjusted	0.97 (0.86, 1.09)	.564
Model 2	Adjusted for age, race, pack-years of smoking	0.97 (0.86, 1.09)	.620
Model 3A	Adjusted for Model 2 and height	0.98 (0.87, 1.11)	.781
Model 3B	Adjusted for Model 2 and weight	0.97 (0.86, 1.10)	.680
Model 4A	Adjusted for Model 3A and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.97 (0.85, 1.09)	.560
Model 4B	Adjusted for Model 3B and presence of type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.97 (0.86, 1.09)	.595
Model 5A	Adjusted for Model 4A and skeletal muscle density	0.96 (0.85, 1.09)	.541
Model 5B	Adjusted for Model 4B and skeletal muscle density	0.97 (0.85, 1.09)	.583

Note: CI = confidence interval; CT = computed tomography; *SD* = standard deviation; HR = hazard ratio; BMI = body mass index. *p-values are calculated using the Cox proportional hazards model.*

had a significantly higher pack-years of smoking, T2D, chronic lung disease, and cardiovascular disease.

Relationships between CT-derived baseline paraspinous SMA and all-cause mortality in men and women are given in Table 3. In men, increased SMA was associated with decreased all-cause mortality in all models. Importantly, adjusting for SMD did not reduce the magnitude of the association, indicating that SMA and SMD are independent predictors of mortality. Each standard deviation (3.5 cm^2) increase in SMA was associated with a 17% decrease in mortality. In women, the association between SMA and mortality was not significant.

Relationships between baseline paraspinous SMD and all-cause mortality in men and women are given in Table 4. In men, increased SMD was associated with decreased all-cause mortality in all models. Adjusting for SMA did not reduce the magnitude of the association, indicating that SMA and SMD are independent predictors of mortality. Each standard deviation (6.99 HU) increase in SMD was associated with an 11% decrease in mortality. In women, the association between SMD and mortality was not significant.

Figure 2 shows Kaplan–Meier survival analyses for paraspinous SMA in men. Compared to men at least 1 *SD* below the cohort median SMA, men with higher SMA had more favorable survival at each time point. Pairwise comparison for the log-rank test based on Tukey's studentized range test shows that the survival probability for $Z > 1$ is significantly different from $Z \leq -1$ ($p < .001$, $\chi^2 = 20.72$, $df = 1$) and $-1 < Z \leq 1$ is also significantly different from $Z \leq -1$ ($p = .039$, $\chi^2 = 5.97$, $df = 1$). However, the survival probability for $-1 < Z \leq 1$ is not statistically different from $Z > 1$ ($p = .65$, $\chi^2 = 0.78$, $df = 1$).

Figure 3 shows Kaplan–Meier survival analyses for paraspinous SMD in men. Compared to men at least 1 *SD* below the cohort median SMD, men with higher SMD had more favorable survival at each time point. Pairwise comparison for the log-rank test based on Tukey's studentized range test shows that the survival probability for $Z > 1$ is significantly different from $Z \leq -1$ ($p = .037$, $\chi^2 = 6.04$, $df = 1$). However, the survival probability for $-1 < Z \leq 1$ is not statistically different from $Z > 1$ ($p = .94$, $\chi^2 = 0.11$, $df = 1$) or $Z \leq -1$ ($p = .29$, $\chi^2 = 2.25$, $df = 1$).

Figure 4 shows the combined effect of SMA and SMD on overall survival. At each time point, men with higher SMA or SMD had more favorable survival, while men with lower SMA or SMD had less favorable survival. Pairwise comparison for the log-rank test based on Tukey's studentized range test shows that the survival probability for $Z > 1$ is significantly different from $Z \leq -1$ ($p < .001$, $\chi^2 = 23.28$, $df = 1$). However, the survival probability for $-1 < Z \leq 1$ is not statistically different from $Z > 1$ ($p = .086$, $\chi^2 = 4.50$, $df = 1$) or $Z \leq -1$ ($p = .14$, $\chi^2 = 3.56$, $df = 1$).

Discussion

The novel finding in this cohort of 11,361 older adults, with over 6 years of follow-up and CT imaging at 33 different sites, is that higher baseline paraspinous SMA and higher baseline SMD were associated with better survival in men, but not women. The association of CT-derived muscle metrics with survival persisted after adjusting for age, race, smoking, cancer history, and other comorbidities. Importantly, after adjusting for SMD (a measure of myosteatosis), SMA (a measure of muscle mass) remained predictive of mortality. Similarly, after adjusting for SMA, SMD remained predictive of survival. This indicates that muscle mass and myosteatosis contribute independently to survival in older adults.

Our results on the relationship between CT-derived muscle mass and all-cause mortality are similar to another study of community-dwelling adults, the Diabetes Heart Study (DHS). In two separate

Table 4. Association Between CT-Derived Baseline Paraspinous Skeletal Muscle Density and All-Cause Mortality in 6,803 Men and 4,558 Women, Aged 60–69 Years, From the CT Arm of the National Lung Screening Trial

Skeletal Muscle Density		HR per *SD* (95% CI)	*p*-Value
Men (*SD* = 6.99 HU)			
Model 1	Unadjusted	0.90 (0.84, 0.98)	.010
Model 2	Adjusted for age, race, pack-years of smoking	0.91 (0.85, 0.99)	.023
Model 3A	Adjusted for Model 2 and height	0.91 (0.84, 0.98)	.018
Model 3B	Adjusted for Model 2 and weight	0.90 (0.83, 0.98)	.011
Model 4A	Adjusted for Model 3A and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.91 (0.84, 0.98)	.012
Model 4B	Adjusted for Model 3B and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.91 (0.84, 0.98)	.017
Model 5A	Adjusted for Model 4A and skeletal muscle area	0.89 (0.83, 0.96)	.002
Model 5B	Adjusted for 4B and skeletal muscle area	0.89 (0.82, 0.96)	.002
Women (*SD* = 7.31 HU)			
Model 1	Unadjusted	0.99 (0.88, 1.12)	.843
Model 2	Adjusted for age, race, pack-years of smoking	1.00 (0.88, 1.13)	.962
Model 3A	Adjusted for Model 2 and height	1.00 (0.89, 1.13)	.997
Model 3B	Adjusted for Model 2 and weight	1.00 (0.89, 1.14)	.964
Model 4A	Adjusted for Model 3A and type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.98 (0.87, 1.11)	.754
Model 4B	Adjusted for Model 3B and presence of type 2 diabetes, chronic lung disease, cardiovascular disease, and cancer	0.99 (0.88, 1.12)	.910
Model 5A	Adjusted for Model 4A and skeletal muscle area	0.98 (0.87, 1.10)	.714
Model 5B	Adjusted for Model 4B and skeletal muscle area	0.99 (0.87, 1.12)	.857

Note: CI = confidence interval; CT = computed tomography; *SD* = standard deviation; HR = hazard ratio; HU = Hounsfield units; BMI = body mass index. *p-Values are calculated using the Cox proportional hazards model.*

cohorts of the DHS (ie, African American and European American), CT measurements of skeletal muscle index (SMI) were performed on paraspinous and psoas muscles. In African Americans with T2D with over 7 years of follow-up, Murea et al. (34) reported an association between baseline paraspinous SMI (hazard ratio [HR] =0.64; p = .004) and psoas SMI (HR = 0.61; p = .004) with all-cause mortality in men, but not women. Similar sex differences were observed in our study. In European Americans with T2D with over 11 years of follow-up, Tucker et al. (38) reported an association between psoas SMI (HR = 0.82; p = .008) and all-cause mortality, but not paraspinous SMI. In that study, the results did not differ significantly between men and women. Unlike our multicenter study, both DHS cohorts were enrolled at a single-center, had slightly younger participants (DHS-AA median age: 56 years; DHS-EA median age: 63 years), had a longer follow-up period, and used a manual approach to measuring muscle (ie, using clinical PACS software at the L4 level). Future longitudinal studies will be needed to confirm the relationship between CT-derived muscle mass and survival in older adults.

Our results on the relationship between CT-derived SMD (a surrogate of myosteatosis) and all-cause mortality compare favorably with the DHS-EA and the Framingham Heart Study. In 839 European Americans with T2D in DHS-EA (38), paraspinous SMD (HR = 0.85, p = .003) and psoas SMD (HR = 0.81, p < .001) were associated with all-cause mortality. However, in 570 African Americans with T2D in DHS-AA, SMD was not associated with mortality (34). In the Framingham Heart Study, Shah et al. (39) reported on the association of CT-derived metrics and health outcomes in 2,924 participants (median age, 50 years). Their principal component analysis of 11 different CT measurements showed that SMD was associated with mortality (39). Although the inconsistency among studies of CT-derived SMD and mortality may be explained in part by different study populations and measurement methods, the underlying mechanisms of how increased fatty infiltration of muscle contributes to decreased survival is an area of active research (35,40).

Unlike our study that evaluated *axial* (ie, paraspinous) muscle metrics, most other large studies in community-dwelling adults have evaluated *appendicular* muscle metrics, typically in the thigh or calf. These CT-derived muscle metrics have been associated with all-cause mortality in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (41), Health Aging and Body Composition Study (42), Osteoporotic Fractures in Men Study (43), and Tobago Health study (44). In the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, Reinders et al. (41) reported on the association of muscle metrics and mortality in 4,824 participants (median age, 76 years) followed for over 8 years. CT-derived SMA and SMD of the thigh were associated with mortality in men and women. In a longitudinal analysis of thigh CT muscle measurements obtained 5 years apart in Health Aging and Body Composition Study, Santansato et al. (42) reported an association between the loss of muscle mass and gain of intermuscular adipose tissue with increased all-cause mortality. In Osteoporotic Fractures in Men Study, Miljkovic et al. (43) reported an association SMD of the calf and mortality in 1,063 men (median age, 77 years) followed for over 7 years. Similarly, in the Tobago Health study, Zhao et al. (44) reported an association of calf SMD and mortality in 1,652 men (median age, 57 years) followed for over 5 years. In sum, these four studies using *appendicular* muscle metrics appear to support our current study using *axial* muscle metrics. This is significant because calf and thigh muscle metrics typically serve as surrogates of lower extremity muscle function, while axial metrics are more indicative of global muscle function (45). Improved survival in older adults appears to depend on the preservation of lower extremity as well as truncal muscle groups.

Our results confirm the sex-specific differences in the association of CT-derived muscle metrics and mortality in several prior studies. In DHS-AA, the association between SMI and mortality was seen in

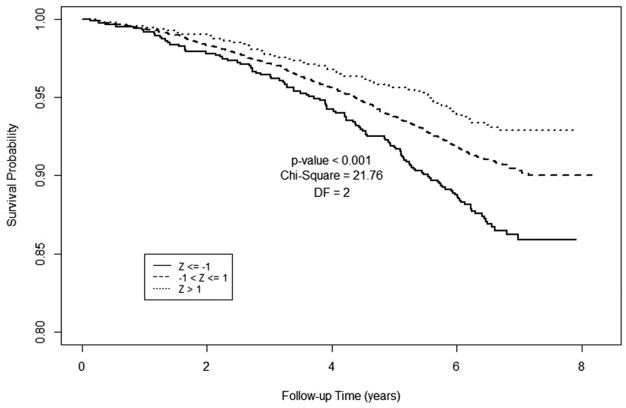

Figure 2. Kaplan–Meier plot for 6,803 men, aged 60–69 years, from the National Lung Screening Trial, based on computed tomography (CT)-derived skeletal muscle area. Survival is compared among three groups stratified by baseline skeletal muscle area: $Z \leq -1$; $Z > -1$ and $Z \leq 1$; $Z > 1$.

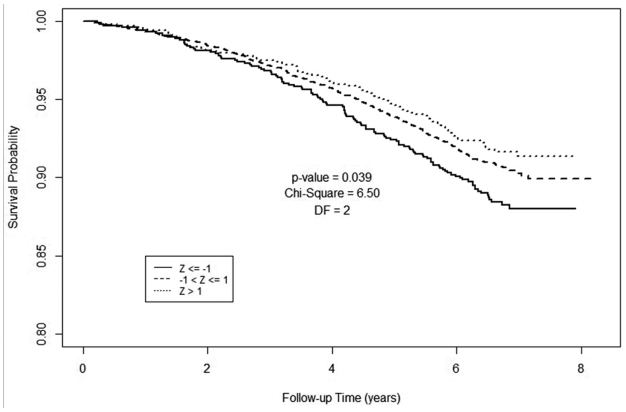

Figure 3. Kaplan–Meier plot for 6,803 men, aged 60–69 years, from the National Lung Screening Trial, based on computed tomography (CT)-derived skeletal muscle density. Survival is compared among three groups stratified by baseline skeletal muscle density: $Z \leq -1$; $Z > -1$ and $Z \leq 1$; $Z > 1$.

men, but not women (34). Similarly, in a study of orthopedic trauma patients, Touban et al. (16) reported on the association between CT-derived psoas SMA and all-cause mortality in 558 older adults (median age, 77 years) followed for 1 year. In men, increased psoas SMA was associated with decreased all-cause mortality (HR = 0.89; confidence interval [CI] = 0.74, 0.96; $p < .002$), but in women the association was not significant ($p = .103$) (16). In a study of hospitalized geriatric patients, Perkisas et al. (33) reported an association between CT-derived intermuscular adipose tissue of the thigh and mortality in men, but not women. The mechanisms underlying the male-specific association between CT-derived muscle metrics and mortality are not well established, but research points to sex differences between hormonal actions, muscle fiber composition, and mitochondrial function that may impact survival (35). For example, in the Framingham Heart Study, sarcopenia appeared to reflect a withdrawal of anabolic stimuli (eg, growth hormone) in men, but an increase in catabolic stimuli (eg, IL-6) in women (46). Besides these differences, men and women may also differ in their physical activity profiles, dietary habits, psychological health, and social behaviors.

Most prior CT studies of muscle have used abdominal CTs and measured various muscles or muscle groups at the level of L3 or

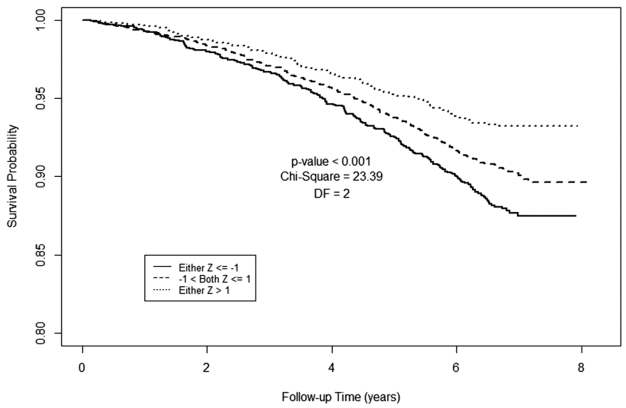

Figure 4. Kaplan–Meier plot for 6,803 men, aged 60–69 years, from the National Lung Screening Trial, based on both skeletal muscle area and skeletal muscle density. Survival is compared among three groups stratified by baseline skeletal muscle area (SMA) and skeletal muscle density (SMD): either SMA or SMD measure $Z \leq -1$; both SMA and SMD $Z > -1$ and $Z \leq 1$; and either SMA or SMD $Z > 1$.

L4 (26). Studies using chest CTs are far less common. Our study results at the level of T12 are consistent with a much smaller study of 274 hip fracture patients followed for over 8 years, where lower paraspinous SMI and SMD were associated with increased all-cause mortality (47).

Studies in community-dwelling older adults have shown that strength and physical performance decline more rapidly than does CT-derived muscle area (48). Weakness and physical performance have consistently been associated with increased risk of mortality, mobility limitations, disability, falls, fractures, and hospitalizations in older adults (49–56). Our evidence and the results of other studies support a relation between CT-derived muscle metrics and mortality in older adults. Taken together, these results raise an important question. What measures should be included in research studies of older adults: (a) CT-derived muscle size and density and/or (b) gait speed and grip strength? To a large extent, the answer depends on feasibility. With our automated approach to measuring muscle size and density on CT images, processing CT scans obtained for other purposes to derive these measures is relatively simple and inexpensive.

Future use of CT in studies of older adults will depend on how quickly such automated approaches to image processing become available. In a recent systematic review, Amini et al. (26) reported on 388 studies that measured muscle mass or myosteatosis using CT. Only 6 of 388 (1.5%) studies used automated methods for muscle segmentation, and none had used an end-to-end pipeline for selecting the correct series, extracting the correct CT slice, and performing muscle measurements (26). This is the first study of such an automated pipeline for skeletal muscle measurements. The automation allowed us to conduct the largest multicenter study to date, evaluating the relationship between CT-derived muscle metrics and mortality in community-dwelling older adults.

Clinical Relevance

The clinical utility of CT compared to DXA for evaluating muscle mass in older adults warrants mention. In an analysis of 5,934 community-dwelling men (65 years and older) from Osteoporotic Fractures in Men Study, three widely used DXA definitions of sarcopenia were evaluated. Importantly, very small improvements in the C-statistic for predicting mortality using DXA were reported,

compared to a reference model using age alone (57). In contrast, a study of 1,326 cancer surgery patients showed that CT-derived muscle mass predicted 1-year mortality (C-statistic = 0.70) better than the modified Frailty Index (C-statistic = 0.55) and the Eastern Cooperative Oncology Group performance score (C-statistic = 0.57) (58). These results, together with more recent data from Sarcopenia Definitions and Outcomes Consortium (13) and the results of our current study, suggest that CT may be preferable to DXA for the evaluation of muscle health in older adults.

The clinical utility of chest rather than abdominopelvic CT exams for analysis of muscle health also merits mention. The lung cancer screening recommendations from the United States Preventive Services Task Force (USPSTF) and Centers for Medicare and Medicaid Services (CMS) were developed based on the NLST data (59). Since then, increasing numbers of smokers, aged 55 years and older, are undergoing screenings using low-dose chest CT scans. To increase the cost-effectiveness of these screenings, some investigators have proposed opportunistic measurements of coronary artery calcium (60), chronic obstructive pulmonary disease (61), and bone mineral density (62). Cressman et al. (63) reported that the cost-effectiveness of lung cancer screening was predominantly driven by non-lung cancer outcomes. Similarly, there is potential for muscle screening to be performed on the same chest CTs that are used for lung cancer screening. As the number of chest CTs performed in older adults increases, such evaluation of muscle metrics may help improve the cost-effectiveness of lung screening programs while at the same time providing valuable prognostic information about overall survival.

Strengths and Limitations

Our study has several limitations. This was a retrospective cohort study that may introduce bias concerning the causal chain between muscle metrics and mortality. The NLST did not collect physical function measurements or lean mass measurements using DXA.

Our study also has several important strengths. This is the largest multicenter study using CT-derived measures of skeletal muscles in community-dwelling older adults. The CT examinations were acquired at 33 medical centers, using CT scanners from four different manufacturers. Unlike most prior studies, we measured muscle attenuation on chest CTs at T12 rather than abdominopelvic CTs. This has broad generalizability since the T12 level is included in the field of view of both chest CTs and abdominopelvic CTs.

Perhaps the greatest strength of our study is that all 11,361 chest CT examinations were evaluated using an open-source, fully automated, image processing pipeline. For researchers, the value of such a pipeline cannot be overstated. In most prior studies using CT to evaluate skeletal muscles, the correct CT series, the correct CT image, and the correct muscle group were chosen individually by the researcher in a very time-consuming process. After that, even more time was spent either on manual or semi-automated segmentation of various muscles to obtain the desired muscle metrics. With the increasing size and complexity of multicenter studies, the burden of such image analysis becomes overwhelming, which motivated us to develop an automated solution. Our results indicate that such an automated pipeline can easily be applied to a multicenter study of older adults with a heterogeneous set of CT images acquired on various scanners. Soon, our pipeline will be adapted to evaluate other muscle groups, including commonly measured total abdominal muscles at the level of L3, as well as other tissues, including visceral, subcutaneous, and intermuscular adipose tissue.

Conclusion

This is the first large study of community-dwelling older adults where CT-derived muscle mass and muscle density showed a robust association with all-cause mortality. Our study confirms that CT-derived muscle metrics are useful prognostic biomarkers in older adults. In the future, a better understanding of the relationships between these muscle metrics and other health outcomes should help target interventions to improve the health of older adults.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None reported.

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