APPENDICULAR LEAN MASS AND MORTALITY AMONG PREFRAIL AND FRAIL OLDER ADULTS

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Abstract: *Objective:* Prefrail and frail older adults are a heterogeneous population. The measurement of appendicular lean mass (ALM) may distinguish those at higher versus lower risk of poor outcomes. We examined the relationship between ALM and mortality among prefrail and frail older adults. *Design:* This was a population-based cohort study. *Setting:* The Third National Health and Nutrition Survey (NHANES III; 1988-1994). *Participants:* Older adults (age ≥65 years) with pre-frailty or frailty defined using the Fried criteria. *Measurements:* ALM was quantified using bioimpedance analysis. Multivariable-adjusted Cox regression analysis examined the relationship between ALM and mortality. Logistic regression analysis was used to determine if ALM added to age and sex improved the predictive discrimination of five-year and ten-year mortality. *Results:* At baseline, the average age was 74.9 years, 66.7% were female, 86.3% and 13.7% were prefrail and frail, respectively. The mean ALM was 18.9 kg [standard deviation (SD): 5.5]. During a median 8.9 years of follow-up, 1,307 of 1,487 study participants died (87.9%). Higher ALM was associated with a lower risk of mortality. In a multivariable-adjusted regression model that accounted for demographic, behavioral, clinical, physical function, and frailty characteristics, each SD increase in ALM was associated with an 50% lower risk of mortality [Hazard Ratio: 0.50 (95% CI: 0.27-0.92); P=0.026]. The addition of ALM to age and sex improved the predictive discrimination of five-year (P=0.027) and ten-year (P=0.016) mortality. *Conclusion:* ALM distinguishes the risk of mortality among prefrail and frail older adults. Additional research examining ALM as a therapeutic target is warranted.

Key words: Lean mass, geriatrics, population-based, bioimpedance analysis.

Introduction

The musculature of the arms and legs, known as appendicular lean mass (ALM), accounts for ≥75% of skeletal muscle in the body, and is required for ambulatory activity and physical functioning (1). Older adults lose approximately 0.1 kg (0.5%) of ALM annually after the age of 40-50 years (1-3). The progressive loss of ALM may be a key element in the development and progression of frailty (4, 5), a syndrome of poor global health that is highly prevalent among older adults that includes unintentional weight loss, impaired physical function, weakness, exhaustion, and low levels of physical activity (6). Prefrail and frail older adults are prone to experience disability, falls, hospitalization, and death (6). However, prefrail and frail older adults are a heterogeneous population with varying degrees of functional disability (7). The measurement of ALM among prefrail and frail older adults may distinguish those at highest risk of poor outcomes, including mortality. We tested the hypothesis that ALM is independently associated with mortality among a population based sample of prefrail and frail older adults aged ≥65 years.

Methods

Study Design and Participants

The Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) was a stratified multistage study conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, to provide health information on a nationally-representative sample of U.S. civilians (8). The NHANES III sample does not include persons residing in nursing homes, members of the armed forces, institutionalized persons, or US nationals living abroad. Participants provided written informed consent prior to completing any study-related activities. Participants in this analysis included adults of age ≥65 years.

Frailty Definition

We implemented a definition of frailty that has been operationalized previously in the NHANES III database (9). The five criteria for frailty included:

1. Low weight-for-height, defined using a body mass index (BMI) ≤18.5 kg/m^2;
2. Slow walking speed, defined using the slowest quintile adjusted for sex, in a timed 2.4-meter walk;
3. Weakness, defined as having any level of difficulty or inability to lift or carry something as heavy as 4.5-kilograms;
4. Exhaustion, defined as having any level of difficulty or inability to walk from one room to another on the same floor;
5. Low levels of physical activity, defined as a self-report of being less active compared to men or women of a similar age.

Participants who met 1-2 or ≥3 of the 5 above-described criteria were classified as prefrail or frail, respectively (9).

Appendicular Lean Mass

ALM was quantified using bioimpedance analysis (BIA). BIA was assessed using a bioresistance body composition analyzer (Valhalla 1990B, Valhalla Medical, San Diego, California) (10). Whole-body BIA measurements were obtained between the right wrist and ankle while lying in the supine position (10, 11). All participants fasted for a minimum of six-hours. Body mass and height were measured with the participant dressed in an exam gown without shoes. ALM was calculated using a validated equation, where ALM (kg) equals: -6.296 + (Height^2/Resistance × 0.227) + (Reactance × 0.072) + (Sex × 9.909) + (Weight × 0.072) + (Sex × Age × -0.098) + (Age × 0.054); where height is in centimeters, weight is in kilograms, sex is equal to 1 for males and 0 for females, and resistance and reactance are in ohms (12). ALM calculated using this equation accounts for 92.3% of the variability in ALM quantified using dual-energy x-ray absorptiometry among prefrail and frail older adults (r=0.961; R^2=0.923).

Mortality Outcome

Vital status was identified using the National Death Index (NDI) database through December 31, 2011. Participants were linked to the NDI database using probabilistic matching that included 12 identifiers such as Social Security number, sex, and date of birth (13).

Covariates

Demographic information including age, sex, and race were reported using a standardized questionnaire (14). Behavioral and clinical information including smoking status, self-rated health, hospitalization, and falls were reported using a standardized questionnaire (14). Cognitive function was quantified using the short portable version of the Mini Mental Status Exam to form a score that ranges from 0 to 17, with higher scores indicating better cognition (15). The presence of comorbid health conditions was self-reported. Laboratory assay procedures have been described in detail (16, 17). Poor balance was defined as the inability to maintain a full tandem stand for 10 seconds (18). Gait speed was assessed using a four-meter walk, timed with a stopwatch.

Statistical Analysis

Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) between ALM and mortality. The assumption of proportional hazards was confirmed using log-log plots. Four regression models were specified to systematically understand the relationship between ALM and mortality after incrementally accounting for important covariates. To explore the discriminative capacity of ALM to prognosticate five- and ten-year year mortality, we calculated the area under the receiver operating characteristic (ROC) curve, known as the C-statistic, using logistic regression models. All analyses incorporated sample weights to account for nonresponse bias and multistage sampling probabilities (19). Stata/SE v.14.1 was used for all analyses.

Results

Cohort Characteristics

The mean age of study participants was 74.9 years and 66.7% were female (Table 1). The majority of study participants were prefrail (86.3%). Weakness was the most common individual frailty component (63.6%), followed by low physical activity (38.4%), slow walking (33.4%), exhaustion (17.1%), and low weight-for-height (6.4%). Participants reported a variety of comorbid health conditions (43.9% with ≥3 conditions). Participants had or were at risk for mobility disability, as reflected by a slow gait speed gait speed (76% <0.8 m/s), poor balance (42.3%), and recent falls (32.4%).

Figure 1
Risk of mortality associated with appendicular lean mass, and results from multivariable model analyses
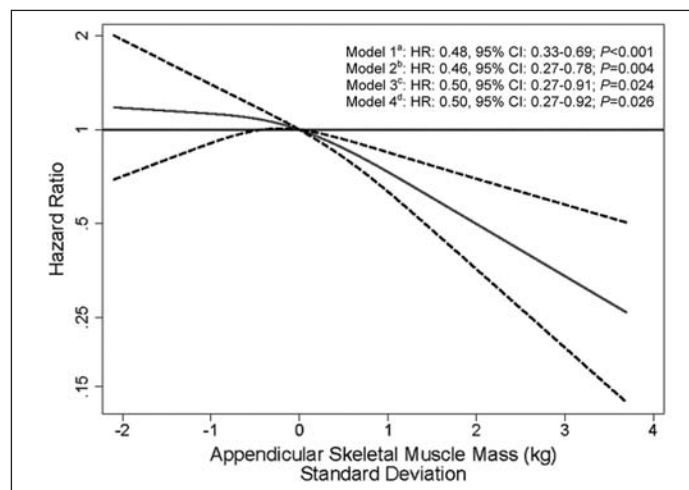
NOTE: Solid curve represents estimate of the hazard ratio (HR) for mortality. Dashed curves represent pointwise 95% confidence intervals (95% CI). The reference point (hazard ratio of 1) represents the sample mean appendicular lean mass (18.9 kg) and each standard deviation represents 5.5 kg. a. Model 1 is adjusted for age, sex, body mass, and height. b. Model 2 is adjusted for the covariates in model 2, and race, smoking status, cognitive function, hypertension, hyperlipidemia, COPD, cancer, arthritis, myocardial infarction, stroke, heart failure, kidney disease, self-rated health, hospitalization, falls, hemoglobin, c-reactive protein, glycated hemoglobin, insulin, glucose, and creatinine. c. Model 3 is adjusted for the covariates in model 3, and poor balance and gait speed. d. Model 4 is adjusted for the covariates in model 3, and stage of frailty (prefrail versus frail).

Appendicular Lean Mass and Mortality

Average ALM was 18.9 kg [standard deviation (SD): 5.5 kg]. During a median follow-up of 8.9 years [interquartile range: 4.6 to 14.6], we observed 1,307 deaths (87.9%). In multivariable-adjusted regression models, each SD increase in ALM was associated with a 50% lower risk of mortality [HR:

0.50 (95% CI: 0.27-0.92); P=0.026]. This relationship was robust to the inclusion of a variety of covariates (Figure). The relationship between ALM and mortality was not modified by sex ($P_{interaction}$=0.73).

Table 1

Characteristics of study participants[a]

Characteristic	Overall (N=1,487) [mean (SE) or (%)]
Age, yrs	74.9 (0.25)
Sex, %	
Male	33.3%
Female	66.7%
Race, %	
White	85.6%
Black	11.6%
Other	2.9%
Body Mass, kg/m²	69.3 (0.61)
Height, m	1.6 (0.003)
Appendicular Skeletal Muscle Mass, kg	18.9 (0.15)
Smoking Status, %	
Never	48.9%
Former	36.7%
Current	14.3%
Cognitive Function, sp-MMSE score	12.2 (0.14)
Comorbid Health Conditions, %	
Hypertension	50.1%
Diabetes	16.4%
Hyperlipidemia	35.5%
COPD	18.2%
Cancer	11.9%
Arthritis	57.5%
Myocardial Infarction	15.6%
Stroke	10.7%
Heart Failure	11.8%
Kidney Disease	29.0%
Self-Rated Health, %	
Excellent	15.4%
Very Good	30.5%
Good	31.3%
Fair	17.5%
Poor	5.3%
Hospitalization (≥1/year), %	23.1%
Falls (≥1/year), %	32.4%
Poor Balance (<10 s tandem balance), %	42.3%
Hemoglobin, g/dL	13.7 (0.05)
Albumin, g/dL	3.9 (0.01)
C-Reactive Protein, mg/dL	0.6 (0.04)
Glycated Hemoglobin, %	5.9 (0.05)
Insulin, pmol/L	89.8 (3.94)
Glucose, mmol/L	6.3 (0.10)
Creatinine, mg/dL	1.2 (0.01)
Gait Speed, meters/second	0.58 (0.009)
Frailty Components, %	
Low Weight-For-Height	6.4%
Slow Walking	33.4%
Weakness	63.6%
Exhaustion	17.1%
Low Physical Activity	38.4%
Frailty Classification, %	
Prefrail (1-2 Frailty Components)	86.3%
Frail (≥3 Frailty Components)	13.7%

a. Values are means (standard error) or percentages (%). sp-MMSE: short-portable version of the Mini Mental Status Exam.

Discriminative Capacity of Appendicular Lean Mass

The addition to ALM to age and sex improved the predictive discrimination of five-year (c statistic 0.693 vs 0.677; P=0.027) and ten-year (c-statistic 0.731 vs 0.741; P=0.016) mortality.

Discussion

The principal finding of this study is that ALM is independently associated with mortality among a population-based sample of prefrail and frail older adults aged ≥65 years. This relationship was consistent in analyses that accounted for other known prognostic factors such as age, sex, comorbid health conditions, and measures of physical functioning. These data indicate that ALM may serve as a sensitive objective measure that addresses the heterogeneity or health risk among prefrail and frail older adults.

Our findings suggest that ALM may have important implications for the longevity among prefrail and frail older adults. In addition to longevity, adequate ALM is necessary for ambulatory activity and physical functioning (6). Given the central role of muscle mass in the development and progression of frailty (4), improvement of ALM may serve as a potential therapeutic target to direct interventions that seek to improve the health outcomes of vulnerable older adults.

In a prior study, exercise improved muscle protein synthesis and ALM among obese frail older adults (20). Exercise may be a promising intervention to prevent the onset or delay the progression of frailty (21). Among 424 sedentary community-dwelling older adults, 12-months of physical activity reduced the risk of being considered frail (P=0.01), compared to a health education group that was not prescribed physical activity (22). Additional studies are needed to assess whether exercise may improve ALM and long term health outcomes among pre-frail

and frail older adults (23).

The main strength of this study is the large sample size that, based on the sampling design, represents the US population of community-dwelling prefrail and frail older adults. Participants in our sample represented a spectrum of age (65-90 years) and ALM (10.6-34.4 kg). The cohort had sufficient length of follow-up to observe a high proportion of deaths, such that 87.9% of the cohort had died by the end of the follow-up period. The limitation to this study is that comorbid health conditions were self-reported. This likely underestimates the prevalence of comorbidities in this population which may attenuate the strength of the association between ALM and mortality.

In conclusion, our findings suggest that community-dwelling prefrail and frail older adults with a high ALM may be less likely to die compared to those with a low ALM. These data may help to identify which prefrail and frail older adults are at the highest risk for poor outcomes. Additional research examining the role of ALM in frailty is warranted.

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