

Research Article

The Predictive Value of the EWGSOP Definition of Sarcopenia: Results From the InCHIANTI Study

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Abstract

Background. Sarcopenia is associated with increased risk of adverse outcomes in older people. Aim of the study was to explore the predictive value of the European Working Group on Sarcopenia in Older People (EWGSOP) diagnostic algorithm in terms of disability, hospitalization, and mortality and analyze the specific role of grip strength and walking speed as diagnostic criteria for sarcopenia.

Methods. Longitudinal analysis of 538 participants enrolled in the InCHIANTI study. Sarcopenia was defined as having low muscle mass plus low grip strength or low gait speed (EWGSOP criteria). Muscle mass was assessed using bioimpedance analysis. Cox proportional and logistic regression models were used to assess risk of death, hospitalization, and disability for sarcopenic people and to investigate the individual contributions of grip strength and walking speed to the predictive value of the EWGSOP's algorithm.

Results. Prevalence of EWGSOP-defined sarcopenia at baseline was 10.2%. After adjusting for potential confounders, sarcopenia was associated with disability (odds ratio 3.15; 95% confidence interval [CI] 1.41–7.05), hospitalization (hazard ratio [HR] 1.57; 95% CI 1.03–2.41), and mortality (HR 1.88; 95% CI 0.91–3.91). The association between an alternative sarcopenic phenotype, defined only by the presence of low muscle mass and low grip strength, and both disability and mortality were similar to the association with the phenotypes defined by low muscle mass and low walking speed or by the EWGSOP algorithm.

Conclusions. The EWGSOP's phenotype is a good predictor of incident disability, hospitalization and death. Assessment of only muscle weakness, in addition to low muscle mass, provided similar predictive value as compared to the original algorithm.

Key Words: Sarcopenia—Aging—Disability—Mortality—Hospitalization

Aging is associated with the loss of muscle mass and strength that has been referred to as sarcopenia (1,2). In older people the main consequence of sarcopenia is the limitation of physical performance, which increases the risk of frailty, falls, hospitalization, disability, and mortality (3–7).

It has been suggested that, by itself, low lean mass is a poor predictor of functional outcomes compared with low muscle strength and functional impairment (8,9). The European Working

Group on Sarcopenia in Older People (EWGSOP) recommended using the presence of both low muscle mass and low muscle function (strength or performance) to define sarcopenia (6), based on the concept that defining sarcopenia only in terms of quantitative muscle mass amount would not capture other important age-related muscle changes that strongly affect muscle quality, strength, and power. The operational definition of sarcopenia of the International Working Group on Sarcopenia (2) also

includes measures of strength and function in addition to quantitative assessment of muscle mass. Moreover, the reports of two consensus conferences, convened by the Special Interest Groups on cachexia-anorexia in chronic wasting diseases and nutrition in geriatrics (European Society for Clinical Nutrition and Metabolism) (10), and by the Society of Sarcopenia, Cachexia, and Wasting Disorders (11), have included both lean mass and gait speed as diagnostic criteria for sarcopenia underlying the importance of each factors especially as predictors of mortality and physical disability. Finally, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project has recently reinforced the role of weakness (defined as low muscle strength) and low muscle mass as key components of the sarcopenia phenotype (12).

Nevertheless, the prognostic value of these definitions has not been fully demonstrated, as only a few studies have formally investigated the predictive value of the proposed algorithms in terms of mortality (13), risk of hospitalization, and incident disability (14). Furthermore, the inclusion of gait speed as a diagnostic criteria for the diagnosis of sarcopenia has been recently questioned (15) because in older people slow walking speed may be the consequence of multiple impairments not related to muscle mass and quality (16,17).

Using data from the population-based InCHIANTI study, we conducted a longitudinal study to investigate the predictive value of the EWGSOP sarcopenic definition, and of its singular diagnostic criteria, in terms of future disability, hospitalization, and mortality.

Methods

Study Population

The InCHIANTI study is an epidemiological, population-based study of randomly selected older people living in the Chianti area, Tuscany, Italy. The study was designed to identify risk factors for late-life disability, as previously described (18). Briefly, participants were selected from the city registries of Greve in Chianti and Bagno a Ripoli using a multistage sampling method. In 1998, 1,453 persons who were randomly selected agreed to participate in the project. The Italian National Research Council on Aging Ethical Committee ratified the study protocol, and participants provided written consent to participate. For this analysis we used data from the second and the third follow-up performed 6 years and 9 years after baseline respectively (2004–2006 and 2007–2009). Data of deaths and hospitalizations were available up to April 2010 and therefore were included in the analysis. Of the 1,067 participants alive at the second follow-up, we excluded 270 participants who did not perform the follow-up visit at the clinical center and 67 participants who did not undergo bioimpedance analyses (BIA, exclusion criteria: leg edema, pacemaker, joint prosthesis, severe varicosities, home visit, and refused). We finally excluded 192 participants because they were younger than 65 years. The analysis was therefore performed in 538 persons (aged 65–94 years), 250 men and 288 women, with complete follow-up data.

Assessment of Sarcopenia

Sarcopenia was defined, according to the EWGSOP criteria, as the presence of low muscle mass, plus low muscle strength, or low physical performance; conversely, the presence of low muscle mass with normal muscle strength and normal physical performance was defined as pre-sarcopenia (6).

Muscle mass was measured by BIA using a Quantum/S Bioelectrical Body Composition Analyzer (Akern Srl, Florence, Italy). Whole-body BIA measurements were taken between the right wrist and ankle with subject in a supine position. Muscle mass was calculated using the BIA equation of Janssen and colleagues (19): Skeletal muscle mass (kg) = $([\text{height}^2/\text{BIA resistance} \times 0.401] + [\text{gender} \times 3.825] + [\text{age} \times -0.071]) + 5.102$, where height is measured in centimeters; bioelectrical impedance analyses resistance is measured in ohms; for gender, men = 1 and women = 0; age is measured in years. This BIA equation was previously developed and cross-validated against magnetic resonance imaging measures of whole-body muscle mass (19); furthermore, in our study, muscle mass assessed by BIA was strongly and significantly correlated with midcalf muscle area assessed using quantitative computerized tomography technique (Pearson correlation coefficient .73, $p < .0001$). Absolute skeletal muscle mass (kg) was converted to skeletal muscle index standardizing by meters squared (kg/m^2) (20). Using the cutoff points indicated in the EWGSOP consensus (6), low muscle mass was classified as skeletal muscle index less than 8.87 and 6.42 kg/m^2 in men and women, respectively. Muscle strength was assessed by grip strength (GS), measured using a hand-held dynamometer (hydraulic hand BASELINE; Smith & Nephew, Agrate Brianza, Milan, Italy). Two trials for each hand were performed and the highest value of the strongest hand was used in the analysis (8). BMI-adjusted values proposed by EWGSOP's consensus were used as cutoff points to classify low muscle strength (men: BMI $\leq 24 \text{ kg}/\text{m}^2$ GS $\leq 29 \text{ kg}$, BMI 24.1–28 kg/m^2 GS $\leq 30 \text{ kg}$, BMI $> 28 \text{ kg}/\text{m}^2$ GS $\leq 32 \text{ kg}$; women: BMI $\leq 23 \text{ kg}/\text{m}^2$ GS $\leq 17 \text{ kg}$, BMI 23.1–26 kg/m^2 GS $\leq 17.3 \text{ kg}$, BMI 26.1–29 kg/m^2 GS $\leq 18 \text{ kg}$, BMI $> 29 \text{ kg}/\text{m}^2$ GS $\leq 21 \text{ kg}$) (6). Usual walking speed (meter/second) on a 4-m course was used as objective measures of physical performance; speed lower than 0.8 m/s identified participants with low physical performance.

Outcomes

Mortality

At the end of the field data collection, mortality data of the original InCHIANTI cohort were collected using data from the Mortality General Registry maintained by the Tuscany Region and the death certificates that are deposited immediately after death at the Registry office of the municipality of residence.

Hospitalization

Information on hospitalization was collected using hospital discharge records extracted from the administrative archives of the Tuscany Health Care System. For this analysis we considered the first hospitalization after the baseline visit that was the day of BIA analysis during the second follow-up.

Incident Disability

Activities of daily living (ADL) and instrumental activities of daily living (IADL) were evaluated through a standardized interview-administered questionnaire. At baseline (second follow-up) prevalent disability was defined as the presence of any difficulty in one or more ADL or IADL, respectively (21,22). At the third follow-up, ADL and IADL status was reassessed using the same questionnaire: incident disability in ADL or IADL was analyzed separately and defined as development of new ADL or IADL disability among subjects free of ADL/IADL disabilities at second follow-up, or increase in the number of ADL/IADL limitations among those who already had

prevalent ADL or IADL disability at second follow-up. However, because of the low incidence of ADL disability ($n = 34$), only IADL disability was considered in the statistical analysis.

Covariates

Socio-demographic variables (age, gender, education) were assessed through survey questions.

The baseline prevalence of specific medical conditions was established using standardized criteria that combined information from self-reported history, medical records, and a clinical medical examination. Diagnostic algorithms were modified versions of those created for the Women’s Health and Aging Study (23). Comorbidity was codified as the sum of 14 diseases including diabetes, hypertension, congestive heart failure, coronary heart disease, arthritis, hip fracture, gastrointestinal disease, hepatic disease, renal failure, peripheral arterial disease, stroke, chronic obstructive pulmonary disease, Parkinson’s disease, and cancer. Cognitive status was explored using the Mini Mental State Examination test.

Biochemical Parameters

Blood samples were obtained from participants after a 12-hour fast. Serum and plasma were stored in a deep freezer at -80°C and were not thawed until analyzed. Hemoglobin levels were analyzed using the hematology autoanalyzer Dasit SE 9000 (Sysmex Corp., Kobe, Japan). Creatinine clearance was assessed using the Cockcroft–Gault formula.

Statistical Analysis

For descriptive purposes, baseline characteristics of the study population were compared according to three groups as follows: (i) no sarcopenia, (ii) pre-sarcopenia, and (iii) sarcopenia, using a chi-square test and the analysis of variance model for categorical and continuous variables, respectively. Preliminary survival analysis showed similar mortality rates for both non-sarcopenic and pre-sarcopenic participants and therefore, in subsequent analyses, participants without sarcopenia were considered as single group.

Cox proportional hazard models and logistic regression models were used to assess the risk of both death and hospitalization and disability respectively. Hazard ratios (HR) and 95% confidence intervals (95% CI) from proportional hazard models were used to estimate the association of sarcopenia with mortality and hospitalization. Three models were fitted for each outcome: unadjusted, age and gender adjusted, and adjusted for potential confounders associated with sarcopenia. The final models included variables found to be independently associated with sarcopenia in our previous cross-sectional analysis on the same sample (24). Three identical logistic models were used to assess the risk of incident IADL disability.

Finally, in order to investigate the individual contributions of GS and walking speed to the predictive value of the EWGSOP algorithm, we built additional models combining low skeletal muscle index with low GS and low gait speed separately. Models were adjusted for age and gender. All analyses were performed using Stata 11.0 for Windows (StataCorp, College Station, TX).

Results

General characteristics of participants according to the presence of sarcopenia or pre-sarcopenia at baseline are presented in Table 1. Mean age of study participants was 77.1 (SD 5.5) years, and 53.5% were women. Median follow-up time was more than 4 years (55 months). Of the 538 participants enrolled into the present study, 55 (10.2%) were identified as affected by sarcopenia and 110 (20.4%) by pre-sarcopenia at baseline.

Of the original 538 participants, 22% developed incident disability in IADL between second and third follow-up. Participants with sarcopenia had significantly higher risk of incident disability compared with not sarcopenic participants (61% vs 18%, $p < .001$).

Results from logistic regression models (Table 2) showed that, after adjusting for potential confounders (age, gender, comorbidities, BMI, education, and hemoglobin), sarcopenia was strongly and independently associated with risk of incidence disability (odds ratio [OR] 3.15; 95% CI 1.41–7.05).

Table 1. Selected General Characteristics of Study Participants According to the Presence of Sarcopenia

Characteristics	Sarcopenia	No Sarcopenia			<i>p</i>	<i>p</i> *
		Low Muscle Mass	Normal Muscle Mass	All		
N	55	110	373	483		
Female (%)	65.4	57.3	50.7	52.2	.062	
Age (y)	83.8 ± 5.9	77.7 ± 4.9	75.9 ± 4.9	76.3 ± 5.0	<.001	
Education (y)	4.7 ± 2.6	6.6 ± 3.7	6.1 ± 3.4	6.3 ± 3.5	.001	.012
BMI (kg/m ²)	25.4 ± 4.0	24.7 ± 3.3	28.4 ± 3.6	27.5 ± 3.9	<.001	.022
SMI (kg/m ²)	6.57 ± 1.29	6.90 ± 1.28	8.58 ± 1.52	8.20 ± 1.63	<.001	<.001
Grip strength (kg)	21.24 ± 5.13	31.21 ± 8.48	34.12 ± 10.85	33.46 ± 10.42	<.001	<.001
4-m walking speed (m/s)	0.73 ± 0.24	1.10 ± 0.16	1.07 ± 0.24	1.07 ± 0.22	<.001	<.001
Comorbidities (<i>n</i>)	2.6 ± 1.2	2.2 ± 1.2	2.0 ± 1.2	2.0 ± 1.2	<.001	.418
ADL disability (%)	5.4	0.9	1.3	1.2	.021	.924
IADL disability (%)	70.9	24.5	26.0	25.7	<.001	.021
MMSE score (<i>n</i>)	23.4 ± 4.1	25.9 ± 3.9	26.0 ± 3.5	26.0 ± 3.6	<.001	.083
Hemoglobin (g/dL)	13.0 ± 1.5	14.0 ± 1.3	14.2 ± 1.3	14.1 ± 1.3	<.001	<.001
Creatinine clearance (mL/min)	51.2 ± 19.7	62.7 ± 16.4	70.5 ± 18.6	68.7 ± 18.4	<.001	.089

Notes: *p* values are for the analysis of variance or chi-squared test comparing subjects with and without sarcopenia. Data are means ± SD unless otherwise indicated. BMI = body mass index; SMI = skeletal muscle index.

*Adjusted for age and sex.

Participants with sarcopenia had also a higher rate of hospitalization (60% vs 48%, $p = .087$) compared to participants without sarcopenia. Cox proportional hazard models displayed in Table 2 showed that, even after adjusting for potential confounders, sarcopenia was significantly associated with hospital admission (HR 1.57; 95% CI 1.03–2.41).

Over the 55 months of follow-up 55 participants (10.2%) died and risk of death was significantly higher for participants with sarcopenia compared with non-sarcopenic people (31% vs 8%, $p < .001$).

Estimates derived from the Cox proportional hazard models showed that, after adjusting for potential confounders, sarcopenic participants were almost two times more likely to die relative to non-sarcopenic individuals even though this relationship was of borderline statistical significance (HR 1.88; 95% CI 0.91–3.91).

Table 3 showed that, after adjusting for age and sex, the alternative sarcopenic phenotype defined as the presence of low muscle mass and low GS, regardless of walking speed performance, predicted the

risk of incident disability (OR 4.78; 95% CI 1.84–12.7) and mortality (HR 2.57; 95% CI 2.24–5.32) as well as the alternative phenotype defined by the presence of low muscle mass and low walking speed, regardless of GS performance (OR for disability 1.64; 95% CI 0.64–4.29 and HR for mortality 1.73; 95% CI 0.74–4.03) or the traditional EWGSOP-defined phenotype (OR for disability 2.50; 95% CI 1.16–5.39 and HR for mortality 2.12; 95% CI 1.05–4.30). Furthermore, compared to EWGSOP-defined sarcopenia, sarcopenic participants defined only by low skeletal muscle index and low muscle strength had a similar predictive value for hospitalization (HR 1.63; 95% CI 1.08–2.44 vs HR 1.64; 95% CI 1.03–2.60, respectively).

Discussion

In this community-dwelling elderly cohort, prevalent sarcopenia (10.2%), assessed with the EWGSOP algorithm, predicts the risk of incident disability, hospitalization, and mortality; furthermore the use of handgrip strength, as a measure of muscle weakness, in addition to reduced muscle mass, to define the presence of sarcopenia, provided similar predictive value than the use of walking speed and low muscle mass in terms of incidence of the adverse outcomes investigated.

Our results on the prevalence of sarcopenia are in line with a recent systematic review that reports a variability in the prevalence of sarcopenia (diagnosed according to the EWGSOP's definition) between 1% and 29% among older adults living in the community (25).

This is the first study that explored the relationship between the EWGSOP's sarcopenic phenotype and risk of hospitalization, whereas our results confirmed previous studies on the predictive role of the EWGSOP diagnostic algorithm on mortality and incident disability.

Results from the Health ABC Study showed that low muscle mass, low muscle density, muscle weakness, and impaired physical function increased the risk of hospital admission (26); Legrand and colleagues (27) recently argued that, in people aged 80 and older, physical performance and muscle strength are strong predictors of hospitalization, independently of muscle mass, inflammatory markers, and comorbidity. Starting from this evidence, and based on the lack of data about the predictive value of the EWGSOP's sarcopenia definition on this outcome, we examined the incidence of hospitalization in our cohort, finding an increased risk of hospital admission for sarcopenic participants compared to the non-sarcopenic counterpart.

Table 2. Association Between Sarcopenia and Incidence of Disability, Hospitalization, and Mortality According to Logistic Regression Model and Cox Regression Models Adjusted for Potential Confounders

	No Sarcopenia (<i>n</i> = 483)	Sarcopenia (<i>n</i> = 55)		
		Unadjusted	Model 1*	Model 2†
Disability				
Events	82		25	
OR	1	6.86	2.50	3.15
95% CI	—	(3.50–13.4)	(1.16–5.39)	(1.41–7.05)
Hospitalization				
Events	231		33	
HR	1	1.57	1.63	1.57
95% CI	—	(1.09–2.26)	(1.08–2.44)	(1.03–2.41)
Mortality				
Events	38		17	
HR	1	4.28	2.12	1.88
95% CI	—	(2.42–7.59)	(1.05–4.30)	(0.91–3.91)

Notes: CI = confidence interval; OR = odds ratio; HR = hazard ratio.

*Adjusted for age, gender.

†Adjusted for age, gender, education, BMI, comorbidities, hemoglobin.

Table 3. Risk of Incident Disability, Hospitalization, and Mortality for Sarcopenic Participants: Role of Each Components of the EWGSOP Sarcopenia Diagnostic Algorithm

Outcome	No Sarcopenia (<i>n</i> = 483)	Sarcopenia: Low Muscle Mass +			
		Low Grip Strength (<i>n</i> = 36)		Low Gait Speed (<i>n</i> = 35)	
		Unadjusted	Age and Sex Adjusted	Unadjusted	Age and Sex Adjusted
Disability					
OR	1	9.88	4.78	6.58	1.65
(95% CI)	—	(4.15–23.5)	(1.84–12.7)	(2.86–15.2)	(0.64–4.29)
Hospitalization					
HR	1	1.67	1.64	1.49	1.67
(95% CI)	—	(1.09–2.57)	(1.03–2.60)	(0.93–2.38)	(0.98–2.83)
Mortality					
HR	1	6.02	2.57	4.09	1.73
(95% CI)	—	(3.31–11.0)	(1.24–5.32)	(2.03–8.20)	(0.74–4.03)

Notes: CI = confidence interval; EWGSOP = European Working Group on Sarcopenia in Older People; OR = odds ratio; HR = hazard ratio.

Four recent prospective studies have evaluated the validity of the EWGSOP criteria for predicting mortality in community-dwelling older adults: Arango-Lopera and colleagues (28) examined 345 residents of Mexico City, who were aged 70 years or older, over 3 years of follow-up; Landi and colleagues (29) followed 364 men and women, who were aged 80–85 years and living in the Sirente area of Italy for 7 years; Kim and colleagues (30) examined 556 Korean men and women, who were aged 65 and older over a 6 years of follow-up, and finally Tiago da Silva Alexandre and colleagues followed 1,149 Brazilians aged 60 years or older over a 5 years of follow-up (31). In all these cohorts, sarcopenia was associated with a higher risk for all-cause mortality and our study confirmed this association. Similar results were also confirmed in different study settings, including hospitalized older people enrolled in the CRITERIA to Assess Appropriate Medication Use among Elderly Complex Patients (CRIME) study (13) and nursing home residents (32).

In agreement with several studies, we did not find an increased risk of death for pre-sarcopenic participants, confirming that low lean mass, by itself, is a poor predictor of adverse outcomes and that considering additional information on muscle strength, and not simply muscle mass, is a critical factor for determining both physical disability and mortality risk in older adults (33–35).

With regard to disability, our results are consistent with a previous report from the Saúde, Bem-Estar e Envelhecimento (SABE) Study that showed, in a cohort of 478 community dwelling non-disabled individuals aged 60 and older, an increased risk of ADL and IADL disability for sarcopenic participants defined according to EWGSOP's algorithm (14).

Recently, the FNHI Sarcopenia Project (12) has extended the methodological approach to the diagnostic characterization of sarcopenia, teasing apart the clinically relevant weakness associated with low lean mass from the clinically relevant slowness, defined as low gait speed, a measure that reflects the integrated performance of numerous organ systems (16,17), one of which is the muscular system. Their findings suggest that, among participants without mobility problems, weakness was likely the key to identify individuals at risk for future mobility impairment or death (15). Walking speed should indeed be considered as a universal biological phenomenon influenced by not only several physiological subsystems such as muscle, but also the central nervous system, the perceptual system, the peripheral nervous system, bone and/or joints, and the systems involved in energy production and/or delivery (16). Our results showing that the sarcopenic phenotype defined only for the presence of low muscle mass and low GS predicts the risk of incident disability and mortality as well as the original EWGSOP phenotype and the alternative phenotype defined for the presence of low walking speed and low muscle mass, suggest that low walking speed might not be an essential criterion for the diagnosis of sarcopenia. Furthermore, especially in hospitalized or institutionalized older people, the assessment of walking speed might be unfeasible because of the functional limitation and disability of the patients (13). Therefore, in order to facilitate the diagnosis of sarcopenia, it might be useful, in persons with low muscle mass, focusing on the assessment of handgrip strength only, a simple and inexpensive objective functional measure that provides important prognostic information and that can be considered a reliable alternative for the functional evaluation of patients unable to walk (36).

Furthermore, using walking speed for screening and diagnosis of sarcopenia might be problematic and might lead to some degree of diagnostic misclassification. Indeed, in older people loss of mobility

is multifactorial and therefore some individuals might have walking impairment because of problems different from muscle pathology. From this point of view, using muscle mass and muscle strength as operational criteria for the diagnosis of sarcopenia refocuses the definition on the muscle, which might have important implications for interventions. For example, screening by walking speed in intervention studies testing interventions that may affect muscle mass and quality may be very problematic because some individuals, those with walking impairment due to extra-muscular problems, would be minimally responsive to interventions focusing specifically on muscle (25).

Our study has several strengths: this is a population-based study on a large cohort of community-dwelling older people and it has explored the association between sarcopenia and three different, important clinical outcomes. On the other hand, in interpreting these findings, some limitations should be considered. First, only 1,067 of the 1,453 original participants of the InCHIANTI study attended the second follow-up: selective survival and a healthy selection bias have to be taken into account. Furthermore, as 270 participants were excluded because they were unable to come to the medical center for the visit, it is likely that our analyses might have underestimated the true prevalence of sarcopenia in this selected population. Second, the limited number of persons with sarcopenia may have caused reduced statistical power in multivariable analyses, increasing the likelihood of Type II error and making it impossible to perform a stratified analysis by sex and age. Finally, the use of BIA for muscle mass assessment presents some drawbacks, mainly due to hydration problems frequently observed in older persons that may result in an underestimation of the body fat and an overestimation of fat-free mass. BIA is not the gold standard for muscle mass quantification but it is considered a valid, portable, and reliable method, widely adopted in previous studies, which can be used for both ambulatory and bedridden patients (25).

In summary, in our sample of Italian community-dwelling older adults, the EWGSOP phenotype is a good predictor of incident disability, hospitalization, and death. Assessment of only muscle weakness, in addition to low muscle mass, provided similar predictive value as compared with the original algorithm, suggesting that walking speed assessment might not be essential for sarcopenia definition.

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