Association of Sarcopenia With Short- and Long-term Mortality in Older Adults Admitted to Acute Care Wards: Results From the CRIME Study

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Background. Sarcopenia is a common condition in older and frail populations, and it has been associated with adverse health outcomes. However, impact of sarcopenia on mortality in hospitalized older adults has rarely been evaluated. Aim of the present study was to investigate the association between sarcopenia and mortality during hospital stay and at 1 year after discharge in older individuals admitted to acute care wards.

Methods. This is a multicentre observational study involving 770 in-hospital patients. Muscle mass was quantified with the bioelectrical impedance analysis. The diagnosis of sarcopenia was based on the algorithm proposed by the European Working Group on Sarcopenia in Older People (EWGSOP). After discharge, participants were followed for 1 year. Mortality was assessed during hospital stay and during 1-year follow-up.

Results. Within the 770 participants (mean age: 81 ± 7 years, 56% women), sarcopenia was present in 214 (28%) of them, 22 participants died during hospital stay, and 113 in the year after discharge. Participants with sarcopenia had a significantly higher in-hospital (6% vs 2%; $p = .007$) and 1-year mortality (26% vs 14%; $p < .001$) as compared with participants without sarcopenia. After adjusting for potential confounders, sarcopenia resulted significantly associated with in-hospital (hazard ratio: 3.45; 95% CI: 1.35–8.86) and 1-year mortality (hazard ratio: 1.59; 95% CI: 1.10–2.41).

Conclusions. Sarcopenia is a prevalent condition among older adults admitted to acute care wards and it is associated with increased short- and long-term mortality in hospitalized older adults.

Key Words: Sarcopenia —Mortality—Acute care—Frailty—Physical performance

CHANGES in body composition, consisting in reduction in lean body mass and redistribution of fat, represent a common feature of advanced age. These modifications are associated with increased risk of adverse health outcomes (1,2). Former studies have shown that reduction in muscle mass, which is quantified in 6% per decade after mid-life (3), may impact on muscle function, leading to impairment in muscle strength and physical performance and increased risk of falls, fractures, and disability (4,5).

Sarcopenia is defined as the concurrent reduction of muscle mass and strength, and this condition is widely prevalent in the elderly population—in particular, it is common among the most frail and complex individuals (6,7). Sarcopenia is a multifactorial syndrome and different factors commonly observed among older adults, and in particular among those admitted to hospital, including multimorbidity,

malnutrition, poor physical activity and inflammation, may play a role in its etiology (8–11). Indeed, hospitalization represents a critical moment in the clinical history of older adults life or disease trajectory. The presence of acute conditions associated with preexisting chronic diseases and geriatric syndromes increases the risk of complications and new disability and put the patients at risk for adverse health outcomes (12).

Prevalence and predictive role of sarcopenia were previously investigated both in nursing home and in the community, but so far, there is no evidence on prevalence and outcomes associated with this condition in hospitalized older adults (13). Aim of the present study was to assess prevalence of sarcopenia in a sample of older adults admitted to acute care wards and to investigate the association of sarcopenia with short- (during hospital stay) and long-term (1 year) mortality.

Methods

Sample and Study Setting

Data are from the CRiteria to Assess Appropriate Medication Use among Elderly Complex Patients (CRIME) project, an observational study performed in geriatric and internal medicine acute care wards of seven Italian hospitals (Gemelli Hospital, Università Cattolica del Sacro Cuore of Rome; University of Perugia; University of Ferrara; National Institute of Hospitalization and Care – INRCA situated in Ancona, Cosenza, Fermo, and Rome). Methodology of the CRIME project has been described in detail elsewhere (14,15). In brief, the study was funded by the Italian Ministry of Labour, Health and Social Policy to collect data about the prescription patterns and to assess quality of prescribing in older adults hospitalized in Italy. All patients consecutively admitted to participating wards, between June 2010 and May 2011, were enrolled in the study. Exclusion criteria were: age less than 65 years and unwillingness to take part to the study. All participants were assessed within the first 24 hours from hospital admission and followed until discharge. After discharge, patients were reassessed at 3, 6, and 12 months. All participating centers obtained ethical approval from their institutions, and all participants signed a written consent.

Data Collection

Participants' data were collected through a dedicated questionnaire, according to the procedure previously used for the study of the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA). The questionnaire was filled in at admission and updated daily by the assessors (16). A 2-day course has been held to train study researchers to perform the assessment using the dedicated questionnaire. They were trained to use a variety of information sources, such as direct observation, interviews with the clients, family, friends or formal service providers, and review clinical records, both medical and nursing.

Sarcopenia

European Working Group on Sarcopenia in Older People (EWGSOP) criteria were used to diagnose sarcopenia. According to this definition, documentation of low muscle mass plus either low muscle strength or low physical performance was required for the diagnoses of sarcopenia (17). In order to assess sarcopenia, the following parameters were collected at hospital admission:

Walking speed was evaluated measuring usual gait speed (expressed in meters per second [m/s]) of participants over a 4-m course. A gait speed less than or equal to 0.8 m/s identified subjects with low physical performance (18).

Muscle strength was tested through the hand grip strength, which was measured using a dynamometer (North Coast Hydraulic Hand Dynamometer, North Coast Medical Inc, Morgan Hill, CA) with the patient seated with the wrist in a neutral position and the elbow flexed 90°. For patients unable to sit, grip strength was assessed lying at 30° in bed with elbows supported, as previously described (19). Reliability of grip strength assessed with this methodology in a sample of 20 in-hospital patients was excellent when compared with the one obtained in the seated position with kappa values ranging from 0.92 for the nondominant hand to 0.94 for the dominant hand. Two trials for each hand were performed, then the best result from the strongest hand was used for the present analyses. According to the criteria proposed by the EWGSOP, low muscle strength was classified as hand grip less than 30 kg in men and less than 20 kg in women (18).

Muscle mass was measured by bioelectrical impedance analysis (BIA), a methodology that was demonstrated reliable in predicting muscle mass respect to the dual-energy x-ray absorptiometry (considered a reliable alternative to the gold standards magnetic resonance imaging and CT scan), even in hospitalized elderly patients (20). The BIA resistance was obtained using a Quantum/S Bioelectrical Body Composition Analyzer (Akern Srl, Florence, Italy) with an operating frequency of 50 kHz at 800 mA. Whole-body BIA measurements were taken between the right wrist and ankle with the subject in a supine position. BIA was not performed in patients with peripheral edema and among those with pacemaker or implantable cardioverter defibrillator. Muscle mass was calculated using the BIA equation of Janssen and colleagues (21). The skeletal muscle index (SMI [kg/m^2]) was obtained dividing absolute muscle mass for squared height. Using the cutoff values indicated in the EWGSOP definition, low muscle mass was classified as an SMI less than 8.87 kg/m^2 in men and less than 6.42 kg/m^2 in women. SMI was not calculated in patients unable to stand, because height could not be measured.

Mortality

In-hospital death was used as a measure of short-term mortality. Data on deaths occurring during hospitalization were collected by study researchers. Length of stay from admission to death was collected and used as temporal function in these analyses.

Death occurring in the year after discharge was used as a measure of long-term mortality. After discharged, patients were reassessed at 3, 6, and 12 months through either ambulatory visits and telephone contacts. The day of discharge from hospital was considered as the follow-up starting point. During each follow-up, data on living status and, eventually, the date of death were collected. Time from discharge to last follow-up was considered as temporal function in our study. No information regarding causes of death was gathered.

Covariates

Functional status was evaluated using the participant's dependency in the following activities of daily living:

transferring, bathing, dressing, eating, bowel and bladder continence, and personal hygiene, with higher values indicating higher level of dependency (22). Cognitive status was assessed using the 30-items Mini-Mental State Examination, and mood was investigated by the use of the 15-items Geriatric Depression Scale (GDS) (23,24).

According to the World Health Organization classification, body mass index (BMI) was categorized as follows: less than 18.5 (underweight), 18.5–24.9 (normal range), 25–30 (overweight), and more than 30 (obese) kg/m^2 (25). Assessors recorded all drugs currently taken by the participants at admission: brand name, formulation, and daily dose were registered. All the drugs were coded according to the Anatomical Therapeutic and Chemical codes (26). The number of drugs used during hospital stay was then calculated and categorized in two groups: (a) no drugs and one to four drugs and (b) more than five drugs (27).

Diagnoses were gathered from the patient, attending physicians and by a careful review of medical charts. Finally, comorbidity was assessed using the Charlson Comorbidity Index by adding scores assigned to specific discharge diagnoses, as elsewhere illustrated (28). This index was also categorized according to its median value of 2 as follows: less than or equal to 2 and greater than 2.

Statistical Analysis

From the original CRIME sample, including 1,123 patients, 353 of them were excluded because of missing data on sarcopenia. Comparing these 353 patients with those included in our analyses, the excluded ones resulted older and presented similar rates of disability, cognitive impairment, and comorbidity. The association of sarcopenia and in-hospital mortality was assessed in the remaining sample of 770 patients. To assess the association of sarcopenia and 1-year mortality, from this sample, we excluded 22 patients who died during hospital stay and 98 patients with incomplete follow-up data, leading to a final sample of 650 patients.

Continuous variables were expressed as mean ± *SD* and countable ones as absolute number and percentage (%) of the total. To compare participants' characteristics, according to the presence of sarcopenia, we used analysis of variance analyses for normally distributed variables, nonparametric Mann–Whitney *U* test for skewed variables, and chi-square analyses for categorical ones.

Differences of mortality rates between sarcopenic participants and nonsarcopenic ones were evaluated through Kaplan–Meier curves. Significance was obtained through the log-rank test. Cox proportional hazards regressions were fitted to evaluate the effect of sarcopenia on time to death, adjusting for potential confounders. To exclude departure from proportionality assumption, the log–log survival function was examined. For each outcome, three Cox proportional regression models were performed: unadjusted, adjusted for age and gender, and adjusted for all confounders associated with sarcopenia at a *p* value less than .05 at the univariate analysis and for those conditions potentially affecting the outcome (heart failure, chronic obstructive pulmonary disease, cancer, and dementia). To exclude departure from proportionality assumption, the log–log survival function was examined. Participants with no evidence of death were censored at the time of their last follow-up (3, 6, or 12 months). A sensitivity analysis has been also performed: the association between sarcopenia and mortality was tested through different models in three subsamples, obtained detracting from the total sample patients with a BMI less than 18.5, those with more than four impaired activities of daily living, and those with a Charlson Comorbidity Index higher than 2 (median value in our sample, interquartile range: 1–4).

Moreover, to test if the association between sarcopenia and mortality was independent from physical performance, a variable of "low physical performance" (low hand grip performance or low walking speed performance as above defined) was entered in the models. Finally, with the same purpose, the association between sarcopenia and mortality was tested excluding 64 patients with normal SMI and normal physical performances from the nonsarcopenic group, through a Cox proportional regression model adjusted for potential confounders. All analyses were performed with SPSS PASW Statistics 18.0 statistical software.

Results

Among the 770 study participants (mean age: 80.8 ± 7 years; 56% women), 214 (28%) met the EWGSOP criteria for the diagnosis of sarcopenia and 556 (72%) did not (Figure 1). Table 1 shows main characteristics of study sample according to the presence of sarcopenia. Patients with sarcopenia were older, more likely men and smokers, suffering from chronic kidney disease, and to live alone at home, when compared with those without sarcopenia. In addition, patients with sarcopenia had a higher rate of disability and comorbidity and lower BMI.

In-Hospital Mortality

Patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia during hospital stay (*p* = .007). During hospital stay, 10 (6%) deaths occurred among patients with sarcopenia and 12 (2%) among those without sarcopenia. As shown in Table 2, the diagnosis of sarcopenia resulted independently associated to mortality during hospital stay either in the unadjusted model (hazard ratio [HR]: 3.19; 95% CI: 1.38–7.38), age- and gender-adjusted model (HR: 3.00; 95% CI: 1.23–7.28), and full adjusted model (HR: 3.45; 95% CI: 1.35–8.86). Finally, the association persisted even when a variable of low physical performance was entered in the full adjusted model (HR: 3.14; 95% CI: 1.25–7.72).

Table 1. Sample Baseline Characteristics According to the Presence of Sarcopenia

	Total	No Sarcopenia	Sarcopenia	
	(*n* = 770)	*n* = 556 (72%)	*n* = 214 (28%)	*p*
Demographics				
Age	80.8 ± 7.0	80 ± 7.1	82.8 ± 6.9	<.001
Gender (women)	428 (56)	327 (59)	101 (47)	.005
Smoker (actual/former)	322 (42)	219 (40)	103 (48)	.034
Alcohol consumption (current)	224 (30)	172 (32)	52 (25)	.051
Living alone	184 (24)	120 (22)	64 (30)	.018
Objective parameters				
Activities of daily living at admission (0–6; compromised)	2.3 ± 2.4	2.1 ± 2.4	2.6 ± 2.4	.024
Mini Mental State Examination (0–30)	23 (17–27)	24 (17–28)	22 (17–27)	.226*
Geriatric Depression Scale (0–15)	4.7 ± 3.5	4.7 ± 3.5	4.8 ± 3.5	.974
Body mass index (Kg/m^2)				<.001
<18.5	25 (3)	4 (1)	21 (10)	
18.5–24.9	266 (36)	167 (31)	99 (49)	
25–30	298 (40)	231 (42)	67 (34)	
>30	158 (21)	144 (26)	14 (7)	
Clinical conditions				
Length of hospital stay (d)	10 (7–14)	10 (7–14)	10 (7–14)	.993*
Use of >5 drugs	479 (62)	354 (64)	125 (58)	.158
Urinary catheter	115 (15)	76 (14)	39 (18)	.115
Pressure ulcers	63 (8)	45 (8)	18 (8)	.884
Diarrhea	30 (4)	20 (4)	10 (5)	.533
Constipation	115 (15)	88 (16)	27 (13)	.310
Fever	84 (11)	55 (10)	29 (14)	.156
Daily pain	259 (34)	176 (32)	83 (39)	.062
Diseases				
Charlson Comorbidity Index >2	338 (44)	229 (41)	109 (51)	.015
Hypertension	583 (76)	429 (77)	154 (72)	.134
Chronic obstructive pulmonary disease	298 (39)	209 (38)	89 (42)	.322
Diabetes	234 (30)	179 (32)	55 (26)	.081
Heart failure	200 (26)	141 (25)	58 (28)	.523
Chronic kidney disease	181 (24)	120 (22)	61 (29)	.047
Dementia	156 (20)	103 (19)	53 (25)	.058
Cerebrovascular disease	152 (20)	103 (19)	49 (23)	.189
Atrial fibrillation	133 (17)	94 (17)	39 (18)	.671
Infections	128 (17)	79 (14)	49 (23)	.005
Cancer	106 (14)	71 (13)	35 (16)	.200
Parkinson's disease	67 (9)	53 (10)	14 (7)	.202

Notes: Values are given as mean ± *SD*, median (interquartile range) or number (%).
*Nonparametric test due to skewed distribution.

One-Year Mortality

As shown in Figure 2, patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia after 12 months from discharge (*p* < .001). During follow-up, 66 (26%) events occurred in the sarcopenic group and 47 (14%) in the nonsarcopenic group. As shown in Figure 2, the diagnosis of sarcopenia resulted independently associated to 1-year mortality in the unadjusted model (HR: 2.12; 95% CI: 1.45–3.10), age- and gender-adjusted model (HR: 1.56; 95% CI: 1.10–2.30), and full adjusted model (HR: 1.59; 95% CI: 1.10–2.41). Such an association was confirmed when individuals malnourished (BMI < 18.5), those with higher comorbidity index (Charlson Comorbidity Index > 2) and those with most impaired activities of daily living (>4) were separately excluded by the total sample (see subgroup analyses in Table 2).

Moreover, similarly to In-hospital mortality, the association persisted even when a variable of low physical performance was entered in the fully adjusted model (HR: 1.83; 95% CI: 1.22–2.83). Finally, the association between sarcopenia and mortality persisted even after excluding from the nonsarcopenic groups—64 patients with normal SMI and preserved physical performances (HR: 1.79; 95% CI: 1.20–2.75).

DISCUSSION

According to our findings, sarcopenia is a highly prevalent condition in hospitalized older adults, being present in almost one out of three patients in our sample. In addition, sarcopenia, independently from potential confounders, found to be associated with mortality during hospital stay and 1 year postdischarge.

Table 2. Association Between Sarcopenia and Mortality (in-hospital and 1 y) According to Cox Regression Models Adjusted for Potential Confounders

	Events			Unadjusted Model		Age- and Gender-Adjusted Model		Full Adjusted Model*	
Outcomes	Frequence (%)	*p*	HR	95% CI	HR	95% CI	HR	95% CI
Total sample (*N* = 770)								
In-hospital mortality								
No sarcopenia	12/556 (2 %)	.007	1	—	1	—	1	—
Sarcopenia	10/214 (6%)		3.19	1.38–7.38	3.00	1.23–7.28	3.45	1.35–8.86
1-y mortality†								
No sarcopenia	66/474 (14 %)	<.001	1	—	1	—	1	—
Sarcopenia	47/176 (26 %)		2.12	1.45–3.10	1.56	1.10–2.30	1.59	1.10–2.41
Subgroup 1 (excluding those with a BMI <18.5) (*N* = 627)								
1-y mortality†								
No sarcopenia	64/468 (14 %)	<.001	1	—	1	—	1	—
Sarcopenia	42/159 (26 %)		2.14	1.45–3.16	1.61	1.08–2.41	1.98	1.30–3.00
Subgroup 2 (excluding those with more than four impaired ADLs) (*N* = 550)								
1-y mortality†								
No sarcopenia	29/408 (8 %)	.001	1	—	1	—	1	—
Sarcopenia	25/142 (20%)		2.62	1.53–4.45	1.97	1.14–3.41	1.90	1.10–3.55
Subgroup 3 (excluding those with a Charlson Comorbidity Index >2) (*N* = 363)								
1-y mortality†								
No sarcopenia	14/272 (5 %)	.001	1	—	1	—	1	—
Sarcopenia	16/91 (18 %)		3.59	1.75–7.36	2.74	1.30–5.76	3.08	1.40–6.87

Notes: Independent variable: sarcopenia at admission. HR = hazard ratio; ADLs = activities of daily living.

*Adjusted for: age, gender, smoking habit, living alone, compromised activities of daily living, body mass index, infectious diseases, chronic kidney disease, chronic obstructive pulmonary disease, heart failure, dementia, cancer, and Charlson Comorbidity Index.

†Twenty-two patients died during hospital stay and 98 with incomplete follow-up data were excluded from this analysis.

Concurrent presence of muscle mass reduction and reduced strength has recently indicated with the name of sarcopenia. Even if sarcopenia has originally been referred exclusively to the loss of muscle mass, nowadays experts believe useful to add at this definition a functional and qualitative component that is endorsed by strength (29–31). Sarcopenia etiology is actually widely discussed, and several determinants have been identified, for example, aging process, genetic predisposition, disease pressures, nutrition issues, and physical activity. Notwithstanding, a univocal cause, is thought, does not exist, so that the definition of syndrome results suitable for such entity (32–38). As other geriatric syndromes, sarcopenia represents a challenging issue for either physicians, researchers, and health care systems due to the increasing risk of disability, mortality, hospitalization, and financial resources expenditure to it related (39–41). As recently stated in a call to action, sarcopenia could be considered one of the determinants of frailty in the elderly, and as such needs to be better investigated (42).

Prevalence of sarcopenia in the elderly people has been addressed by a number of studies, across several settings and assessed with different criteria. Figures span from 3% in home-dwelling older adults to 33% among institutionalized individuals with substantial differences across ages and gender (43–46). To our knowledge, only one study assessed the prevalence of sarcopenia among hospitalized older adults beyond the present one. Gariballa and Alessa, among 432 individuals aged 65 years or older admitted to an acute care ward, have observed sarcopenia in 1 out of 10 participants (43). In contrast, in our population, sarcopenia was present in 3 out of 10 participants. Several explanations could be given to justify such contrasting findings. First, in the study of Gariballa and Alessa, subjects with unstable conditions and severe medical or psychiatric illness, including those with malignancy, severe dementia, and living in institution, were excluded. Second, assessment of sarcopenia was exclusively based on handgrip strength and mid-arm muscle circumference. The choice of this different methodology could have determined an underestimation of the condition.

Several studies have assessed the association of sarcopenia with negative health outcomes, including mortality. Landi and colleagues showed that among home-dwelling older adults in Italy, sarcopenia was associated with a 2-fold higher mortality rate. Similarly, Arango-Lopera and colleagues demonstrated that in a sample of 345 older adults in Mexico, sarcopenia was associated with a significantly increased mortality rate (11). These results were confirmed in other settings: Nursing home residents affected by sarcopenia had a 6-month mortality HR of 2.34 in the study of Landi and colleagues (47,48), and hospitalized older adults without sarcopenia were shown to have a lower 6-month mortality rate as compared with those with sarcopenia.

To note, even if disability was previously supposed to be a consequence of sarcopenia, we cannot exclude the hypothesis that it could contribute to its development,
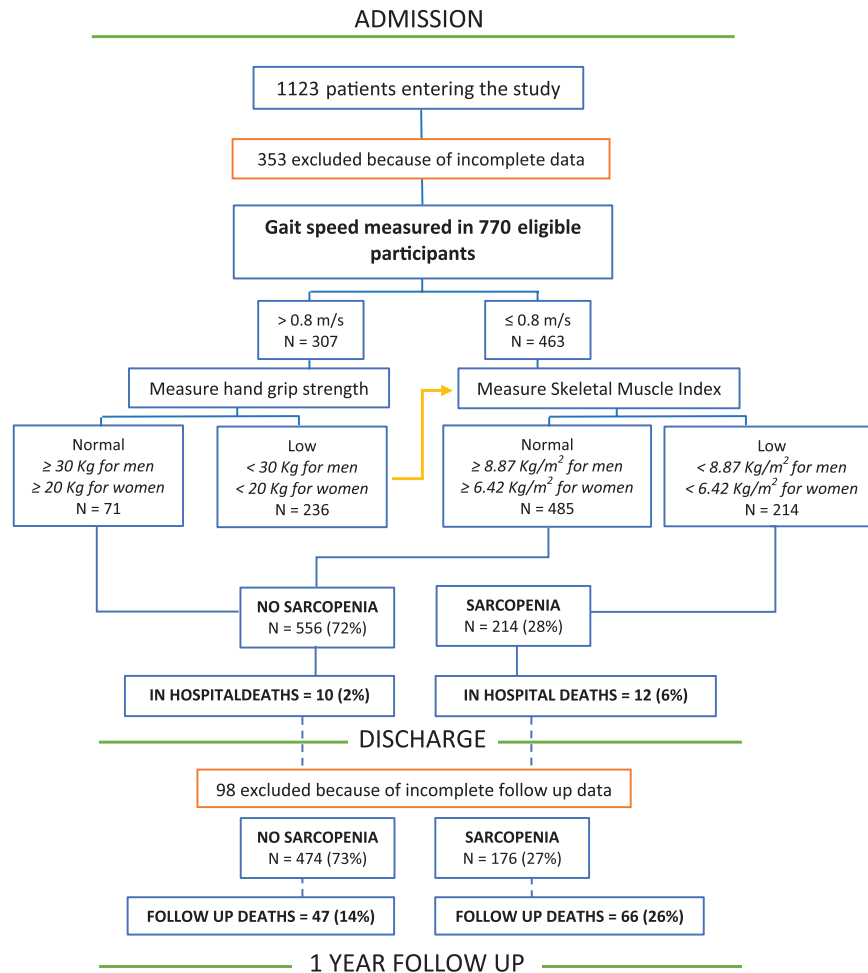
ADMISSION

1123 patients entering the study

353 excluded because of incomplete data

Gait speed measured in 770 eligible participants

> 0.8 m/s
N = 307

≤ 0.8 m/s
N = 463

Measure hand grip strength

Measure Skeletal Muscle Index

Normal
≥ 30 Kg for men
≥ 20 Kg for women
N = 71

Low
< 30 Kg for men
< 20 Kg for women
N = 236

Normal
≥ 8.87 Kg/m^2 for men
≥ 6.42 Kg/m^2 for women
N = 485

Low
< 8.87 Kg/m^2 for men
< 6.42 Kg/m^2 for women
N = 214

NO SARCOPENIA
N = 556 (72%)

SARCOPENIA
N = 214 (28%)

IN HOSPITALDEATHS = 10 (2%)

IN HOSPITAL DEATHS = 12 (6%)

DISCHARGE

98 excluded because of incomplete follow up data

NO SARCOPENIA
N = 474 (73%)

SARCOPENIA
N = 176 (27%)

FOLLOW UP DEATHS = 47 (14%)

FOLLOW UP DEATHS = 66 (26%)

1 YEAR FOLLOW UP

Figure 1. Study profile using the EWGSOP-suggested algorithm for sarcopenia.

according to some authors that suppose a bidirectional relationship of sarcopenia and disability (5,40). For this reason, we repeated the analysis after exclusion of participants with severe disability, confirming the association between sarcopenia and 1-year mortality. When similar analyses were performed excluding malnourished patients, and those with higher levels of comorbidity, the direction of the association remained the same.

Interestingly, association between sarcopenia and mortality remained statistically significant even when physical performance was tested per se as a potential confounder and after excluding those with preserved physical performance and normal SMI from the nonsarcopenic group.

Some limitations of the present study need to be mentioned. First, the original aim of the CRIME project was not to investigate predictive role of sarcopenia, so that its methodology was adapted to the purpose of the present study. In particular, the use of BIA to assess muscle mass might raise some concerns. BIA is not the gold standard for assessment of muscle mass and, in our sample, fluid and electrolytes imbalance, prevalent conditions in hospitalized older adults, could have led to misclassification of sarcopenia. Previous studies have shown BIA is a valid, portable, and reliable method to assess lean body mass, and it provides an accurate estimate of skeletal muscle mass when compared with dual-energy x-ray absorptiometry (20,49), but more studies need to be carried out to better validate its reliability in estimating body composition in acute settings, respect to other gold standards (50,51). In addition, the definition of sarcopenia given in the present study, in line with the criteria suggested by the EWGSOP, that is based on expert opinions and that lacks of confirmation through a data-driven approach, could be responsible for a misclassification of this condition in our sample. Second, participants' acute conditions, often related to momentary functional impairment, could have contributed to an overestimation of the diagnosis of sarcopenia in our sample. Third, we cannot exclude that the association between sarcopenia and mortality is related to residual confounding since data on relevant confounders (including admission diagnoses) were not collected. Finally, in the present study, we were not able to differentiate sarcopenia and cachexia.
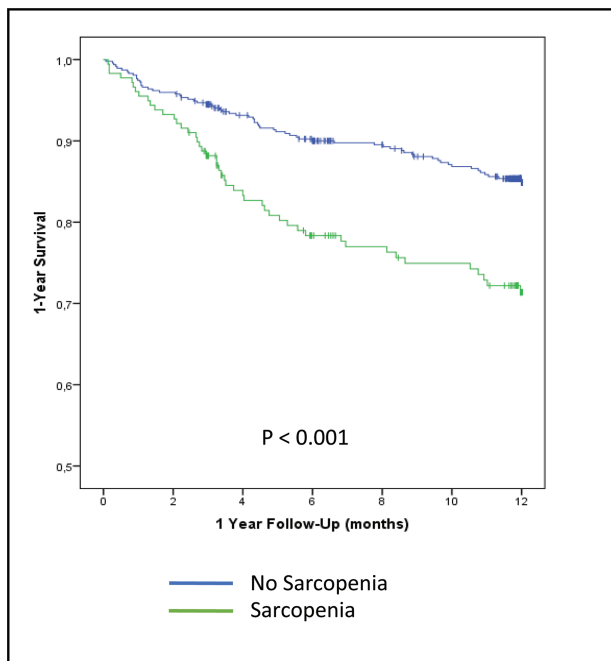
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Figure 2. Kaplan–Meier curves for 1-year survival according to the presence of sarcopenia (significance obtained with log-rank test).

Indeed, these two conditions may overlap in acutely ill older adults because they share common etiological pathways. However, the association between sarcopenia and mortality was confirmed after exclusion of patients presenting common features of cachexia, including low BMI and high level of comorbidities.

In conclusion, sarcopenia is a highly prevalent condition among elderly individuals admitted to acute care wards and represents an independent risk factor for mortality, both on the short and long term. However, evidence on negative effects of sarcopenia is still limited, and more studies are needed to confirm the association between this condition and negative health outcomes and to identify its determinants in order to target potential interventions.

CONFLICTS OF INTEREST

None.

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