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1. Introduction

Sarcopenia is a progressive loss of skeletal muscle mass, muscle strength and muscle function, with significant health consequences. A recent review showed sarcopenia to be correlated with mortality, functional decline, a higher rate of falls and a higher incidence of hospitalizations (1). The strongest evidence was found for the correlation between sarcopenia and mortality, with a pooled odds ratio of 3.596. The impact on public health is less straightforward, due to the large variability in the prevalence of sarcopenia, based on different definitions and cut-off points. This is relevant, because the prevalence of sarcopenia in Europe is likely to rise in the coming years. Predictions are that there will be a 63.8% to 72.4% increase by 2045, depending on prevalence estimates used (2). To emphasize the extremes, one study compared eight definitions of sarcopenia and found a prevalence between 4.4% and 94% (3). Other studies withheld lower values: in community-dwelling patients. Beaudart et al found a prevalence of 8.4% to 27.6% using different diagnostic criteria (4). However, none of these different diagnostic criteria of sarcopenia demonstrated their superiority in prediction of hard outcomes such as fractures, falls, admission in nursing homes, or mortality (5).

Furthermore the care setting may play an important role. In 2014, the International Sarcopenia Initiative classified the prevalence of sarcopenia according to care setting (6). Community-dwelling elderly had a prevalence of 1–29% (up to 30% in women), elderly in acute hospital care had a prevalence of 10% (only one study was included) and those in long-term care institutions had a prevalence of 14–33% (up to 68% in men) (6). An Australian study, using bio-impedance absorptiometry (BIA) and cut-off points suggested by the European Working Group on Sarcopenia in Older People (EWGSOP), found a sarcopenia prevalence in nursing home residents of 40.2% (7). This is a little more than the prevalence found in Chinese nursing homes, where four criteria were used, with a range of 31.4%-38.3% (8).

In 2010, a systematic review investigated different risk factors for nursing home admission. Predictors with strong evidence were functional impairment, cognitive impairment, higher age, low self-rated health status and a high number of prescriptions (9). Some of these factors are certainly linked (10, 11), but the two most important seem to be functional and cognitive decline. Functional decline is not limited to older people, but already starts in the middle ages of life. Fifteen percent of community-dwelling persons in the age category 55-64 year old has problems with activities of daily life, compared to 20-25% of those aged 65 years or older (10). One important factor leading to functional decline is sarcopenia (12), which is predictive of loss of independence in elderly men and women (13, 14). Therefore, it seems logical that the incidence of sarcopenia in nursing homes is higher than in community-dwelling elderly. Although some studies have shown a higher risk of institutionalization among frail people, to our knowledge, no study has shown yet a clear relationship between sarcopenia and nursing home admission (15).

Another question is whether the presence of sarcopenia still remains relevant on hard outcomes in nursing home residents. One study from Italy with a follow-up period of 6 months, showed an adjusted hazard ratio for mortality of 2.34 when sarcopenia was present (16). In this article, the prevalence of sarcopenia in Belgian nursing home residents and its relation with long-term mortality will be investigated. Such correlation should support sarcopenia screening in a nursing home, where most patients already show important difficulties in functional performance.

2. Materials and Methods

2.1. Patient recruitment

This study consists of two phases. The first part was conducted from October 2007 through April 2008. In this period, a longitudinal cohort study was set up in 52 nursing homes in Antwerp (Belgium), in which 737 healthy male and female participants of 65 years and older in residential homes were included. This cohort study was part of a larger study on nutritional and immunological issues in nursing home elderly (trial number NCT 00849277). (17) Following data were procured: anthropometrics, body composition (muscle mass), functional status, nutritional status and a number of laboratory parameters.

Exclusion criteria for the trial were: cognitive deficits; current infectious disease; any disorder having a negative influence on the immune system (such as cancer, chronic inflammatory disease); allergy to influenza vaccine, eggs, neomycin amphotericin B, erythromycin or amantadine; the use of immunosuppressive drugs or antineoplastic medication; the use of antibiotics within 6 weeks prior to the study entry; use of any investigative drug within 90 days prior to study entry, and a markedly abnormal result on any of the screening laboratory tests. Of the participants, patients with a pacemaker or limb prosthesis were excluded (as those are contraindications for BIA). (17)

The second part consists of long-term follow-up data. After 9 years, the nursing homes were contacted in order to check the current health status of the original participants. Mortality was the main outcome. For those participants for which there was no clear data available at the nursing home, local city administrative services were contacted to find out whether the former resident was still alive or not.

2.2. Measurements

Anthropometric data consisted of weight and length.

Body composition was estimated using bio-electrical impedance analysis (BIA). The Body Explorer (Juwell Medical ®) with an operating frequency of 50 kHz at 800 μA was used. The subjects were supine on a nonconducting surface. Their arms were abducted away from their trunk and the legs slightly separated for a few minutes. Four electrodes were attached to the right hand and ankle. The young reference population was recruited among healthy students (aged 20-30 years) at the university of Antwerp campus. As it is known that

the hydration status can change throughout the day, all the BIA measurements were performed in the morning, between mealtimes, to minimize possible fluctuations. No prehydratation was given before the investigation. Patients also were not kept sober before measurements.

Skeletal muscle mass (SM) was calculated using the following BIA equation of Janssen et al (18): SM (kilograms) = [0.401 x (height^2/resistance) + (3.825 x gender) – (0.071 x age) + 5.102], where height is in centimetres, age in years, resistance in ohms, male = 1 and female = 0. Absolute SM was converted to a muscle mean index (MMI) by dividing the absolute SM by the square of the height in meters (14) and to a skeletal muscle index (SMI) by multiplying by 100 and dividing by the weight (19). The equation by Janssen et al was used because this is the only equation used to devise cut-off values that are endorsed by the European Working Group on Sarcopenia in Older People in their article from 2010 (20).

Sarcopenia was defined as an SMI or MMI 2 standard deviations (SD) or more below the normal sex-specific means for young persons.

Functional assessment was done by measuring the timed get up and go test (21) and the Katz profile. For the timed up and go, we asked participants to stand up from an armchair, walk a distance of 3 m and return to a seated position in the chair. The score was the time in seconds needed to perform the test. The Katz scale is a scale to assess the functional status through measurement of the ability to perform activities of daily living independently. Six items (bathing, dressing, using the toilet, transfer, continence and feeding) are scored from 1 ‘totally independent’ to 4 ‘totally dependent’. Thus, the score for Katz scale varies from 6 to 24.

Nutritional assessment was done with the Mini Nutritional Assessment –Short Form (MNA-SF) (22) and of the following laboratory parameters measured at baseline: albumin, pre-albumin, retinol-binding protein and transferrin. Also, 25 (OH) vitamin D3 was measured.

2.3. Statistics

Statistical analysis was done with SPSS 20 (SPSS Inc., Chicago, IL, USA). Descriptive statistics describe demographic and key clinical characteristics of the study population. A Shapiro-Wilk test was used for assumption of normality. Student’s *t*-tests were used to test for differences in the distribution of continuous variables. A chi-square test was used for significance of associations with categorical variables. p-values < 0.05 were considered statistically significant. p-values were adjusted for multiple comparisons using the Bonferroni method. Correlations were measured by Pearson’s correlation coefficient (PCC). Multiple cox proportional regressions were used to determine odds ratios (OR), each time adjusted for the confounding variables age and gender. Also Kaplan-Meier analysis was used for survival analysis.

2.4. Informed Consent

Ethical approval for this study has been granted by the University of Antwerp’s Medical Research ethics committee, for both parts of the study.

3. Results

3.1. Baseline Characteristics

Of the 745 included patients, 547 (73.4%) were women, 182 (24.4%) were men. Of 16 (0.02%) patients, the gender was not noted. Mean age at start of the study was 84.6 ± 7.2 years (range 55 -102 years). Percentage of distribution according to decade was 3.1% for 60-69 year old (n=23), 17.0% for 70-79 year old (n=127), 54.8% for 80-89 year old (n=408), 23.6% for 90-99 year old (n=176), 0.8% for 100-109 year old (n=6) and of 0.7% the exact date of birth was missing (n=5).
Further baseline characteristics are summarized in table 1. Distribution of gender by age group is summarized in table 2. Included in table 2 is the distribution of the presence of sarcopenia according to age group and gender. Thirty-six patients were either lost-to-follow up (n=28) or no date of death was obtained (n=8). Of the remaining 709 patients, the mean follow-up time was 1632 ±1026 days (median 1541 days, range 40-3296 days). At the endpoint of follow-up, 597 (80.1%) patients died, 120 (16.1%) were still alive and of 28 (3.8%) patients the fate was unknown.

The age at the start of the study was a relevant factor for survival rates ($p < 0.001$).

3.2.Muscle measurements

Of the total group of 745, bio-impedance analysis data was obtained in 582 patients (78.7%). However, due to other missing data - either height or weight - values for skeletal muscle mass is available in only 404 patients (54.2%). For distribution according to gender and age group see table 2.
Mean value for absolute skeletal muscle mass in the total group was 18.9 ± 5.6 kg (median 17.7 kg, range 9.0 – 36.5 kg). Mean value for absolute skeletal muscle mass in men was 25.8 ± 3.7 kg (median 25.4 kg, range 18.2 – 36.5 kg) and in women 16.1 ± 3.2 kg (median 15.6 kg, range 9.0 – 29.7 kg). When skeletal muscle index was calculated, 17% (n=70) had severe sarcopenia, 45% (n=181) moderate sarcopenia and 38% (n=153) no sarcopenia. For men percentages were 22% (n=26), 69% (n=81) and 9% (n=11) respectively and for women, 15% (n=44) 35% (n=100) and 50% (n=142).
Mean age for men in the ‘no sarcopenia’, ‘moderate sarcopenia’ and ‘severe sarcopenia’ groups were 87.2, 84.3 and 87.0 years respectively. Mean age for women in the ‘no sarcopenia’, ‘moderate sarcopenia’ and ‘severe sarcopenia’ groups were 84.0 years, 83.7 years and 86.6 years respectively. The difference between corresponding groups in both genders was not significant.

3.3. Functional measurements

The timed up and go was measured in 483 patients (64.8% of total), of which 355 women and 128 men. In the total group, mean time was 27.6 ± 15.6 seconds (median 23.4, range 6.9 - 114.9), in women separately 29.5 ± 16.3 (median 24.8, range 7.0 - 114.9) and in men 22.5 ± 12.5 (median 18.6, range 6.9 - 81.0) seconds.

The Katz scale was scored in 606 patients (81,3% of total), of which 447 women and 159 men. In the total group, mean score was 11.7 ± 4.8 (median 10.0, range 6-24). Women separately scored 11.9 ± 4.8 (median 11.0, range 6-24), and men 11.4 ± 5.0 (median 9.0, range 6-23). There was no statistical difference between gender (p=0.373).

3.4.Nutritional measurements

The MNA-SF was performed in 432 patients (60.0%). Mean value is 12.6 ± 1.5 (median 13.0, range 4 - 14). Divided in three classes, 1.4% (n=6) classified as 'malnourished' (scores 0-7), 14.8% (n=64) as 'at risk of malnutrition' (scores 8-11) and 83.8% (n=362) as 'normal nutritional status' (scores 12-14). There was no difference between gender (p=0.622).
For laboratory parameters we refer to table 1.

3.5. Mortality determinants

Following items were significant ($p < 0.05$) on univariate analysis with mortality as outcome: sarcopenia, gender, BMI, skeletal muscle mass, age, MNA class and functional level. MNA was divided in two classes: 'normal nutritional state' versus 'at risk of malnutrition' and 'malnutrition'. Skeletal muscle masss was divided in three percentile groups. Age was divided per decade. A Cox-regression analysis (forward building method) model was made using the 7 initial items for multivariate analysis. In this model, after 7 steps, only MNA, skeletal muscle mass and age were still significant. Odds ratio for age was 1.076. Odds ratio for MNA was 0.701 for the 'normal nutritional state' and 1.574 for the 'at risk of malnutrition' and 'malnutrition'. Odds ratio for skeletal muscle mass was 1.171 for the highest percentile group, 2.277 for the middle percentile group and 4.842 for the lowest percentile group. Sarcopenia was not withheld in this model. Results are shown in table 3.

Another model was performed, in which sarcopenia, gender, BMI, skeletal muscle mass, age, MNA class and functional level were used in a Cox-regression analysis (forward building method), with as outcome mortality after each year of screening: so calculations were made for mortality after 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years and 9 years. Age was not divided in decades. MNA was divided in two classes: 'normal nutritional state' versus 'at risk of malnutrition' and 'malnutrition'. For skeletal muscle mass, both absolute skeletal muscle mass as mean muscle index were used. Age was the most consistent mortality determinant throughout all 9 years except the first year, with odds ratios between 1.068-1.088. MNA was also significant in the 4^{th} up until the 8^{th} year, with odds ratios between 1.602 and 1.829. Not having sarcopenia was significant for mortality in the 9^{th} year, with an odds ratio of 0.596 (see Figure 1). Results are shown in table 3.

When mean muscle index was used in Kaplan-Meier survival analysis, there was no significant difference in the overall group (see Figure 2) or in women apart. Only in men was there a significant difference between the three groups (p=0.031). When the percentile groups of skeletal muscle mass were used, a significant difference was seen in the total group (p=0.015, see Figure 3), as also in both men and women apart (p=0.014).

4. Discussion

Using BIA, the prevalence of sarcopenia in this cohort was higher than in comparative literature, with a large difference between the genders. In men, 91% had sarcopenia compared to 50% in women. It is not clear why there is such a big difference with the data available in the literature. One reason could be the difference in admittance criteria for nursing homes between countries. In Belgium, one must have at least moderate to severe functional or cognitive limitations before being considered for admittance to a nursing home. This of course does not explain the gender difference. An age effect is not likely as the mean age between genders is not significantly different. Although men have more muscle mass at a younger age than women (23), there is hardly any data about the difference in decline between men and women on a long term. From literature it is already hypothesized that sarcopenia has a possible different pathophysiological evolution in men and women. Sarcopenia in men appears to be more driven by the catabolic influence of myostatin, while in women anabolic decline represented by reduced IGF-1 potentially contributes to sarcopenia (24). Higher muscle mass in men also means higher reference values for 'normal' muscle mass in elder men compared to older women, thus potentially leading to a higher number of men eligible for a sarcopenia diagnosis. Another explanation could be that the men in this cohort had more comorbidities than women, leading to sarcopenia in an earlier stage. Unfortunately, this could not be controlled for in a correct way because for the extensive follow-up time of this cohort, either the evolution of comorbidities was not noted or the patient files of the deceased were not available. One last remarks that has to be made is that it is known that BIA tends to overestimate muscle mass (25-27). Correcting for this, perhaps the prevalence of sarcopenia would even higher. However, the equation of Janssen et al was used, which was developed and cross-validated against magnetic resonance imaging measures of whole-body muscle mass (18, 19). There has been a recent study trying to provide BIA equations that will be better to predict muscle mass in specific cohorts, which certainly deserves attention in the future (28). It must also be stated that using single-frequency BIA has a lower precision than multi-frequency BIA (29).

After multivariate analysis, age, MNA-SF and skeletal muscle mass were significantly predictive for long-term mortality. Age is a known risk factor for mortality, certainly in the elderly (30, 31). The nutritional state is also a well-known risk factor for mortality in both hospitalized patients (32) and nursing home populations (33, 34). The relation of muscle mass and mortality however has not been consistent (35). The variability of measurement techniques might have an impact in this regard. Sarcopenia as a compounded construct has the same variability, e.g. where muscle mass is sometimes measured simply by taking the calf circumference (36). In the current study, cut-off values according to Janssen et al are used as suggested by the EWGSOP (20). Using these cut-off values in multivariate analysis, only a significant correlation with mortality is seen at 9 years of follow-up. The relation of muscle mass with mortality is confirmed when absolute skeletal muscle mass data were categorized according to percentage groups. Indeed, odds ratios for mortality for the lowest, middle and highest muscle mass group were 4.8, 2.3 and 1.2 respectively. When the cut-off points for the mean muscle index are used however, no clear relation with mortality was found in the entire group. Only in men was the mean muscle index related to mortality. These data suggest that the classic cut-off values are perhaps less useful in this specific cohort of elderly with already important functional problems. Therefore we hypothesize

that in nursing home residents, other cut-off values should be used to better predict mortality, as the currently used values are not representative for this group of people with a high prevalence of expected (very) low muscle mass.

Although vitamin D was not a relevant predictor of mortality, the mean level was very low in this population (15.6 ± 8.6 ng/dL). This is however not an uncommon finding in institutionalized elderly (37). It is thought that exposure to the sun and related factors such as skin type and clothing are perhaps not the most important factors, as there seems to be an North-South paradox in Europe (38). Other determinants, such as nutrition, food fortification, supplement use and BMI could be potentially critical factors (39).

There are a few limitations to the study. Not enough information on the evolution of comorbidities, e.g. the occurrence of dementia, could be a bias for mortality. Also, although the sample size remained large, there were only muscle mass values available in 54.2% of the study group.

The strengths of this study are the large sample of institutionalized persons (n=745), the number of different nursing homes (n=52), the nearly complete follow-up data (96.2%) and the length of follow-up (mean follow-up time was 1632 ±1026 days). To our knowledge, this study provides the longest follow-up data in this specific cohort of institutionalized elderly with regards to muscle mass measurements.

5. Conclusion

In summary, it seems to remain useful to screen for muscle mass in institutionalized elderly, because there is a clear and significant correlation with long-term mortality. The cut-off values for muscle mass using BIA should be re-evaluated, since they seem to fall short in persons on the lower end of muscle mass values. More studies are needed to define and confirm these new cut-off values.

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