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MORTALITY AS AN ADVERSE OUTCOME OF SARCOPENIA

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Abstract: Sarcopenia has an important impact in elderly. Recently the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as the loss of muscle mass plus low muscle strength or low physical performance. Lack of clinical sounding outcomes (ie external validity), is one of the flaws of this algorithm. The aim of our study was to determine the association of sarcopenia and mortality in a group of Mexican elderly. A total of 345 elderly were recruited in Mexico City, and followed up for three years. The EWGSOP algorithm was integrated by: gait speed, grip strength and calf circumference. Other covariates were assessed in order to test the independent association of sarcopenia with mortality. Of the 345 subjects, 53.3% were women; with a mean age of 78.5 (SD 7) years. During the three year follow-up a total of 43 (12.4%) subjects died. Age, cognition, ADL, IADL, health self-perception, ischemic heart disease and sarcopenia were associated in the bivariate analysis with survival. Negative predictive value for sarcopenia regarding mortality was of 90%. Kaplan-Meier curves along with their respective log-rank test were significant for sarcopenia. The components of the final Cox-regression multivariate model were age, ischemic heart disease, ADL and sarcopenia. Adjusted HR for age was 3.24 (CI 95% 1.55-6.78 p 0.002), IHD 5.07 (CI 95% 1.89-13.59 p 0.001), health self-perception 5.07 (CI 95% 1.9-13.6 p 0.001), ADL 0.75 (CI 95% 0.56-0.99 p 0.048) and sarcopenia 2.39 (CI 95% 1.05-5.43 p 0.037).

Key words: Sarcopenia, survival, nutrition in elderly.

Introduction

Since one of its first definitions, sarcopenia has been characterized as a muscle deficiency, subsequently evolving to a more complex construct that involves loss of skeletal muscle mass, poor strength, and low physical performance (1, 2). Different factors may contribute to its development, including: age, nutrition, low physical activity, cognition and chronic diseases (3, 4). Nowadays, there is no widely accepted operational definition, nor a group of instruments to measure its components (5). Nevertheless, large population-based studies have reported sarcopenia prevalence between 8 and 50% in people over 50 years; with main population characteristics varying depending on ethnicity, setting, age and diagnostic methodology (6). Moreover, our group has recently reported a prevalence of 33.6% in Mexico City (7).

Recently the European Working Group on Sarcopenia in Older People, by an algorithm of sarcopenia diagnosis (ASD EWGSOP), defined sarcopenia as the loss of muscle mass plus low muscle strength or low physical performance, associated with age; developing an algorithm that classifies subjects by means of gait speed, grip strength and muscle mass (either with BIA or DEXA, specifying cut-points) . Other sarcopenia criteria have been proposed, including only some of these components (muscle mass, muscle function and physical performance) (see table 1) (1, 8).

Sarcopenia represents a significant change in health status and is associated with adverse outcomes such as falls, fractures, functional decline, increased mortality, and low quality of life (9-11).Thus early diagnosis of sarcopenia is critical to prevent these adverse outcomes (12). It also should be stressed that sarcopenia plays a main role in frailty; it usually heralds the rest of its components and is a main determinant of its pathophysiology (13, 14).

The aim of our study was to determine the association of sarcopenia defined by the ASD EWGSOP and mortality in a group of Mexican elderly.

Table 1
Comparison of criteria for defining sarcopenia

	Definition	Components
EWGSOP	Low gait speed plus low muscle mass or normal gait speed with low grip strength and low muscle mass	Muscle mass (DEXA, BIA, anthropometry), muscle function (grip strength) and physical performance (walking speed)
IWGS	Age-associated loss of skeletal muscle mass and function, associated or not with increased fat mass	No operational definition
NMEHS	Muscle mass <2SD below the mean reference of a young population	Only muscle mass (DEXA)

Material and methods

This study cohort was integrated in Mexico City in 2007, and has been followed since. The cohort characteristics are published elsewhere (7). In brief, this cohort includes 345 70-

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year or older subjects living in Mexico City. Survival was determined after the third wave of follow up and through the mortality registry, available in a public internet resource, and updated every three months (15).

The main variables considered in the analyses were socio-demographic characteristics (age, gender, education, and marital status), anthropometry (weight, knee height, body mass index, grip strength, and calf circumference), clinical (cognition, depression, anxiety, ADL, IADL, balance and gait, nutrition status, abuse, number of comorbidities, number of drugs used, weight loss, smoking, ischemic heart disease, stroke, hypertension, cancer and diabetes) and sarcopenia. Sarcopenia was defined according to the ASD EWGSOP. The ASD combines an estimate of muscle mass and function, in addition to physical performance. Muscle mass was assessed by means of calf circumference, with a cut-off point of 31cm or less for diminished muscle mass, as described by Rolland et al (16). Muscle function was measured by means of grip strength, with cut-off points adjusted for gender: 20kg for women and 30kg for men, meaning low muscle functioning, according to EWGSOP recommendations for grip strength. Finally, physical performance was defined according to gait speed by means of the 4-meter walking test, with a cut-off point of less than 0.8m/s for low physical performance (9).

Cognition was assessed with the Mini-Mental Status Exam (MMSE), analyzing the data as a continuous variable (score 0 to 30) (17). Depression was assessed with the Center for Epidemiologic Studies Depression Scale (CES D) (18). Activities of daily living and instrumental activities were assessed using the Katz and Lawton indexes respectively (19, 20). The Timed-Up and Go test was used to assess balance and gait status (21). The Mini-Nutritional Assessment scale in its Spanish validated version was used (22). Number of comorbidities and drugs used were assessed with an open question, then specific diseases were asked on purpose; diabetes, hypertension, stroke, cancer and ischemic heart disease. Frailty was assessed with the Study of Osteoporotic Fractures (SOF) index, where frailty is considered present if 2 items out of three (self-report of lack of energy and weight loss plus inability to rise from a chair 5 times) (23). Weight loss was assessed in the last six months, irrespective of intentionality. Smoking status was positive only if the subject was a current smoker.

Descriptive statistics were reported; for continuous variables, mean and standard deviations and for dichotomous or ordinal variables, absolute and relative frequencies; in order to summarize the general characteristics of the sample. Then to test the association between mortality and sarcopenia, we tested each of the variables; an independent T-test for continuous variables and chi square test for dichotomous variables. Those variables with an statistical significance ($p<0.1$) were graphed in a Kaplan-Meier curve and compared depending on survival status (lost to follow-up subjects were censored) at three years; testing the statistical difference with a log-rank test. All significant variables in these first analyses were entered in a multiple Cox-regression model to test the independent association between the variables and survival. Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals were reported. In addition, predictive values for mortality were calculated for sarcopenia. STATA 12 program was used for data analysis.

Results

Of the 345 subjects, 53.3% were women; and the mean age of the entire sample was of 78.5 (SD 7) years. The average of school years was 5 (SD 5) and the frequency of the subjects with a couple was of 41.1 % (n=142) (see table 2). Regarding anthropometry (see table 3), BMI had a mean of 26.4 (SD 4.5) kg/m2, with 3.2% (n=11) underweight, 23.2% (n=85) normal, 48.1% (n=169) overweight and 22% (n=80) obese. Mean calf circumference was of 33.6 (SD 3.83) cm, mean grip strength 19.9 (SD 7.9) kg and mean gait speed 0.67 (SD 0.27) m/s. At least 35% of the subjects had difficulties with one ADL in contrast to the 98% of the subjects who had at least one difficulty with instrumental ADL. Mean scores for MMSE and CES D were 21 (SD 6) and 12 (SD 9) respectively. The mean score for the MNA test was 25.18 (SD 3.13). The mean number of drugs used was of 4 (SD 2), with 82.9% of the subjects with at least one drug. Regarding comorbidities, the mean number was of 3 (SD 3), with hypertension as the most frequent. On the other hand, comorbidities like ischemic heart disease were present in 7.2% (n=25), stroke, hypertension 56% (n=200), cancer 5.5% (n=19), diabetes 24.3% (n=84) and frailty 42.8% (n=148) (see table 4).

Table 2
General characteristics

Characteristics	Gender		
	Men	Women	Total
	(n=161)	(n=184)	(n=345)
Age, mean (SD), years	78.5 (7)	78.6 (7)	78.5 (7)
Scholarship, mean (SD), years	6 (5)	5 (5)	5 (5)
With a Couple, No. (%)	89 (55.2)	53 (28.8)	142 (41.1)

Sarcopenia was present in a total number of 116 (33.6%) subjects. During the three year follow-up a total of 43 (12.4%) subjects died. Age, MMSE score, Katz score, Lawton score, health self-perception, ischemic heart disease and sarcopenia were associated in the bivariate analysis with survival, with an statistical significance of <0.1 (see table 5). Negative predictive value for sarcopenia regarding mortality was of 90%. Kaplan-Meier curves along with their respective log-rank test were significant for sarcopenia (see figure 1).

The components of the final Cox-regression multivariate model were age, ischemic heart disease, ADL and sarcopenia. Adjusted HR for age was 3.24 (CI 95% 1.55-6.78 p 0.002),

IHD 5.07 (CI 95% 1.89-13.59 p 0.001), health self-perception 5.07 (CI 95% 1.9-13.6 p 0.001), ADL 0.75 (CI 95% 0.56-0.99 p 0.048) and sarcopenia 2.39 (CI 95% 1.05-5.43 p 0.037) (see table 6).

Figure 1
Kaplan-Meier survival curves for sarcopenia

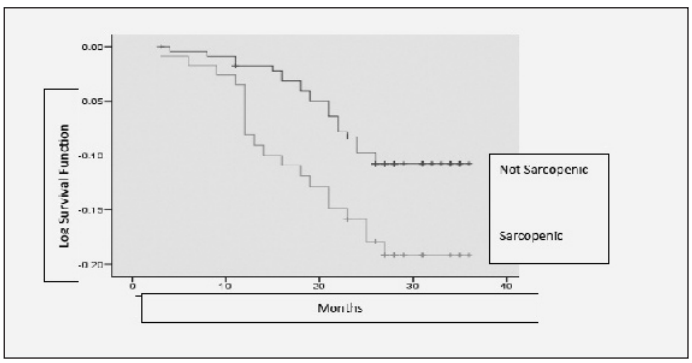

Table 3
Anthropometry

Characteristics	Gender		
	Men (n=161)	Women (n=184)	Total (n=345)
Weight, mean (SD), kilograms	69.2 (12.9)	60.6 (11)	64.6 (12.7)
Height, mean (SD), meters	1.6 (0.72)	1.47 (0.63)	1.53 (0.93)
Adjusted Height, mean (SD), meters	1.62 (0.54)	1.5 (0.56)	1.56 (0.83)
BMI, mean (SD), kg/m2	26.52 (3.7)	27.8 (4.9)	27.2 (4)
Adjusted BMI, mean (SD), kg/m2	26.03 (4)	26.8 (4.8)	26.4 (4.5)
Stratified Adjusted BMI			
Underweight, No. (%)	6 (3.7)	5 (2.7)	11 (3.2)
Normal, No. (%)	44 (27.3)	41 (22.3)	85 (23.2)
Overweight, No. (%)	83 (51.5)	86 (46.7)	169 (48.1)
Obese, No. (%)	28 (17.4)	52 (28.2)	80 (22)
Calf Circumference, mean (SD), centimeters	34.3 (3.6)	33 (4)	33.6 (3.83)
Grip Strength, mean (SD), kg	25.2 (7.7)	15.4 (4.6)	19.9 (7.9)
Gait Speed, mean (SD), m/s	0.74 (0.29)	0.61 (0.25)	0.67 (0.27)

Table 4
Clinical Characteristics

Characteristics	Gender		
	Men (n=161)	Women (n=184)	Total (n=345)
MMSE, mean (SD)	21 (6)	20 (6)	21 (6)
CES D, mean (SD)	9 (7)	15 (10)	12 (9)
Katz, mean (SD)	5 (1)	5 (1)	5 (1)
Lawton, mean (SD)	5 (1)	6 (1)	5 (1)
MNA, mean (SD)	25.62 (2.95)	24.8 (3.23)	25.18 (3.13)
Number of Comorbidities, mean (SD)	4 (3)	4 (2)	3 (3)
Number of drugs, mean (SD)	3 (3)	3 (3)	4 (2)
Ischemic Cardiopathy, No. (%)	15 (9.3)	10 (5.4)	25 (7.2)
Stroke, No. (%)	9 (5.6)	5 (2.7)	14 (4)
Hypertension, No. (%)	82 (50.9)	118 (64.1)	200 (56)
Cancer, No. (%)	6 (3.7)	13 (7)	19 (5.5)
DM, No. (%)	47 (29.2)	37 (20.1)	84 (24.3)
Frailty, No. (%)	60 (40.5)	88 (59.4)	148 (42.8)

Table 5
Survival description

Characteristic	Status at 3 years		Unadjusted Hazard
	Death (n=43)	Alive (n=302)	Ratio (CI 95%), p
Women, No. (%)	19 (44.1)	165 (54.6)	0.68 (0.37-1.24) 0.21
>80 years, No. (%)	28 (65.1)	83 (27.4)	4.36 (2.33-8.17) <0.001
Scholarship, mean (SD) y	4.58 (5.15)	5.35 (4.56)	0.96 (0.89-1.03) 0.96
With a Couple, No. (%)	13 (9.2)	129 (42.7)	0.61 (0.32-1.17) 0.13
Weight, mean (SD), kilograms	63.59 (11.34)	64.81 (12.9)	0.99 (0.97-1.01) 0.6
MMSE, mean (SD)	17.72 (7.57)	20.96 (5.66)	0.93 (0.89-0.97) 0.001
CES D, mean (SD)	12.7 (9.03)	12.2 (9.22)	1 (0.97-1.03) 0.81
Katz, mean (SD)	4.65 (1.94)	5.34 (1.18)	0.75 (0.63-0.89) 0.001
Lawton, mean (SD)	5.02 (1.3)	5.45 (1.07)	0.74 (0.58-0.93) 0.013
MNA, mean (SD)	24.77 (3.72)	25.23 (3.03)	0.96 (0.88-1.05) 0.38
Number of Comorbidities, mean (SD)	3.35 (2.03)	3.89 (2.43)	0.9 (0.78-1.04) 0.16
Number of drugs, mean (SD)	3.02 (2.63)	3.16 (2.64)	0.98 (0.87-1.1) 0.78
Ischemic Cardiopathy, No. (%)	7 (16.3)	18 (6)	2.71 (1.2-6.09) 0.016
Stroke, No. (%)	1 (2.3)	13 (4.3)	0.55 (0.07-4) 0.56
Hypertension, No. (%)	22 (51.2)	178 (58.9)	0.74 (0.4-1.35) 0.33
Cancer, No. (%)	4 (9.3)	15 (5)	1.9 (0.68-5.34) 0.22
DM, No. (%)	15 (34.9)	69 (22.8)	1.7 (0.9-3.18) 0.097
Weight Loss, No. (%)	19 (44.2)	108 (35.8)	1.38 (0.75-2.52) 0.3
Current Smoking, No. (%)	5 (11.6)	30 (9.93)	1.18 (0.46-3.01) 0.71
Health Self Perception (Excellent), No. (%)	36 (83.7)	264 (87.4)	0.12 (0.036-0.4) 0.001

Table 6
Cox regression model of multivariate survival analysis, final adjusted model

Characteristic	Adjusted Hazard Ratio (CI 95%)	Significance
>80 years	3.24 (1.55-6.78)	0.002
Ischemic Heart Disease	5.07 (1.89-13.59)	0.001
ADL	0.75 (0.56-0.99)	0.048
Sarcopenia	2.39 (1.05-5.43)	0.037

Discussion

To our knowledge, this is the first study to report external validity of the European algorithm for sarcopenia diagnosis. Subjects who were diagnosed as sarcopenic had 1.39 times more risk of dying independent of other known risk factors such as IHD, ADL, age or gender.

In another recent report on mortality and sarcopenia in Latin-American elderly, where they used only the definition of sarcopenia as low muscle mass measured by DEXA in a longer follow-up of more than ten years. This study also demonstrated an association between mortality and sarcopenia, although it adjusted for some confounding variables, it did not adjust for chronic conditions such as hypertension. Lack of adjustment for other well-known mortality risk factors could make this association weaker; nevertheless, a mortality trend was found from over two years of follow-up (24).

In a recent study by Landi et al, the adjusted mortality HR in sarcopenic subjects was 2.34, (95% CI: 1.04-5.24); very similar to our findings, with adjustments to other comorbidities in addition to geriatric conditions. However they studied

institutionalized elderly and followed them for only 6 months (25).

The difficulty of having too expensive tools to make an accurate diagnosis, in an early stage in order to prevent premature mortality and functional decline makes the use of cheap tools and widely available, a screening tool for a great number of elderly, discarding those who tested negative in the screening due to the high negative predictive value found in our population; more than 90% of those with a negative test, will have an excellent prognosis; on the other hand, only those elders who are positive in the test will require a more profound assessment in order to determine if they are really sarcopenic, and at the same time determine the extent of the problem.

Regarding mortality, it is of importance the fact that sarcopenia had an independent association, because this should be one of the end-points in addition to institutionalization, functional decline, amongst others.

Also, there is an imperious need to assess this phenomenon throughout all the age range of elders, in order to know the trajectories and impacts of sarcopenia in these groups of age. Future studies should indicate efficacy of the variables indicated in our cohort; and establish different cut-points in each of the components of sarcopenia individually or grouped.

Conclusions

The EWGSOP ASD used in Mexican population gave a global estimate of sarcopenia prevalence of 33.8% in community dwelling individuals older than 70 years, and showed an increase in mortality risk in those subjects identified as sarcopenic, and this increased risk was found to be independent of other mortality risk factors.

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