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Original Article

Diagnostic and prognostic value of calf circumference for sarcopenia in community-dwelling older adults

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ABSTRACT

Background: An age-dependent normative values of calf circumference (CC) has been recently proposed as an accessible proxy for muscle mass. However, its usefulness to estimate sarcopenia has not been assessed. The objectives of the present study were to determine if the substitution of the classical way to assess muscle mass by these values have enough diagnostic accuracy and prognostic value among older adults living in the community.
Methods: Data from the Toledo Study of Healthy Ageing (TSHA) were used. CC was measured using an anthropometric tape. We used two age-groups CC cut-off points: the TSHA CC median and the one proposed in the Longevity Check-up 7+ (Lookup 7+) project. Sarcopenia was defined based on the European Working Group on Sarcopenia in Older People (EWGSOP2), the Foundation for the National Institutes of Health (FNIH), and FNIH criteria standardized for our population (sFNIH). Frailty (according to the Frailty Phenotype and the Frailty Trait Scale-5) and disability (Katz index) were assessed at baseline and follow-up. Mortality and first hospitalization were also recorded. Logistic (incident frailty and worsening disability) and Cox (mortality and hospitalization) regressions were performed. Diagnostic accuracy was assessed through Kappa index, AUCs, positive and negative predictive values. Predictive ability was assessed through AUCs and integrated AUCs (IAUCs).
Results: 1531 participants (74.8 ± 5.8 years; 45.6% men) were included in the analysis. Prevalence rates of sarcopenia were 22.7% (sFNIH), 15.0% (FNIH), and 13.9% (EWGSOP2). Using TSHA-based cut-points of CC, the prevalence of sarcopenia was 16.8% (sFNIH), 11.0% (FNIH), and 11.5% (EWGSOP2). According to LC7+-based CC cut-off points, sarcopenia prevalence was 17.6% (sFNIH), 11.9% (FNIH), and 12.4% (EWGSOP2). CC cut-off points showed low-to-moderate agreement (Kappa Index values between 0.49 and 0.69) with appendicular lean mass for the evaluation of sarcopenia. Sarcopenia identified by Lookup 7+ and TSHA CC cut-off points was associated with the adverse events examined, with similar AUCs and IAUCs than original sarcopenia definitions, and were lost after adjustment by baseline frailty, except when the original EWGSOP2 definition was used.
Conclusions: Using normalized values of CC as a criteria of muscle mass shows moderate agreement with classical criteria for diagnosing sarcopenia and offer similar predictive value in community-dwelling older adults.

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1. Background

Average individuals lose approximately 1% of their skeletal muscle mass per year past the age of 70(1). Muscle strength and power also decrease with advancing age, at a faster rate than muscle mass [1–4]. When the loss of muscle mass and muscle strength and/or function exceeds predefined thresholds, a condition known as sarcopenia ensues [5]. The latter is associated with a wide spectrum of negative health outcomes, including poor quality of life [6], falls [7], frailty [8], disability [9], and mortality [10,11]. In recognition of its clinical relevance, sarcopenia has been included in the International Classification of Diseases-10 (ICD-10) with a specific code [12,13].

Notwithstanding, the lack of an univocal operational definition of sarcopenia has hampered its widespread clinical implementation [14,15]. Among the most popular diagnostic criteria for sarcopenia are those proposed by the Foundation for the National Institutes of Health (FNIH) [16] and the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [17]. In both cases sarcopenia status is determined based on the co-occurrence of low muscle strength and low muscle quantity or quality. However, the quantification of muscle mass through instrumental examinations (e.g., dual-energy X-ray absorptiometry, DEXA) is not readily available in non-specialized clinical centers or primary care. Hence, alternative approaches have been proposed. Calf circumference (CC) is an anthropometric measure that has been endorsed as a specific marker of lean mass by the World Health Organization (WHO) [18] and expert panels [19,20]. Accordingly, CC may be used to estimate muscle mass [21], although its sensitivity for identifying sarcopenia has been questioned [22]. Martone et al. [23] have recently provided normative values for CC across ages using data collected in 11,814 Italian adults older than 45 years enrolled in the Longevity Check-up 7+ (Lookup 7+). In the study, 4644 participants were older than 65 (54.4% women). In the Spanish population, some studies have proposed including calf circumference in the measurement of sarcopenia [24,25], especially in addition to the SARC-F questionnaire [25,26]. However, to the best of our knowledge, none of them have attempted to replace the muscle mass measurement within different sarcopenia definitions and compare its diagnostic ability. Moreover, neither have they included normative values from large population-based studies, something that has been proposed by EWGSOP2 (Cruz Jentoft et al., 2019).

The primary objective of the present study was to determine the predictive ability of CC cut-off points proposed by Martone et al. [23] and those standardized for the Toledo Study for Healthy Ageing (TSHA) [27] in predicting sarcopenia according to different operational definitions. We also compared the predictive ability of different definitions of sarcopenia in predicting negative health events.

2. Methods

Data for the present study were obtained from the TSHA [27] database. TSHA is a prospective cohort study that includes community-dwelling individuals 65 years and older living in rural and urban areas in the province of Toledo, Spain.

Participants signed an informed consent prior to enrolment. TSHA was conducted according to ethical standards laid down in the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Toledo Hospital, Spain.

In this work we have used data from the second wave (2011–2013, ethics committee approval protocol number 15072010.93), when DXA was done in the participants, as the baseline measurement and Wave 3 (2014–2017, 13072012.72) as the follow-up measurement. Wave 3 assessment was performed 2.99 (range 2–5.4) median years after the Wave 2. Of the 2242 individuals included in Wave 2 of the TSHA, we were unable to include 105 individuals because they did not attend the visit in which sarcopenia measurements were assessed, 17 individuals who did not have handgrip measure, 311 did not present gait speed measurement, 269 who did not attend the Dual-Energy X-ray Absorptiometry (DEXA) visit or the DEXA measurement was not valid (Fig. 1).

2.1. Study variables

2.1.1. Calf circumference

Calf circumference was measured at the point of maximum circumference in a plane parallel to the floor with a plastic tape [28]. Participants was sitting with the knee and the ankle at 90 degrees and the

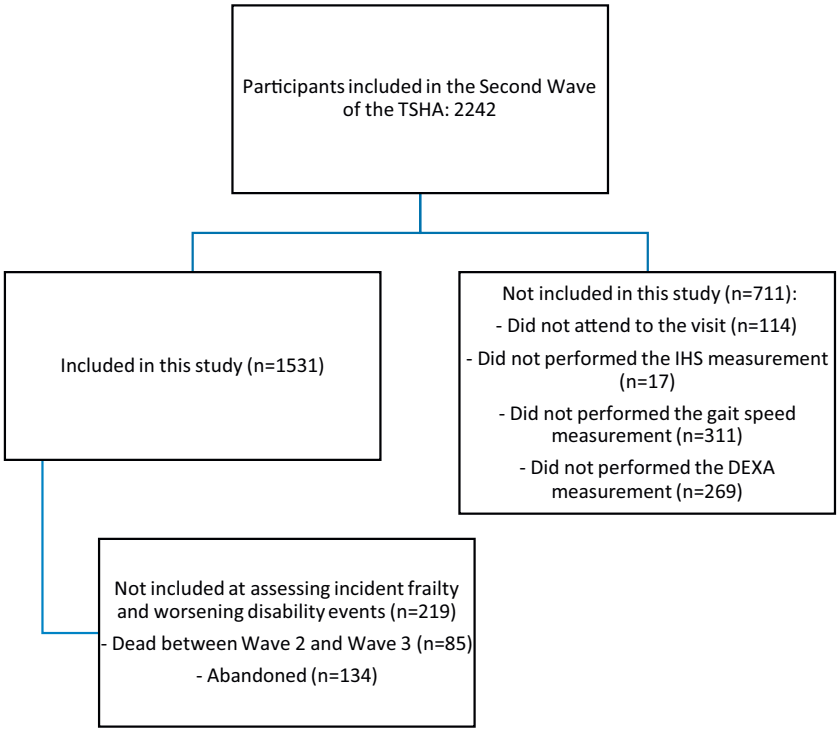

Fig. 1. Study flow chart diagram.

feet on the floor. The measurement was done directly on the skin, and it was performed by trained health care professionals. The values were rounded to the nearest cm.

To assess metrics accuracy and the association of CC with the adverse outcomes, we have included two cut-off points. These cut-off points are the median of this cohort (TSHA), as well as Lookup 7+ [23].

2.1.2. Measurements

2.1.2.1. Body composition. Lean soft tissue mass was assessed using Dual-Energy X-ray Absorptiometry (DEXA) (Hologic, Serie Discovery QDR, Bedford, MA, USA). Appendicular Lean Mass (ALM) was obtained by the sum of upper and lower limbs muscle mass. DEXA scans were analyzed by the Physician's Viewer (apex System Software, version 3.1.2: Bedford, USA) software.

Body Mass Index (BMI) was obtained according to standard procedures (adjusted to the nearest 0.1). BMI- adjusted by ALM (ALM/BMI) was determined.

2.1.2.2. Isometric handgrip strength (IHS). IHS was assessed by using a hydraulic JAMAR dynamometer (J. A. Preston Corporation, Clifton, NJ, USA) according to international standard procedures [29]. The best of three attempts performed with the dominant hand was considered. One minute of resting between performances was permitted to participants.

2.1.2.3. Gait speed. Gait speed at usual pace was assessed on a 3-meter track. The best of two performance was registered. Data were recorded in meters per second (m/s).

2.2. Sarcopenia definitions

Sarcopenia was defined using three different well-established definitions: the Foundation for the National Institutes of Health (FNIH) [16], the FNIH standardized to our population [30], and the European Working Group on Sarcopenia in Older People (EWGSOP2) proposed in 2019 [17]. Participants met sarcopenia if they met the three criteria, similar to the categories established by FNIH and FNIHs and to the category of severe sarcopenia of the EWGSOP2. In our study, we used the CC cutoff points proposed in Lookup 7+ and TSHA to substitute the criteria classically used to assess muscle mass (i.e. appendicular mass) in these three definitions, without any changes on gait speed and strength.

2.3. Health negative events

Frailty and disability status were assessed at baseline and 2.99 (2.0–5.4) median years after the first assessment.

2.4. Frailty

Frailty was assessed according to Fried's Frailty Phenotype (FFP) [31], standardized to our population [32], and Frailty Trait Scale-5 (FTS5) [33]. Subjects were considered as frail if they met $\geq$3 criteria according to the FFP [31] or present a score $\geq$25.25 according to the FTS5 [33].

2.5. Disability

Katz Index [34] was used to assess the ability to perform basic activities of daily living (BADL). Worsening disability was defined as any worsening in any category of BADL. This change was used as a dichotomous variable, with 0 being those who have not worsened and 1 being those who suffered the event (worsened in their disability).

2.6. Hospitalization

Hospitalization was obtained from the hospital record of the complex Hospital of Toledo database. Hospitalization mean follow-up time was 3.63 (median; range: 0.03–5.24) years.

2.7. Mortality

Vital status and mortality dates were ascertained from the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare) and phone calls to family contact. Median follow-up time for mortality was 6.29 (range: 0.59–7.47) years.

2.8. Covariates

2.8.1. Comorbidity

Comorbidity was assessed through the Charlson Comorbidity Index [35].

2.8.2. Polypharmacy

Polypharmacy was defined as the use of 5 or more drugs.

2.9. Statistical analysis

Descriptive data was presented as mean (standard deviation) and N (percentages). Differences for continuous variables between groups were tested using Mann-Whitney. Chi-squared tests were used for the comparison between categorical variables.

The median CC values of our population according to sex and different age groups were used as cut-off points. In addition, we also used the median of the cut-off points obtained in LC7+. For each definition of sarcopenia, we estimated the concordance between CC cut-off points according to sex and group of age specific median and appendicular mass criteria.

To comprehensively describe diagnostic test accuracy for each sarcopenia definition, the area-under-the curve (AUC), sensitivity and specificity, positive and negative likelihood ratios, positive and negative predictive values, and the Youden's J statistic were calculated.

To assess the effect of sarcopenia (original definitions and their variants according to CC cut-off points) on adverse events, we used Cox proportional hazard models for death and hospitalization and multivariate logistic model for incident frailty and worsening disability. This relationship was estimated using three nested regression models: (Model 1) raw model; (Model 2) adjusted by age, gender, comorbidity and polypharmacy; and (Model 3) model 2 adjusted additionally by frailty (Supplementary Fig. S1). When worsening disability was the outcome, Model 3 added Katz Index score.

Using model 2 estimates, we computed the Integrated area under the curve (IAUC) for death and hospitalization and area under de curve (AUC) for incident frailty and worsening disability.

All the analyses were computed using R for windows version 4.1.2.

3. Results

Characteristics of the study participants according to the sarcopenia status are shown in Table 1. 1531 were included. Of those, 348 (22.73%), 229 (14.96%), 212 (13.85%) met sarcopenia criteria according to the different definitions.

Regardless of the sarcopenia definition, older adults with sarcopenia were older, presented higher BMI, higher prevalence of frailty, disability, polypharmacy, malnutrition or cognitive impairment. In addition, significant higher rates in incident frailty, worsening disability, hospitalization and mortality rates were observed in participants with sarcopenia.

Table 1
Baseline characteristics of the population and prevalence of sarcopenia according to different definitions.

Variable	Whole sample	sFNIH		FNIH		EWGSOP2	
		No Sarcopenia	Sarcopenia	No Sarcopenia	Sarcopenia	No Sarcopenia	Sarcopenia
N (%)	1531	1183 (77.27)	348 (22.73)	1302 (85.04)	229 (14.96)	1319 (86.15)	212 (13.85)
Age, mean (SD)	74.76 (5.76)	73.90 (5.52)	77.67 (5.59)***	73.95 (5.43)	79.38 (5.40) ***	73.91 (5.31)	80.03 (5.64) ***
Male, n (%)	698 (45.59)	639 (54.02)	59 (16.95) ***	588 (45.16)	110 (48.03)	599 (45.41)	99 (46.70)
CC, mean (SD)	34.87 (4.46)	34.85 (4.31)	34.91 (4.95)	34.88 (4.38)	34.80 (4.91)	35.08 (4.42)	33.56 (4.53)***
Charlson Index, mean (SD)	1.19 (1.63)	1.09 (1.53)	1.53 (1.90) ***	1.14 (1.54)	1.45 (2.04)	1.15 (1.57)	1.45 (1.95)
Height, mean (SD)	158.72 (9.16)	161.02 (8.58)	150.90 (6.28) ***	159.52 (9.08)	154.15 (8.23) ***	159.50 (9.07)	153.84 (8.12) ***
Weight, mean (SD)	73.66 (12.83)	74.50 (12.82)	70.81 (12.48) ***	73.95 (12.85)	72.02 (12.62) *	75.03 (12.75)	65.15 (9.68) ***
BMI, mean (SD)	29.22 (4.45)	28.69 (4.21)	31.04 (4.77) ***	29.04 (4.37)	30.30 (4.78) ***	29.49 (4.49)	27.56 (3.85) ***
Gait speed, mean (SD)	0.80 (0.27)	0.87 (0.26)	0.55 (0.15) ***	0.84 (0.26)	0.54 (0.16) ***	0.84 (0.27)	0.54 (0.16) ***
IHS, mean (SD)	24.07 (9.22)	26.57 (8.83)	15.58 (4.01) ***	25.53 (9.00)	15.82 (5.32) ***	25.38 (9.03)	15.93 (5.50) ***
IHS in men, mean (SD)	31.00 (8.34)	32.06 (7.78)	19.46 (4.70) ***	33.07 (7.21)	19.95 (4.31) ***	32.78 (7.42)	20.22 (4.70) ***
IHS in women, mean (SD)	18.27 (4.93)	20.13 (4.62)	14.79 (3.35) ***	19.32 (4.42)	12.00 (2.65) ***	19.23 (4.50)	12.17 (2.65) ***
ALM, mean (SD)	17.72 (3.95)	18.49 (3.95)	15.07 (2.57) ***	17.97 (3.99)	16.26 (3.35) ***	18.14 (3.96)	15.06 (2.65) ***
ALM in men, mean (SD)	20.80 (3.12)	21.10 (2.98)	17.57 (2.68) ***	21.23 (2.95)	18.48 (2.97) ***	21.37 (2.91)	17.35 (1.85) ***
ALM in women, mean (SD)	15.13 (2.43)	15.43 (2.47)	14.56 (2.23) ***	15.28 (2.43)	14.21 (2.19) ***	15.46 (2.41)	13.05 (1.22) ***
Frail according to FP, n (%)	48 (3.16)	20 (1.71)	28 (8.09) ***	15 (1.16)	33 (14.54) ***	19 (1.45)	29 (13.74) ***
Frail according to FTS5, n (%)	150 (9.93)	30 (2.56)	120 (35.50) ***	64 (4.96)	86 (39.09) ***	80 (6.13)	70 (34.15) ***
Polypharmacy, n (%)	789 (51.53)	547 (46.24)	242 (69.54) ***	637 (48.92)	152 (66.38) ***	656 (49.73)	133 (62.74) ***
Disabled at baseline, n (%)	244 (16.11)	140 (11.97)	104 (30.14) ***	170 (13.17)	74 (33.04) ***	175 (13.39)	69 (33.17) ***
Incident frailty according to FP, n (%)	45 (3.66)	19 (1.96)	26 (10.04) ***	25 (2.32)	20 (12.99) ***	25 (2.30)	20 (14.18) ***
Incident frailty according to FTS5, n (%)	94 (8.21)	47 (4.86)	47 (26.40) ***	63 (6.07)	31 (28.97) ***	66 (6.37)	28 (25.69) ***
Worsening disability, n (%)	313 (24.11)	221 (21.95)	92 (31.62) ***	249 (22.37)	64 (34.59) ***	255 (22.57)	58 (34.52) ***
Hospitalization, n (%)	415 (27.11)	276 (23.33)	139 (39.94) ***	310 (23.81)	105 (45.85) ***	324 (24.56)	91 (42.92) ***
Mortality, n (%)	212 (13.85)	145 (12.26)	67 (19.25) ***	148 (11.37)	64 (27.95) ***	155 (11.75)	57 (26.89) ***

*: p-value <0.05. **: p-value<0.01. ***: p-value<0.001. ALM: Appendicular Lean Mass. EWGSOP: European Working Group on Sarcopenia in Older People. FNIH: Foundation for the National Institutes of Health sarcopenia criteria. IHS: Isometric Handgrip Strength. sFNIH: Foundation for the National Institutes of Health sarcopenia criteria standardized to our population. PASE: Physical Activity Scale for the Elderly.

3.1. Interscale agreement

Supplementary Table S1 shows the agreement between the different definitions of sarcopenia. Level of concordance were low between sFNIH with FNIH (0.53) and EWGSOP2 (0.44); and moderate between FNIH and EWGSOP2 (0.70).

3.2. Adverse events and sarcopenia definitions

Associations between mortality, hospitalization, incident frailty and worsening disability according to different sarcopenia definitions are shown in Supplementary Table S2 . In the univariate (Model 1) and multivariate analysis (Model 2), all the definitions of sarcopenia were able to predict all the adverse events, except for the hospitalization when the EWGSOP2 were the definition chosen and age, sex, comorbidity and polypharmacy were added to the model. We did exploratory analyses by adding Model 2 variables of malnutrition, cognitive impairment, physical activity or educational level, without substantially modifying the results shown in Model 2 (data not shown). However, once we added frailty (Model 3), the only event that sarcopenia could predict was worsening disability when FNIH was the chosen definition.

Table 2
Median values of calf circumference in the TSHA and Longevity Check-up 7+.

	TSHA		Longevity Check-up 7+	
	Men Cut-off point	Women Cut-off point	Men Cut-off point	Women Cut-off point
65–69	34.0	34.0	36.3	34.2
70–74	35.0	34.0	36.0	34.0
75–79	34.0	34.0	35.4	34.0
80+	34.0	33.0	35.0	33.1

TSHA: Toledo Study of Healthy Ageing.

3.3. Calf circumference cut-off points

LC7+ and TSHA calf circumference cut-off points according to sex and age group are displayed in Table 2. According to the proposed CC cut-off points in LC7+, 270 (17.6%; sFNIH), 182 (11.89%; FNIH) and 190 (12.41%; EWGSOP2) were identified as sarcopenic. On the other hand, 257 (16.78%; sFNIH), 169 (11.04%; FNIH) and 176 (11.50%; EWGSOP2) met sarcopenia criteria according to TSHA CC cut-points.

The accuracy metrics of the sarcopenia appendicular mass criterion and calf circumference are shown in Table 3. Although sensitivity was very high regardless of the scale used to assess sarcopenia and the proposed cut-off points, sensitivity did vary substantially, being the lowest for the sFNIH definition and the highest for the EWGSOP2. This was true regardless of the cut-off points used. Similarly, the level of agreement between the original definition and the adaptation using the twin cut-off points ranged from 0.49 (sFNIH-TSHA) to 0.69 (EWGSOP2-LC7+).

The predictive ability of different adverse events according to age, sex, comorbidity and polypharmacy is shown in Table 4. The consideration of these covariates explained between 71% and 78% of the risk of suffering the different events studied. Assessment of sarcopenia increased the predictive capacity of the model by up to 5.26% (when the event studied was incident frailty according to FP and the definition of sarcopenia was EWGSOP). For its part, when frailty was added to Model 1, the values for AUC were higher than Model 1, even when sarcopenia was included, except when the event to be predicted was incident frailty by FP. Nevertheless, the highest AUCs were found in those models that included both frailty and sarcopenia.

In all cases considered, even when potential confounders such as age, sex, and comorbidity were added, individuals meeting sarcopenia criteria had a significantly increased risk of death (HRs ranged from 1.41 to 1.51) and incident frailty (FP: ORs ranged from 2.41 to 3.64; FTS5: ORs ranged from 2.81 to 4.04) (Table 5). On the other hand, sarcopenic individuals also had an increased risk of hospitalization, which was significant for all

Table 3
Calf circumference cut-off points for appendicular lean mass sarcopenia criteria and accuracy metrics with the standard reference.

Sarcopenia definition	Calf circumference cut-off point	Sensitivity (%)	Specificity (%)	Youden's J Statistic	+LR	−LR	+PV	−PV	Kappa Index
sFNIH [n = 956 (48.47%)]	Longevity Check-up 7+ [n = 881 (62.44%)]	0.54 (0.49; 0.59)	0.93 (0.91; 0.94)	0.47	7.38	0.50	0.69	0.87	0.50 (0.45; 0.56)
	TSHA [n = 893 (57.54%)]	0.53 (0.48; 0.59	0.93 (0.91; 0.94)	0.45	7.22	0.51	0.68	0.87	0.49 (0.44; 0.55)
FNIH [n = 956 (62.97%)]	Longevity Check-up 7+ [n = 881 (62.44%)]	0.62 (0.56; 0.59	0.97 (0.96; 0.98)	0.59	19.19	0.39	0.78	0.93	0.64 (0.58; 0.70)
	TSHA [n = 893 (57.54%)]	0.58 (0.52; 0.59	0.97 (0.96; 0.98)	0.55	17.91	0.43	0.77	0.93	0.61 (0.55; 0.67)
EWGSOP2 [n = 956 (46.90%)]	Longevity Check-up 7+ [n = 881 (62.44%)]	0.72 (0.66; 0.59	0.97 (0.96; 0.98)	0.69	22.10	0.29	0.78	0.96	0.69 (0.63; 0.74)
	TSHA [n = 893 (57.54%)]	0.68 (0.62; 0.59	0.97 (0.96; 0.98)	0.65	21.84	0.33	0.78	0.95	0.67 (0.61; 0.73)

+LR = Positive Likelihood Ratio; −LR = Negative Likelihood Ratio; +PV = Positive Predictive Value; −PV = Negative Predictive Value.

Table 4
Integrated (IAUC) and areas under the curves (AUC) for predicting adverse events.

	Mortality (IAUC)		Hospitalization (IAUC)		Worsening disability (AUC)		Incident Frailty (FP) (AUC)		Incident Frailty (FTS5) (AUC)
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1
Model 1	0.7318	0.7553	0.7138	0.7246	0.7421	0.7632	0.7583	0.7829	0.7569
Original definitions									
sFNIH	0.7405	0.7558	0.7194	0.7263	0.7515	0.7653	0.8145	0.8214	0.8129
FNIH	0.7370	0.7567	0.7180	0.7263	0.7635	0.7683	0.7945	0.8029	0.8069
EWGSOP2	0.7410	0.7567	0.7158	0.7248	0.7516	0.7673	0.8109	0.8177	0.7882
LC7+ CC cut-off points									
sFNIH	0.7389	0.7576	0.7187	0.7267	0.7483	0.7647	0.7967	0.8064	0.7839
FNIH	0.7393	0.7575	0.7175	0.7262	0.7463	0.7638	0.8037	0.8112	0.7834
EWGSOP2	0.7383	0.7570	0.7175	0.7262	0.7465	0.7634	0.8001	0.8086	0.7812
TSHA CC cut-off points									
sFNIH	0.7389	0.7574	0.7191	0.7268	0.7459	0.7640	0.7836	0.7993	0.7784
FNIH	0.7394	0.7573	0.7178	0.7263	0.7450	0.7630	0.7910	0.8026	0.7762
EWGSOP2	0.7386	0.7571	0.7173	0.7259	0.7431	0.7631	0.7896	0.8009	0.7743

AUC: Area Under the Curve. EWGSOP: European Working Group on Sarcopenia in Older People. FNIH: Foundation for the National Institutes of Health sarcopenia criteria. IAUC: Integrated Area Under the Curve. In bold: p-value <0.05. LC7+: Longevity Check-up 7+ study. Model 1: adjusted by Age, Gender, Charlson Index and Polypharmacy. Model 2: Model 1 + frailty status (FTS5) at baseline. When incident frailty (FP) was the event, the model was adjusted by frailty status according to FP (robust or prefrailty). sFNIH: Foundation for the National Institutes of Health sarcopenia criteria standardized to our population. TSHA: Toledo Study of Healthy Ageing.

the sarcopenia definitions and cut-off points (HRs ranged from 1.30 to 1.33), except for the EWGSOP2-TSHA cut-off points [HR (95%CI): 1.27 (0.98, 1.65), p-value 0.066]. Finally, only the proposed cut-off points in LC7+ were able to be significantly associated with worsening disability (ORs ranged from 1.63 to 1.77), while TSHA showed a non-significant trend (p-value <0.09).

As with the original definitions, once adjusted for frailty status at baseline, the association was lost.

4. Discussion

The present study compared the predictive ability of different definitions of sarcopenia when using the original criteria to define low muscle mass against the one proposed by us according to CC measurements and its prediction in negative adverse outcomes. Our findings indicate that calf circumference cut-off points present a low-to-moderate agreement with appendicular lean mass as domain of muscle mass in the evaluation of sarcopenia. According to them, the highest agreement was present when the EWGSOP2 was the definition chosen. Moreover, we also compared the ability of different sarcopenia definition for predicting negative adverse outcomes. Despite the previous comments on the concordance between the original definition and those proposed by the calf circumference cut-off points, the predictive capacity of the different negative health events was very similar to the original definition (Table 2).

Sarcopenia is a highly prevalent age-related disease associated with negative outcomes in older adults [36–38]. Nevertheless, there exist considerable controversy about how sarcopenia should be defined and operationalized. In this sense, the prevalence of sarcopenia seems to be highly dependent on the definition, cut-off points proposed for its identification and on the study population. In a systematic review, Mayhew et al. [37] estimated the presence of sarcopenia ranged between 9.9% and 40.4% depending on the definitions and criteria chosen to identify this pathology. To overcome this handicap, we have evaluated our hypothesis using three definitions of sarcopenia. In our population, the prevalence of sarcopenia ranged from 13.85% to 22.73% according to the original definitions, and 11.04% to 16.78% according to the CC cut-off points.

According to our results, the ability to predict adverse events of the different definitions of sarcopenia (FNIH, sFNIH and EWGSOP2) is quite similar to each other (Table 4). Only for predicting incident frailty, where the predictive ability does differ by 2% depending on the tool used, the rest of the results differ in a non-relevant manner (<1%) regardless of the scale with which the individuals are classified.

To date, few studies have attempted to compare the sensitivity and specificity of different definitions of sarcopenia in the same population, and have related it to adverse events. Locquet et al. performed a comparison of five sarcopenia screening methods including data from 306 older adults. As in our results, the agreement between the 5 definitions was very low, ranging from 0.14 to 0.71, the highest being that found between the definition proposed by Cruz-Jentoft et al. in 2010 [39], together with that of Fielding et al. [5].

However, the predictive ability of the different definitions was not evaluated. Woo and colleagues [40] evaluated the ability of six definitions of sarcopenia to capture incident slow gait speed, hospital

Table 5
Associations between sarcopenia definitions and adverse events.

			Model 1		Model 2		Model 3	
Sarcopenia definitions and events		**CC Cut-off point**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Death								
sFNIH		LC7 +	1.81 (1.34, 2.44)	<**0.001**	1.50 (1.09, 2.05)	**0.012**	1.21 (0.86, 1.70)	0.276
		TSHA	1.74 (1.28, 2.36)	<**0.001**	1.51 (1.09, 2.08)	**0.013**	1.27 (0.91, 1.79)	0.159
FNIH		LC7 +	2.05 (1.47, 2.85)	<**0.001**	1.44 (1.02, 2.02)	**0.036**	1.09 (0.75, 1.60)	0.650
		TSHA	1.97 (1.40, 2.78)	<**0.001**	1.44 (1.02, 2.05)	**0.040**	1.17 (0.80, 1.69)	0.420
EWGSOP2		LC7 +	2.00 (1.44, 2.77)	<**0.001**	1.41 (1.01, 1.98)	**0.044**	1.08 (0.74, 1.57)	0.681
		TSHA	1.94 (1.38, 2.72)	<**0.001**	1.43 (1.01, 2.02)	**0.044**	1.16 (0.80, 1.67)	0.426
Hospitalization		**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	
sFNIH	LC7 +	1.71 (1.37, 2.14)	<**0.001**	1.33 (1.06, 1.67)	**0.015**	1.12 (0.88, 1.42)	0.374	
	TSHA	1.67 (1.34, 2.10)	<**0.001**	1.33 (1.05, 1.68)	**0.017**	1.17 (0.92, 1.49)	0.190	
FNIH	LC7 +	1.84 (1.44, 2.36)	<**0.001**	1.31 (1.01, 1.68)	**0.039**	1.03 (0.78, 1.35)	0.848	
	TSHA	1.80 (1.39, 2.33)	<**0.001**	1.30 (1.01, 1.69)	**0.046**	1.10 (0.84, 1.44)	0.507	
EWGSOP2	LC7 +	1.80 (1.41, 2.30)	<**0.001**	1.30 (1.01, 1.66)	**0.042**	1.03 (0.78, 1.35)	0.849	
	TSHA	1.74 (1.35, 2.24)	<**0.001**	1.27 (0.98, 1.65)	0.066	1.08 (0.82, 1.41)	0.595	
Incident frailty (FP)		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	
sFNIH	LC7 +	4.25 (2.30, 7.84)	<**0.001**	2.86 (1.49, 5.47)	**0.002**	-		
	TSHA	3.65 (1.96, 6.81)	<**0.001**	2.41 (1.24, 4.69)	**0.010**	-		
FNIH	LC7 +	5.50 (2.90, 10.45)	<**0.001**	3.64 (1.86, 7.14)	<**0.001**	-		
	TSHA	4.74 (2.45, 9.20)	<**0.001**	3.04 (1.52, 6.08)	**0.002**	-		
EWGSOP2	LC7 +	5.18 (2.73, 9.83)	<**0.001**	3.49 (1.78, 6.82)	<**0.001**	-		
	TSHA	4.50 (2.32, 8.73)	<**0.001**	2.92 (1.47, 5.84)	**0.002**	-		
Incident frailty (FTS5)		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	
sFNIH	LC7 +	4.78 (3.02, 7.58)	<**0.001**	3.07 (1.88, 4.99)	<**0.001**	-		
	TSHA	4.54 (2.84, 7.23)	<**0.001**	2.81 (1.72, 4.62)	<**0.001**	-		
FNIH	LC7 +	5.24 (3.12, 8.80)	<**0.001**	4.04 (2.31, 7.06)	<**0.001**	-		
	TSHA	5.00 (2.93, 8.52)	<**0.001**	3.62 (2.04, 6.40)	<**0.001**	-		
EWGSOP2	LC7 +	4.78 (2.86, 8.01)	<**0.001**	3.87 (2.22, 6.76)	<**0.001**	-		
	TSHA	4.61 (2.71, 7.83)	<**0.001**	3.49 (1.98, 6.16)	<**0.001**	-		
Worsening disability		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	
sFNIH	LC7 +	2.63 (1.65, 4.20)	<**0.001**	1.63 (1.00, 2.66)	**0.0481**	1.34 (0.80, 2.24)	0.262	
	TSHA	2.51 (1.57, 4.04)	<**0.001**	1.55 (0.94, 2.55)	0.0838	1.30 (0.77, 2.18)	0.325	
FNIH	LC7 +	2.74 (1.64, 4.58)	<**0.001**	1.77 (1.03, 3.01)	**0.0371**	1.37 (0.77, 2.44)	0.289	
	TSHA	2.62 (1.54, 4.46)	<**0.001**	1.66 (0.96, 2.88)	0.0703	1.31 (0.73, 2.35)	0.366	
EWGSOP2	LC7 +	2.61 (1.56, 4.35)	<**0.001**	1.72 (1.01, 2.93)	**0.0467**	1.33 (0.75, 2.37)	0.332	
	TSHA	2.50 (1.47, 4.26)	<**0.001**	1.62 (0.94, 2.81)	0.0832	1.28 (0.71, 2.30)	0.405	

CC: Calf Circumference. EWGSOP: European Working Group on Sarcopenia in Older People. FNIH: Foundation for the National Institutes of Health sarcopenia criteria. In bold: p-value <0.05. LC7 +: Longevity Check-up 7 +. Model 1: raw model. Model 2: adjusted by Age, Gender, Charlson Index and Polypharmacy. Model 3: Model 2 + frailty status at baseline. LC7 +: Longevity Check-up 7 + . NA: Not Applicable. TSHA: Toledo Study of Healthy Ageing. sFNIH: Foundation for the National Institutes of Health sarcopenia criteria standardized to our population.

stay of more than 20 days and mortality after 10 years. All definitions had a similar ability to predict physical limitation, long hospital stay or mortality.

Nevertheless, the time required for administration, the elevated costs related to these tests, the need for professionals trained in each technique, as well as the absence of portability, mean that these tests are not widely used in routine clinical practice [41]. In fact, the muscle mass criterion cannot be performed in one out of three hospitalized older adults [42], so the inclusion of CC as a proxy for it could facilitate the evaluation of this geriatric disease. In hospitalized older adults, CC has shown an ability to predict sarcopenia according to the cut-off points proposed by the EWGSOP2 (AUC = 0.82) [43].

Our study extols the role of calf circumference as a proxy for appendicular mass, a tool much simpler and cheaper to perform than other measures of muscle mass, and valid for detecting individuals at higher risk of negative health events. In fact, it has been proposed that the presence of low CC, in addition to sarcopenia, may increase the association of the latter with mortality [44]. In addition, our cut-off points for the identification of sarcopenia are similar to previous studies. Jeong et al. found AUC = 0.716 for CC < 34 in men and <33 in women using the Asian Working Group for Sarcopenia 2019 criteria [45]. For the same definition of sarcopenia, Hwang et al. using data from a cohort of individuals over 50, proposed cut-off points of 33 for men and 32 for women, with AUC of 0.81 and 0.75, respectively [46]. According to the muscle mass criteria proposed in the EWGSOP2 definition, cut-off points of 34 cm for men and 33 cm for women showed low overlap in a cohort of older adult cancer survivors [47]. Using the NHANES database, Gonzalez et al. have proposed cut-off points of 33 for men and 32 for women to identify the presence of low muscle mass [48]. These criteria have been recommended for the recognition of low muscle mass [49] As we age, there is a state of anabolic resistance evidenced in the processes of synthesis and degradation of muscle proteins [50]. Additionally, total and protein intake may be reduced [51,52] and periods of sedentarism increases [53], which would support this state of anabolic resistance. Weight loss as well as low levels of physical activity are two of the criteria used to identify frailty [31].

On the other hand, our results could support the presence of different phenotypes based on the presence of frailty and sarcopenia, something that has been previously proposed [8,9,54–56]. Several authors have mixed frailty and sarcopenia. It is true that these entities that have been highly associated with negative health events in older adults share certain domains, can coexist in the same individual, but they are distinct entities [30,57], with biological processes that are similar but not equal [58,59], and different clinical prognoses [8,9,57]. From a cross-sectional point of view, a low proportion of people with sarcopenia present frailty, and conversely, one out of four individuals with frailty does not present

sarcopenia [30,60]. According to our results, frailty could mediate between sarcopenia and all the negative health events evaluated. Only for worsening disability, as long as the chosen definition is FNIH, sarcopenia maintained a significant association with the adverse event. In fact, although sarcopenia is a good predictor of frailty [8], in terms of disability, both entities must coexist to predict this outcome [9]. Furthermore, we have previously shown that sarcopenia may not increase the risk of death associated with frailty [8,9]. Given that the above statement was evaluated in our (TSHA) and other populations using a single definition of sarcopenia, we wanted to evaluate whether this finding is maintained by evaluating different definitions of sarcopenia (both the original and those proposed on the basis of CC). On the other hand, according to our results, the presence of this age-related geriatric syndrome seems to mediate the relationship of certain adverse health-related events [61]. A non-significant association was observed for sarcopenia in relation to hospitalization (p-value 0.06). In the Toledo study, we already showed that sarcopenia increased the risk of hospitalization, independently of frailty [62].

Our study has several strengths that should be mentioned. Firstly, we have included several definitions of sarcopenia allowing us to compare the results in the same population. Likewise, we have evaluated CC cut-off points proposed in the literature and according to our population, standardized by sex and age ranges. In addition, it is worth noting the number of adverse events studied, the follow-up time, and the evaluation of two frailty tools. Finally, we have included several confounding variables that have not been shown to significantly influence our results.

Our study presents some limitations that should be mentioned. In the TSHA, calf measurements were taken to the nearest cm, whereas other studies collected to the mm. Furthermore, despite the fact that the CC measurements were made following the standard guidelines, CC measurements may depend on certain aspects such as the posture of the individuals [45], or the presence of edema, something that in our cohort has not been contemplated. In addition, because of the volume of TSHA participants, the median follow-up between wave 2 and wave 3 was almost 3 years, with ranges between 2 and 5.4 years. Since follow-up time cannot be accounted for in incident frailty and worsening disability, this difference in follow-up time between participants may interfere in our results. Moreover, it should be mentioned that our participants were community-dwelling older adults, therefore, extrapolation to populations with other conditions, such as hospitalized or institutionalized older adults, among others, should be evaluated.

In addition, we did not examine the ideal cutoff point for this. We used fix values as cut-off points coming from normative data from the TSHA and Lookup 7+, following previous recommendations [17], but we did not look for finding the best cut-off point. Comparing the median-CC of the Italian and Spanish cohort provide a higher construct validity and, as a consequence, we could recommend the use of distribution cutoff points in order to extrapolate these results to other cohorts. Of course, this fact should be evaluated in other cohorts.

5. Conclusions

Calf circumference may be suitable for screening for sarcopenia. Because of the relationship between sarcopenia and various adverse events, its evaluation should be routinely performed in the management of older adults.

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Statements and declarations

The authors declare no competing interests.

Declaration of interests

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Appendix A. Supplementary data

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