Anthropometric indicators as predictors of dynapenia in older people: a cross-sectional analysis

Indicadores antropométricos como preditores de dinapenia em pessoas idosas: uma análise transversal

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Abstract

Introduction: Due to aging, older people become more prone to dynapenia, which increases the risk of mortality. It is therefore essential to propose low-cost tools to screen for this outcome. **Objective:** To analyze the predictive ability of anthropometric indicators for screening dynapenia in older people. **Methods:** We conducted a cross-sectional census epidemiological study of 196 older people. The predictors listed were: body mass index (BMI), arm circumference (AC), calf circumference (CC), arm muscle circumference and corrected arm muscle area. Student's t or Mann-Whitney U tests (comparisons) and the receiver operating characteristic curves (predictive ability) were used in the analyses. A significance level of 5% was adopted for all analyses. **Results:** The prevalence of dynapenia was 26.60% in older men and 24.80% in older women. It was also observed that older people with dynapenia had lower values for anthropometric indicators compared to those without dynapenia (p < 0.05). In older men, the indicator most sensitive to dynapenia was BMI (71.43%), while the most specific was AC (93.10%). Among older women, the indicator most sensitive to dynapenia was CC (76.92%) and the most specific was AC (77.27%). **Conclusion:** BMI and CC were found to be better at screening older men and older women for dynapenia, respectively. In addition, AC was the indicator that best identified older people of both sexes without the outcome.

Keywords: Anthropometry. Aging. Epidemiology. Functional physical performance.

Resumo

Introdução: *Como consequência do envelhecimento, a pessoa idosa torna-se mais propícia ao acometimento da dinapenia, o que aumenta o risco de mortalidade. Torna-se imprescindível, portanto, a proposição de ferramentas de baixo custo para o rastreio de tal desfecho.* ***Objetivo:*** *Analisar a capacidade preditiva de indicadores antropométricos para o rastreio da dinapenia em pessoas idosas.* ***Métodos:*** *Pesquisa epidemiológica censitária e transversal, conduzida com 196 pessoas idosas. Os preditores elencados foram: índice de massa corporal (IMC), circunferência do braço (CB), circunferência da panturrilha (CP), circunferência muscular do braço e área muscular do braço corrigida. Nas análises foram utilizados os testes t de Student ou U de Mann-Whitney (comparações) e a* curva *receiver operating characteristic (capacidade preditiva). Em todas as análises foi adotado um nível de significância de 5%.* ***Resultados:*** *A prevalência de dinapenia foi na ordem de 26,60% nos homens e de 24,80% nas mulheres. Observou-se que as pessoas idosas com dinapenia apresentaram menores valores nos indicadores antropométricos quando comparadas às sem dinapenia (p < 0,05). No sexo masculino, o indicador mais sensível à dinapenia foi o IMC (71,43%), enquanto o mais específico foi a CB (93,10%). Entre as mulheres, o indicador mais sensível à dinapenia foi a CP (76,92%) e o mais específico foi a CB (77,27%).* ***Conclusão:*** *Verificou-se que o IMC e a CP demonstraram, respectivamente, melhor capacidade para o rastreio dos homens e das mulheres com dinapenia. Ademais, a CB foi o indicador que melhor identificou as pessoas idosas, de ambos os sexos, sem o desfecho.*

Palavras-chave: *Antropometria. Envelhecimento. Epidemiologia. Desempenho físico funcional.*

Introduction

Dynapenia is a term of Greek origin,[1] used to describe the decline in muscle strength resulting from weakness throughout aging.[2,3] The expression means "poverty of strength" and is used with the purpose of distinguishing changes in muscle mass and strength in older people.[1] Different aspects appear to be related to dynapenia, which can be exemplified by cognitive impairment, rheumatic disease,[4] reduced gait speed, limitations in basic daily activities, episodes of falls, chronic diseases[5] and mortality.[6,7]

Thus, dynapenia is characterized as an adverse outcome for the health of older people, making it necessary to identify it early.[2,8] Accordingly, the literature suggests the use of the handgrip strength test (HGS) for the diagnosis of muscle weakness.[9,10] To achieve the objective of the test, a hand-held hydraulic dynamometer is necessary,[2-9] an instrument that is scarce in outpatient clinics and health units, especially in developing countries such as Brazil.[8,9] This fact, in clinical practice and in the field of public health, can impact the identification of dynapenia in older people.[8,9]

Therefore, the need to propose tools that are more accessible to the reality of such locations for screening dynapenia in older populations has been highlighted.[8,9] In this context, evidence suggests that older people with dynapenia tend to present lower values in anthropometric indicators in comparison with older people without this outcome.[5,9,11,12] This leads to the plausibility of the hypothesis that such indicators are accurate for dynapenia and, therefore, can be used to screen for this morbidity.

After searching the literature, only one study with such an investigation perspective was found in Brazil, which was limited to females only and included, in addition to older women, adult women in the post-menopausal period.[9] In view of this, there is a need to carry out health surveys, especially in places that show low demographic and economic indicators, considering the difficulties in accessing and offering health services in these locations; the proposition of low-cost and easy-to-use tools can help with health surveillance measures and optimize the screening of muscle weakness during aging.[8,9] To this end, this study aimed to analyze the predictive ability of anthropometric indicators for screening older people for dynapenia.

Methods

We conducted a cross-sectional study, structured according to or suggested by Strengthening the Reporting of Observational Studies in Epidemiology,[13] In addition, it was constructed from data from the third wave of an epidemiological, census and home-based research carried out from January to March 2018 in Aiquara, Bahia, Brazil.[14] The eligible people participating were residents of the urban area of the municipality and registered in the Family Health Strategy (FHS), which covers 100% of

the population of Aiquara.[14] The study was approved by the Research Ethics Committee of Southwestern State University. Bahia, under Opinion No. 1.575.825/2016 and CAAE 56017816.2.0000.0055. All participants signed an informed consent form.

Eligibility criteria

The study included non-institutionalized older people, living in urban areas and sleeping at home at least four nights a week. The exclusion criteria were: older people not found at home after three visits at different times; and < 13 points on the Mini Mental State Examination (MMSE).[15]

Predictors (anthropometric indicators)

Height was measured using a 210-cm stadiometer (WiSO®), with the person in orthostasis, maintaining an upright position, in contact with the wall and with feet together, looking at a horizontal axis.[14] Weight was measured using a portable digital balance (Plenna®). Based on this information, the body mass index (BMI) was calculated. For calf circumference (CC) and arm circumference (AC), an inelastic flexible anthropometric tape (Sanny®), was used, with a precision of 1 mm.[14] CC was measured at its greatest circumference in the plane perpendicular to its longitudinal axis, and AC was measured at the midpoint between the lateral edge of the acromion and the head of the radius. Both measures were taken on the right limb.[14]

The triceps skinfold thickness (TST) was measured using a properly calibrated Lange® adipometer (Santa Cruz, CA), with 1 mm precision. The measurement was carried out in the posterior region of the arm, at the same point used to measure AC, on the right upper limb.[14] With the AC and TST values, the arm muscle circumference (AMC; in cm) and corrected arm muscle area (AMA-c; in cm²) were calculated, using the equations: AMC = (AC – [π/10 x TST])[16] and AMA-c according to sex: men = AC – ([π/10 x TST]²/4π) – 10; women = AC – ([π/10 x TST]²/4π) - 6.5.[17]

Outcome (dynapenia)

The diagnosis of dynapenia was made based on the values in kilogram-force (kgf), obtained through the HGS test, carried out with a Saehan handheld dynamometer, SH5002 (Saehan Corporation, Masan, South Korea).

The test was carried out with the person sitting, with the el-bow flexed at 90° and the forearm in a neutral position.[18] Throughout the test, the person was encouraged to press the dynamometer handle with maximum force[19,20] for five seconds.[20] Subsequently, participants who had HGS less than or equal to the 25th percentile (≤ P25) were classified as dynapenic: 29.00 kgf in males and 17.75 kgf in females.

Statistical analysis

The first part of the data analysis was conducted using the Statistical Package for Social Sciences (SPSS® 21.0, 2013, Inc, Chicago, IL). To describe the characteristics of the participants, absolute and relative frequencies, means, medians, standard deviations and interquartile range were calculated. Furthermore, the response percentage of all variables (missing) was calculated. The Komolgorov-Smirnov test was used to analyze the normality distribution of continuous variables. Next, Student's t was used for comparisons of variables that showed normal distribution and the Mann-Whitney U test for non-normal distributions.

Finally, the verification of the diagnostic power of anthropometric indicators on dynapenia was carried out using the parameters provided by the receiver operating characteristic (ROC) curve, verified using MedCalc (version 19.4.1, 2018). To this end, the accuracy values of each indicator were initially analyzed on the basis of the comparison of the areas under the ROC curve.[21] Subsequently, the best cutoff points and their respective sensitivity/specificity values were identified by the Youden index.[22] A 95% confidence interval was adopted for all analyses (α ≤ 0.05).

Results

The identification of older people was carried out with the support of the FHS. With the help of community health workers, all households in the urban area where older people reside were visited. Thus, 314 older people were identified, and of these, 196 made up the study participants, as shown in Figure 1. Among the participants, there was a greater representation of women (59.70%; n = 117), who demonstrated a mean age of 71.92 ± 7.91 years. The mean age of the men was 72.51 ± 8.20 years. The prevalence of dynapenia in males was 26.60% (n = 21) and in women, 24.80% (n = 29).

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┌──────────────────────┐
│ Initial older        │
│ population           │          ┌────────────────────────┐
│ (n = 314)            │─────────▶│ Refusals to participate in │
└──────────────────────┘          │ the study (n = 17)        │
           │                      └────────────────────────┘
           ▼
┌──────────────────────┐
│ Selected older       │
│ persons (n = 297)    │          ┌────────────────────────────────┐
└──────────────────────┘─────────▶│ Excluded (n = 23)              │
           │                      │ Cognitive impairment (n = 19)  │
           │                      │ Severe stroke sequelae (n = 4) │
           │                      └────────────────────────────────┘
           │                      ┌────────────────────────────────┐
           │─────────────────────▶│ Could not be found after three │
           │                      │ visits on different days and   │
           │                      │ shifts (n = 16)                │
           │                      └────────────────────────────────┘
           │                      ┌────────────────────────────────┐
           │─────────────────────▶│ Did not provide anthropometric │
           │                      │ and/or handgrip strength       │
           │                      │ measurements (n = 62)          │
           ▼                      └────────────────────────────────┘
┌──────────────────────┐
│ Older persons        │
│ included in the      │
│ study (n = 196)      │
└──────────────────────┘
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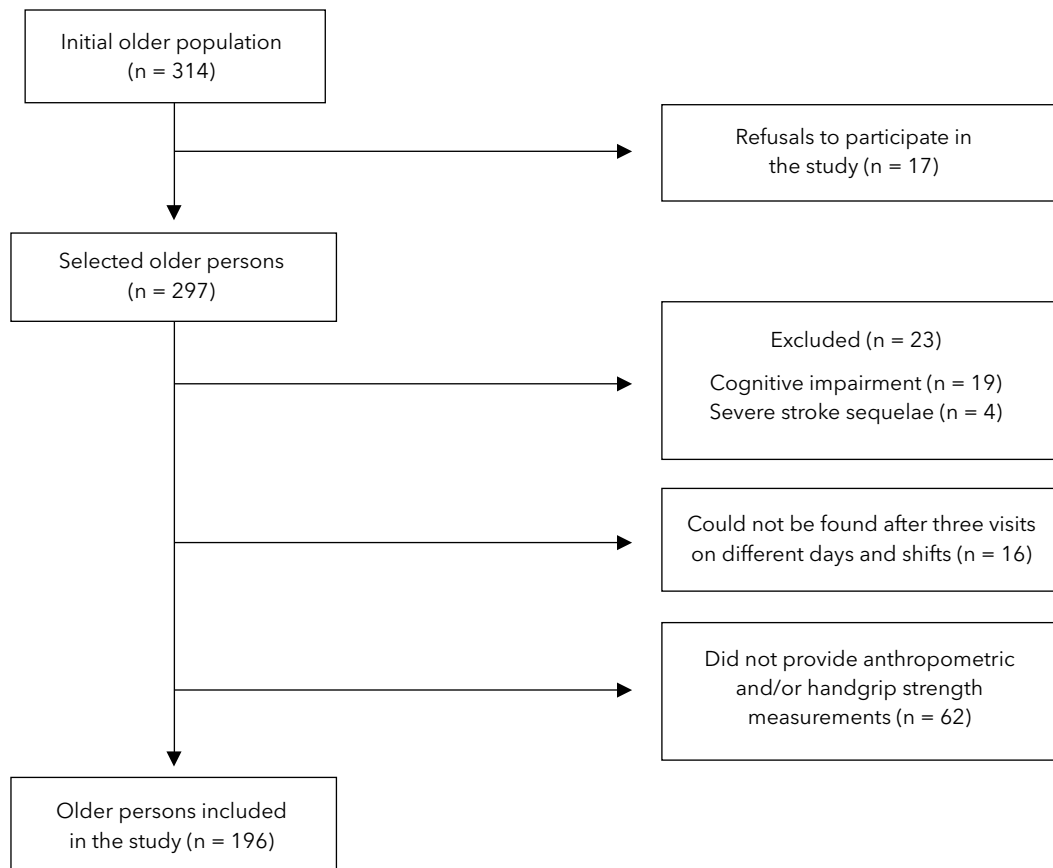
Figure 1 - Decision diagram in the selection process of older persons participating in the study.

Among older males, values for height, weight, BMI, CC, AC, AMC and AMA-c were significantly higher in the group without dynapenia (p < 0.05). In females, there was a difference between the mean values of all anthropometric indicators, with higher values in older women without dynapenia (p < 0.05) (Table 1).

Figures 2 and 3 show the areas of the ROC curves of the anthropometric indicators of the older men and women, respectively. In both sexes, BMI, AC, CC, AMC and AMA-c showed a lower limit of the AUC confidence interval > 0.50. This result shows that the nutritional status indicator (BMI) and muscle mass indicators (CC, AC, AMC and AMA-c) were accurate in predicting dynapenia in older people of both sexes. It is noteworthy that among these indicators there was no difference when comparing the ROC curves (p > 0.05) in either sex.

The cutoff points and sensitivity and specificity values are shown in Table 2. In males, the following values were identified: BMI = 25.19 kg/m²; CC = 31.90 cm; AC = 25.50 cm; AMC = 23.11 cm; and AMA-c = 32.52 cm². Of these, BMI was the most sensitive indicator (71.43%) and CC was the most specific (94.74%). For females, the cutoff points identified for the indicators were: BMI = 26.79 kg/m²; CC = 33.20 cm; AC = 21.38 cm; AMC = 21.38 cm; and AMA-c = 29.88 cm². CC was the most sensitive (76.92%), while AC, AMC and AMA-c showed equal specificities (77.27%).

Discussion

The main evidence of this study showed that all anthropometric indicators analyzed (BMI, CC, AC, AMC and AMA-c) demonstrated predictive ability for dynapenia; This is considered the lower limit of the confidence intervals of the accuracies found (areas under the ROC curve), which presented values > 0.5 for all variables, in both sexes, with no difference between them.

Table 1 - Measures of central tendency and dispersion of anthropometric indicators according to dynapenia in older people of both sexes

Variable	% response	Males		p-value
		Dynapenia		
		No (n = 58)	Sim (n = 21)	
Height (cm)+	100	164.64 (6.02)	160.42 (6.32)	**0.008@**
Weight (kg)*	100	69.55 (13.70)	61.30 (18.90)	**0.001#**
Body mass index (kg/m²)*	100	26.35 (5.02)	24.51 (7.52)	**0.024#**
Calf circumference (cm)+	98.70	35.82 (3.09)	33.10 (3.50)	**0.001@**
Arm circumference (cm)+	100	29.71 (2.99)	27.02 (3.37)	**0.001@**
Triceps skinfold thickness (mm)*	100	10.90 (5.50)	9.80 (5.20)	0.085#
Arm muscle circumference (cm)+	100	26.03 (2.51)	24.08 (2.74)	**0.004@**
Corrected arm muscle area (cm²)+	100	44.46 (10.59)	36.75 (10.50)	**0.005@**

Variable	% response	Females		p-value
		Dynapenia		
		No (n = 88)	Yes (n = 29)	
Height (cm)+	100	151.65 (5.67)	147.41 (6.60)	**0.001@**
Weight (kg)+	100	65.13 (13.95)	55.65 (11.99)	**0.001@**
Body mass index (kg/m²)+	100	28.26 (5.51)	25.66 (5.44)	**0.029@**
Calf circumference (cm)*	100	34.20 (5.30)	31.90 (2.60)	**<0.001#**
Arm circumference (cm)+	100	30.33 (3.99)	26.96 (4.57)	**<0.001@**
Triceps skinfold thickness (mm)+	100	22.89 (6.96)	17.95 (5.91)	**0.001@**
Arm muscle circumference (cm)+	99.10	23.14 (2.52)	21.71 (2.96)	**0.014@**
Corrected arm muscle area (cm²)*	100	36.47 (10.17)	28.65 (13.55)	**0.010#**

Note: +mean and standard deviation; *median and interquartile interval; @p-value obtained using Student's t test; #p-value obtained using Mann-Whitney U test. Values in bold indicate p < 0.05.

Table 2 - Cutoff points, sensitivity and specificity of anthropometric indicators used as predictors of dynapenia in the study population

Variable	Males		
	Cutoff point	Sensitivity (95%CI)	Specificity (95%CI)
Body mass index (kg/m²)	25.19	71.43 (47.80 - 88.70)	58.62 (44.90 - 71.40)
Calf circumference (cm)	31.90	42.86 (21.80 - 66.00)	94.74 (85.40 - 98.90)
Arm circumference (cm)	25.50	38.10 (18.10 - 61.60)	93.10 (83.30 - 98.10)
Arm muscle circumference (cm)	23.11	47.62 (25.70 - 70.20)	87.93 (76.70 - 95.00)
Corrected arm muscle area (cm²)	32.52	47.62 (25.70 - 70.20)	87.93 (76.70 - 95.00)

Variable	Females		
	Cutoff point	Sensitivity (95%CI)	Specificity (95%CI)
Body mass index (kg/m²)	26.79	72.41 (52.80 - 87.30)	62.50 (51.50 - 72.60)
Calf circumference (cm)	33.20	76.92 (56.40 - 91.00)	67.82 (56.90 - 77.40)
Arm circumference (cm)	21.38	57.14 (37.20 - 75.50)	77.27 (67.10 - 85.50)
Arm muscle circumference (cm)	21.38	57.14 (37.20 - 75.50)	77.27 (67.10 - 85.50)
Corrected arm muscle area (cm²)	29.88	57.14 (37.20 - 75.50)	77.27 (67.10 - 85.50)

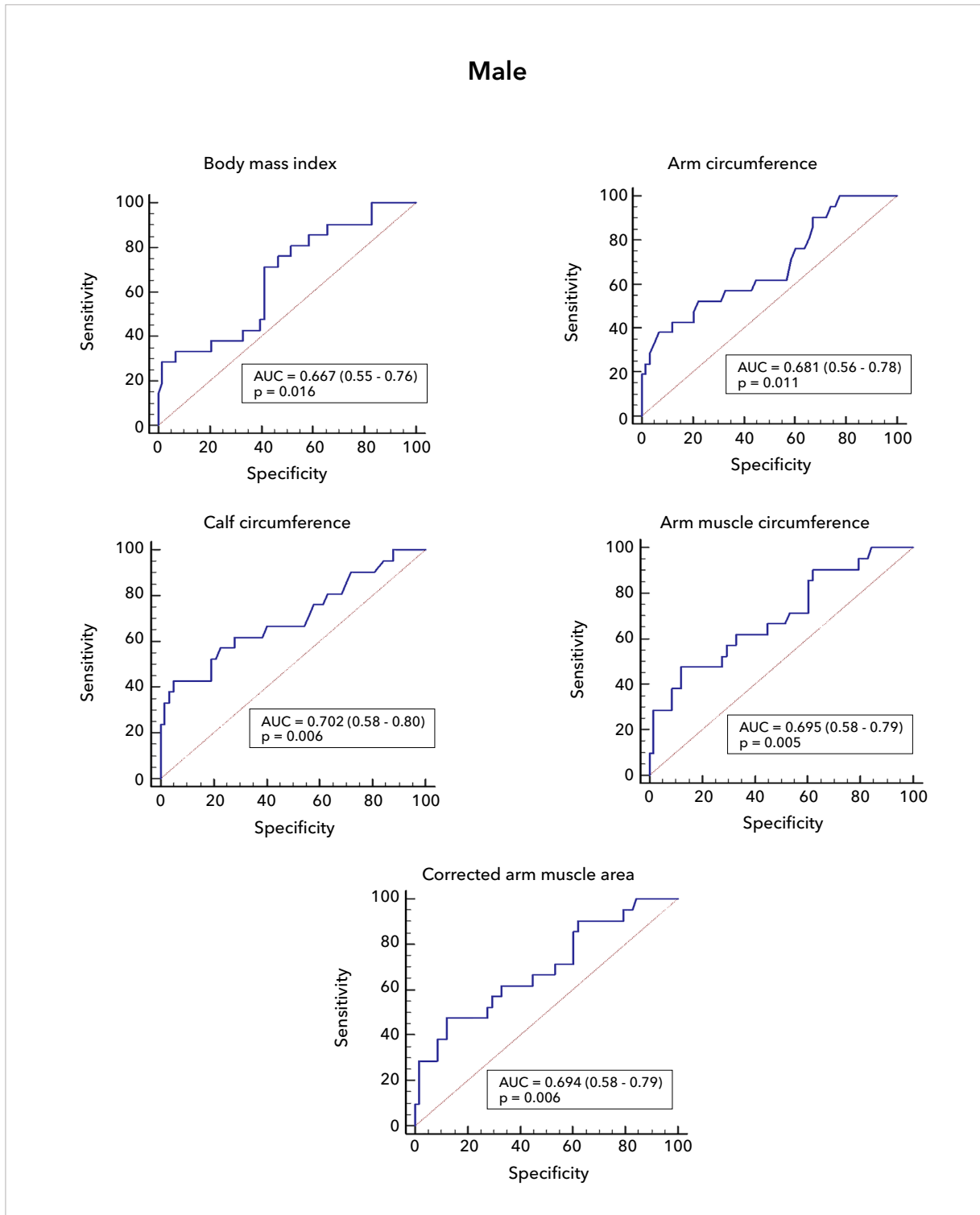Note: 95%CI = 95% confidence interval.

Figure 2 - Receiver operating characteristic curves of anthropometric indicators used as predictors of dynapenia in older males.
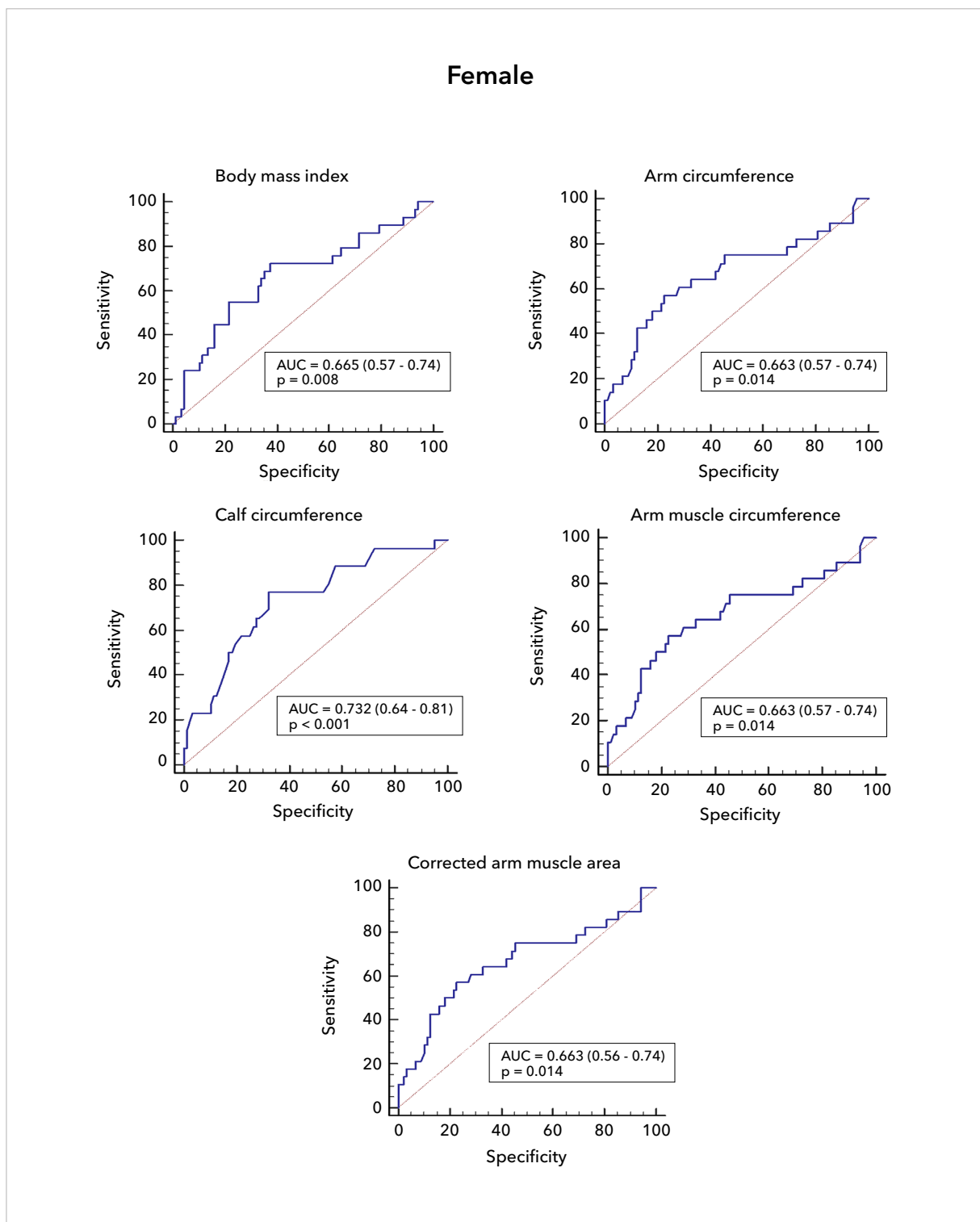
Note: AUC = area under the curve.

Figure 3 - Receiver operating characteristic curves of anthropometric indicators used as predictors of dynapenia in older females.

Note: AUC = area under the curve.

The difference in anthropometric indicators observed between older people with and without dynapenia can be explained based on the body structure of these individuals. It is known, for example, that one of the factors that affect HGS is height and weight.[23] Corroborating this evidence, a prospective study conducted in the Netherlands, with 555 older people, identified a positive association of height and weight with HGS.[24] According to the authors, the individual's height expresses their bone composition, and those taller tend to have greater limb length, which reflects in a greater lever arm, making it possible to generate greater force.[24] The relationship of weight and HGS is evidenced by dynapenia, which is commonly observed in underweight individuals, who have less muscle mass.[23]

In this way, the relationship between BMI and dynapenia is also elucidated, since the first is a measurement obtained from the two variables in question, height and weight. Furthermore, it is worth noting that BMI is used as an instrument to assess the nutritional status of older people and tends to change as people age, making them prone to low weight and consequently to a deficit in muscle strength.[25]

In Brazil, another study also points to the use of anthropometric indicators as an instrument to evaluate the nutritional status of older people, such as CC and AMA-c.[26] Muscle mass indicators, such as CC and AC, can identify malnutrition in older people from the investigation of conditions marked by low muscle mass reserve, while through TST, it is possible to measure nutritional status, considering body fat.[27] Accordingly, it is highlighted that malnutrition directly influences strength by promoting a reduction in protein levels, which are used as a source of muscle energy.[25] Therefore, it is expected that non-dynapenic older people will show higher values in indicators that reflect muscle mass and body fat.

Corroborating the present study, other authors also indicated the predictive ability of muscle mass indicators in dynapenia in a cross-sectional epidemiological investigation carried out with 273 postmenopausal women (adults and older women) in Jequié-BA, Brazil.[9] In this population, the best cutoff points found for each indicator were as follows: BMI = 24.80 kg/m²; CC = 34.40 cm; AC = 31.40 cm; AMC = 21.10 cm; and AMA-c: 29.00 cm². Of these, it is observed that CC, AC, AMC and AMA-c cutoffs were close to those evidenced in the present study. Furthermore, in the aforementioned

study, the indicator with the highest sensitivity was CC, and those with the highest specificity were AMC and AMA-c.[9] In the present study, older women showed CC as the most sensitive indicator. The ones with the highest specificity were the same, along with AC.

The differences found between the studies, with regard to sensitivity and specificity, may be linked to the specific differences of each individual. The study carried out with women in the postmenopausal period covered those aged 50 years and older,[9] which possibly limits the comparison between such results, given the repercussions of advancing age on the musculoskeletal system.

Furthermore, other factors may be related to these differences, such as the area covered, population contingent and different socioeconomic profile between Aiquara and Jequié. These differences in socioeconomic profile end up influencing employment opportunities and can have an impact on the lifestyle and health conditions of these women. Healthy food consumption, work, physical exercise and access to health services may vary among the same population in these municipalities and contribute to differences in health indicators, including the prevalence of dynapenia.

The accuracy of muscle mass indicators on dynapenia can be understood physiologically from the analysis of body structure. No other studies were found in the national literature that aimed to evaluate anthropometric variables as discriminators of dynapenia in older people, which limits this discussion. However, an association between the outcome and some of these variables was identified in different studies among healthy older people[12,28] and adults and older people with chronic diseases.[29,30]

Among Brazilian individuals from 70 municipalities, of both sexes and aged 50 years or older, an association was observed between BMI and dynapenia, such that a higher BMI value was associated with better HGS. Furthermore, it was observed that normal-weight and overweight older people had respectively 54 and 74% less chance of being dynapenic, when compared to those with low weight.[5] In this case, it can be speculated that high BMI results from a greater level of skeletal muscle mass, which directly influences the individual's weight. On the other hand, it is worth highlighting that adipose tissue, in individuals with a higher BMI, can affect muscle strength, by limiting the muscle's ability to contract.[31] Furthermore, authors of a previous study

with older people of Aiquara found that those with low weight were 2.20 (95%CI: 1.26 - 3.82) times more likely to experience dynapenia.[32]

The relationship between CC and dynapenia was evident in the Northeast and Southeast regions of Brazil, in studies conducted with older people from Campina Grande-PB[28] and São Caetano do Sul-SP.[12] In Campina Grande, older people with smaller calf circumference were approximately twice as likely to experience dynapenia (OR: 2.21; 95%CI: 1.15 - 4.25).[28] In Caetano do Sul, older people with lower CC were 50% more likely to end up with the outcome (p < 0.05) compared to those with CC above the cutoff point used in the study (≤ 33 cm for women and ≤ 34 cm for men).[12] In this last study, the authors suggested that an individual's muscle mass is directly related to muscle strength and that CC is an anthropometric measurement that reflects muscle reserve, and therefore, it is a sensitive variable for the muscle mass of older people, as it expresses changes in fat-free mass,[12] which corroborates the findings of the present study, as this anthropometric measurement was the one with the greatest sensitivity in females and the highest specificity in males.

In the study carried out in Caetano do Sul, in addition to CC, AC also showed an association with dynapenia.[12] This relationship is also observed among adults and older people living with chronic diseases, such as in individuals with chronic kidney disease, residents of the city of Curitiba-PR, in the southern region of Brazil.[29] In this study, HGS was used to assess the risk of malnutrition and inflammation in 238 patients undergoing hemodialysis. As a result, the authors identified that lower HGS was associated with lower AC (OR: 1.33; 95%CI: 1.03 - 1.70).[29] This finding, in turn, can be understood on the basis of the assumption that AC, although not used alone to check strength among men, for example, is related to muscle mass.[27] Therefore, a lower AC will result in lower muscle mass, which can contribute to dynapenia.

With regard to AMC and AMA-c, it is noteworthy that no studies were found in the literature that pointed to the relationship between such variables and dynapenia in the exclusively older population of both sexes. In addition to the study conducted with postmenopausal women,[9] an association between HGS and AMC and AMA-c was also demonstrated in adults and older people living with the human immunodeficiency virus (HIV).[30] The study, which was carried out with 242 patients from the Hospital Universitário Gaffrée e Guinle, in Rio de Janeiro-RJ, Brazil, revealed that HGS was associated with muscle mass variables (AMC and AMA) in both sexes (p < 0.001), without, however, showing any relationship with the fat mass variable (fat area of the arm). Such results allowed the authors to speculate that HGS is possibly related to muscle mass. [30]

Given the above, the ability of BMI, CC, AC, AMC and AMA-c to predict dynapenia can be understood from two perspectives. The first is that these anthropometric indicators are related, among other factors, to the loss of muscle mass. And the second is that dynapenia is triggered by the reduction in muscle strength, which can be influenced by the decrease in this mass.

This fact becomes relevant, in clinical practice, in the screening of older people with a greater probability of developing dynapenia, aiming at the functioning of these individuals and greater independence and autonomy. Some of these measures, however, may be a little more complex to obtain, such as the AMC and AMA-c, in addition to requiring another specific measure, TST, which is measured by an instrument that requires technical skill in its use, the adipometer.

On the other hand, BMI, CC and AC are easy to measure and require simple instruments, which can be easily handled by any health professional when screening older people with a dynapenic profile. The use of a scale and a stadiometer to measure BMI and only an anthropometric tape to measure CC and AC will possibly facilitate screening even in primary care in surveillance actions.

In addition to being easy to measure, BMI, CC and AC show good sensitivity and specificity in both sexes. Among men, BMI was the most sensitive measure, while CC was the most specific, followed by AC. Among women, CC was the most specific measurement, followed by BMI, which also showed high sensitivity, while AC showed greater specificity, together with AMC and AMA-c. In this context, because of the simplicity of measurement and high sensitivity and specificity presented, it is recommended that in males BMI associated with CC or AC be used to screen for dynapenia, and in females, CC or BMI in association with AC.

This study has some limitations, such as the loss of part of the population segment, which did not participate in anthropometric and/or HGS measurements. Furthermore, as this was a census study, carried out in a small municipality in the interior of Bahia, caution must be

taken when applying such results to populations with different characteristics. On the other hand, the study had strengths, such as its originality. To date, no research has been found at the national level that aimed to identify the predictive capacity of anthropometric indicators on dynapenia in the older population of both sexes. The only study found was limited to the postmenopausal female population, with a convenience sample,[9] while the present study, in addition to presenting a new proposal, was a census survey. Therefore, it is believed that this study will contribute to the scientific field and clinical practice, making it possible to intervene in a timely manner, avoiding greater physical impairments to older people and, consequently, providing them with better well-being.

Conclusion

Our results showed that BMI, CC, AC, AMC and AMA-c were able to predict dynapenia in the older population of Aiquara-BA, Brazil, with no difference between them. In addition to being easy to measure, BMI, CC and AC showed good sensitivity and specificity in both sexes.

Authors' contributions

All authors participated in the project conception, study design, and writing and critical review of the manuscript. Furthermore, PSS and LS carried out the analysis and interpretation of the data. All authors declare that there is no conflict of interest and approved the final version of the manuscript. In addition, they are responsible for all aspects of the work, including ensuring its accuracy and completeness.

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