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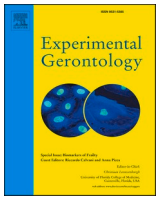

Relationship between quadriceps femoris echotexture biomarkers and muscle strength and physical function in older adults with heart failure with preserved ejection fraction

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ABSTRACT

Background: Muscle wasting is pronounced in patients with heart failure with preserved ejection fraction (HFpEF). The quadriceps femoris echotexture biomarkers assessed by ultrasound (US) have not been studied in these patients.
Objective: To describe echotexture biomarkers assessed by the US and to assess their relationship with sex, age, body mass index (BMI), self-reported outcomes, muscle strength and physical function in older adults with HFpEF.
Methods: A cross-sectional study was conducted. Patients 70 years and older with HFpEF were included. The sex, age, BMI, and self-reported outcomes were collected. The US assessed muscle and subcutaneous fat tissue contrast, correlation, energy, homogeneity, and entropy at rest and maximal voluntary isometrical contraction (MVIC). The six-minute walk test (6MWT), the short physical performance battery (SPPB), the timed up and go test (TUG), the usual pace gait speed test (UGS), and the fast pace gait speed test (FGS) were used to assess physical function. The five-repetitions sit-to-stand test (5-STS) was performed to assess muscle strength. Bivariant Pearson correlations and subsequent multivariate linear regression analyses were conducted.
Results: Seventy-two older adults with HFpEF [81.06 years, 29.13 BMI, and 55.60% females] were recruited. In women, relaxed and MVIC muscle energy and entropy explained 35.40% of the TUG variance; relaxed muscle entropy and MVIC muscle energy shared 24.00% of the UGS variance; relaxed and MVIC muscle entropy, MVIC muscle contrast and MVIC muscle energy explained 32.60% of the FGS variance, adjusted all the models by age and BMI.
Conclusions: Echotexture biomarkers are related to women's muscle strength and physical function, especially muscle energy, contrast, and entropy. Echotexture biomarkers assessed by the US could facilitate the management of older adults with HFpEF, monitor its progression and assess the effectiveness of treatments on the musculoskeletal structure.
Trial registration: NCT03909919. April 10, 2019. Retrospectively registered.

Abbreviations: HFpEF, Heart Failure with preserved Ejection Fraction; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; US, Ultrasound; MVIC, Maximal Voluntary Isometrical Contraction; GLCM, Grey-Level Co-occurrence Matrix; ALS, Amyotrophic Lateral Sclerosis; BMI, Body Mass Index; NYHA, New York Heart Association class; MMSE, Mini-Mental State Examination; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology Statement; ROI, Range Of Interest; IDM, Inverse Difference Moment; 5-STS, Five-repetitions sit-to-stand; SPPB, Short Physical Performance Battery; 6MWT, Six-Minute Walking Test; UGS, Usual pace Gait Speed; FGS, Fast pace Gait Speed; aCGA, Abbreviated Comprehensive Geriatric Assessment; SD, Standard deviation; t-test, Student's *t*-test; r, Pearson correlation coefficient; ρ, Spearman's rho; R^2, Coefficient of determination; SPSS, Statistical Package for the Social Sciences..

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1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a chronic, clinical, and heterogeneous syndrome characterized by showing a left ventricular ejection fraction (LVEF) $\geq$ 50% (McDonagh et al., 2021; Heidenreich et al., 2022). Older adults with HFpEF account for >50% of all patients with heart failure (HF) and show symptoms and/or signs of HF caused by a structural or functional cardiac abnormality (McDonagh et al., 2021; Heidenreich et al., 2022). Furthermore, older adults with HFpEF used to have a higher number and more severe comorbidities than patients with heart failure with reduced ejection fraction (HFrEF) (McDonagh et al., 2021; Heidenreich et al., 2022).

Sarcopenia is a muscle disease characterized by low muscle strength and low muscle quantity and quality (Cruz-Jentoft et al., 2019). Sarcopenia is one of the most common comorbidities in patients with HFpEF (McDonagh et al., 2021; Heidenreich et al., 2022). On the one hand, HF-related factors like hormonal changes, physical inactivity, oxidative stress or inflammation potentially lead to other geriatric syndromes such as sarcopenia (Beltrami et al., 2021; Curcio et al., 2020). On the other hand, sarcopenia induces altered muscle contraction and metabolic and endocrine abnormalities that may contribute to cardiovascular remodelling and dysfunction and the development of HFpEF (Kinugasa and Yamamoto, 2017). Furthermore, sarcopenia has been associated with a worse prognosis and reduced aerobic capacity and quality of life in patients with HFpEF (Bekfani et al., 2016; Konishi et al., 2020). These studies show the importance of sarcopenia and muscle atrophy in older adults with HFpEF (Bekfani et al., 2016; Konishi et al., 2020; Bekfani et al., 2020), constructs that could be easily assessed in clinical practice through ultrasound (US) assessment.

US is a portable, cheap, simple, easy-to-use, widely available, non-invasive, and cost-effective tool which rapidly enables the physician to perform a quantitative assessment of muscle architecture (Galindo Martín et al., 2017; Perkisas et al., 2021). Thus, the US has sufficient potential to be used in clinical practice to assess muscle architecture (Perkisas et al., 2021). The US also allows assessing muscle quantity and quality with high resolution within a relatively short period (Galindo Martín et al., 2017; Ismail et al., 2015). In this way, the US is considered a reliable and valid tool to assess the muscle quantity of pennate muscles in older adults, such as the quadriceps femoris muscle (Nijholt et al., 2017), by analyzing the muscle thickness (Ismail et al., 2015). Ultrasound has shown good intra-observer and inter-observer reliability and also allows muscle quality assessment by analyzing muscle echo-intensity (Galindo Martín et al., 2017; Ismail et al., 2015; Sipilä and Suominen, 1993).

The quadriceps femoris is the most ultrasonographical investigated muscle because it is easy to measure, is a good predictor of whole-body muscle mass, and can be directly related to physical function measures (Nijholt et al., 2017; Kawai et al., 2018). Resting quadriceps femoris muscle thickness has been studied in patients with HFpEF and HFrEF and healthy older adults (Morimoto et al., 2020; Nakano et al., 2020). Muscle thickness and echo-intensity of the quadriceps femoris at rest and in maximal voluntary isometrical contraction (MVIC) were related to muscle strength and physical function in older adults with HFpEF (Fuentes-Abolafio et al., 2022a). Furthermore, body composition, muscle strength and physical function differences have been observed between both sexes in older adults and patients with HFpEF (Kawai et al., 2018; Fuentes-Abolafio et al., 2022a; Kitamura et al., 2014; Butler et al., 2009). Echotexture analyses of US images may provide information on tissue homogeneity changes in older adults with HFpEF through second-order analyses based on the grey-level co-occurrence matrix (GLCM) (Martínez-Payá et al., 2018; Escriche-Escuder et al., 2022). Echotexture biomarkers can investigate the relationship between neighbouring pixel intensities and provide information about grey-level patterns (Gdynia et al., 2009). These parameters have been previously characterized in healthy individuals, in patients with amyotrophic lateral sclerosis (ALS) or in women with metastatic breast cancer (Martínez-Payá et al., 2018; Escriche-Escuder et al., 2022; Molinari et al., 2015). However, to our knowledge, echotexture analysis of US images has not been performed in older adults with HFpEF. Thus, the objectives of the present study were to describe echotexture biomarkers in older adults with HFpEF and to assess the relationship between echotexture biomarkers with age, body mass index (BMI), muscle strength and physical function in older adults with HFpEF, stratified by sex.

2. Material and methods

2.1. Design and participants

A cross-sectional study was carried out. Seventy-six older adults with HFpEF were recruited as volunteers between April 2019 and March 2020 from the Heart Failure Unit of the Internal Medicine Department at the Regional University Hospital of Malaga (Spain). Inclusion criteria: patients with HFpEF older than 70 years diagnosed according to the consensus statement of the European Society of Cardiology (Ponikowski et al., 2016). Exclusion criteria: older adults with HFpEF with a New York Heart Association (NYHA) class = 4; older adults hospitalised 3 months ago or less; older adults with a score on the Mini-Mental State Examination (MMSE) < 24; older adults who were not able to stand up from the chair at least five times or who were not able to walk.

2.2. Ethics and consent

Ethical approval was obtained from the Provincial Ethics Committee of Malaga, Spain (26032020). The study was carried out following the Helsinki Declaration and was implemented and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) (Supplementary Appendix A). The study was registered on the ClinicalTrial.gov database as NCT03909919. Moreover, all participants in this study signed an informed consent form before enrolment.

2.3. US assessment

The US analysed the right quadriceps femoris muscle. Transverse images were taken 15 cm from the upper edge of the patella. A B-mode ultrasound device (The Esaote MyLab One; Esaote, Genova, Italy) equipped with a linear array transducer 5 cm long was used to take US images. A frequency of 10 MHz, 4 cm deep, and 42% of the gain were also the parameters used to acquire the US images. Coupling gel was abundantly applied to minimise distortion generated by underlying tissues. Shaving was not needed. The transducer was placed perpendicular to the axis of the limb and transversely in the direction of the fibres. Before performing the US measurements, the older adults rested for 5 min (Lopez et al., 2019). Older adults were seated in a chair with their hip and knee at 90° of flexion (Supplementary Appendix B). The evaluator was placed in front of the patient, holding the transducer with one hand and the patient's leg with the other. To adequately capture a static image in a contraction state, the participant performed a manually resisted voluntary isometric contraction of 5 s by the physician. Images were taken in two situations: non-contraction (relaxed) and MVIC.

2.4. Outcomes

2.4.1. Echotexture biomarkers

The following echotexture biomarkers were obtained (Martínez-Payá et al., 2018; Escriche-Escuder et al., 2022):

- Contrast: the contrast assesses the variation between the contiguous pixels. When there is a high variation, the contrast is also high.
- Textural correlation: for those ranges of interest (ROI) in regions with similar levels of grey, the value of the textural correlation is higher.

- Energy: this parameter is related to the ROI's homogeneity. When the area is homogeneous, the energy value is also high. Energy is also known as the angular second moment.
- Homogeneity: this parameter is associated with the local homogeneity of the pixels. The homogeneity is higher when the ROI is homogeneous. Homogeneity is also known as inverse difference moment (IDM).
- Entropy: the entropy parameter is inversely related to homogeneity. Thus, a lower entropy is obtained when the homogeneity of the ROI is high.

The combination of these five echotexture biomarkers in relaxed and MVIC situations and different tissues (quadriceps femoris muscle and subcutaneous fat tissue) allowed for obtaining twenty echotexture variables:

1. Relaxed Muscle Echotexture Biomarkers: homogeneity, entropy, energy, contrast, and textural correlation.
2. MVIC Muscle Echotexture Biomarkers: homogeneity, entropy, energy, contrast, and textural correlation.
3. Relaxed Subcutaneous Fat Tissue Echotexture Biomarkers: homogeneity, entropy, energy, contrast, and textural correlation.
4. MVIC Subcutaneous Fat Tissue Echotexture Biomarkers: homogeneity, entropy, energy, contrast, and textural correlation.

2.5. Secondary outcomes

Clinical-epidemiological: age, sex, NYHA class, comorbidities, number of drugs that the patient takes each day and the most prescribed drugs, history of smoking and history of alcohol, marital status, academic degree, the number of falls in the last year, blood and urinary biomarkers, and echocardiographic outcomes.

Anthropometric data: height, weight, and BMI.

2.6. Muscle strength

Five-Repetitions Sit-to-Stand (5-STS): older adults should stand up and sit down five times as quickly as possible. Older adults could not use their hands to push up from the chair. The back of the chair was stabilised against a wall to ensure stability and safety. A stopwatch measured the time taken to perform the five repetitions (Paul and Canning, 2014; Bohannon, 2006).

2.7. Physical function

Short Physical Performance Battery (SPPB): this battery is formed by three balance tests (feet together, semi tandem, and tandem for 10 s each), the 4 m gait speed test, and the 5-STS. Each test is scored from 0 (worst performance) to 4 (best performance). A score of 0 is assigned to those older adults who can not perform each test. Scores from 1 to 4 are based on older adults' time performing each test. The total score for the whole battery is the addition of the 3 tests and ranges from 0 to 12 points (Guralnik et al., 1994; Guralnik et al., 2000).

Timed Up and Go Test (TUG): patients started this test sitting in a chair. When the physician indicated the beginning of the test, they stood up from the chair and walked 3 m at a pace as quickly, comfortably, and safely as possible until they reached a line on the floor. Then, patients turned, returned to the chair, walked, and sat again (Podsiadlo and Richardson, 1991). Older adults could use their hands to stand up from the chair. The score was the time taken to complete the test, measured by a stopwatch.

Six-Minute Walking Test (6MWT): in this test, two marks were placed on the ground at 30 m in a closed corridor longer than 30 m. Older adults walked, as quickly as possible, from one end to the other for 6 min. The distance older adults walked for 6 min was recorded (Guyatt et al., 1985; Crapo et al., 2002).

Gait speed test: older adults started from a standing position and walked 4 m. The test was performed twice: at their usual pace or gait speed (UGS) and the other at a fast pace or gait speed (FGS). The time taken to perform the 4 m was measured using a stopwatch, and the gait speed was calculated as m/s (Middleton et al., 2015).

2.8. Self-reported

Abbreviated Comprehensive Geriatric Assessment (aCGA): aCGA assesses functional, emotional, and cognitive components, and it is a short version of a comprehensive geriatric assessment with greater reliability (Overcash et al., 2005; Overcash et al., 2006). The aCGA is formed by the 15 most relevant items from the Mini-Mental State Examination, the Katz Index, the Lawton & Brody Scale and the Geriatric Depression Scale (Overcash et al., 2005; Overcash et al., 2006).

2.9. Sample size

The sample size was calculated using the software G Power 3.1.9.2 (University of Düsseldorf, Germany) and following the alternative hypothesis: to detect a moderate bivariate correlation ($r = 0.4$) (Fuentes-Abolafio et al., 2022a) between the echotexture biomarkers and the muscle strength or the physical function, considering a significance level of 0.05 (error $\alpha < 5\%$), and statistical power of 0.95 (95%), a sample consisting of 59 older adults with HFpEF would be needed.

2.10. US data processing and analysis

Captured images were exported in BMP format with a specific size of 800 × 652 pixels and 100 dpi. MATLAB software (Version R2018b, MathWorks, Natick, USA) was used for image processing and analysis. The same evaluator performed the MATLAB analysis of all images to reduce inter-rater variability. A MATLAB code was created specifically for this project. In this code, the researcher had to record a reference line of 1 cm, which formed the width of the ROI. The research could rely on the line that shows the cm of the depth of the US image to record the reference line of 1 cm. Then, the researcher could select a ROI with a width of 1 cm and a height from the femur to the superficial layer of the skin (Fig. 1). The following three points were taken as references: the superior limit of the femur bone, the inferior limit of the skin, and the superior limit of the fascia between quadriceps femoris muscle and subcutaneous fat tissue. This type of assessment showed a high test–retest reliability score (ICC = 0.963) with an average coefficient of variation of 4.2% (Watanabe et al., 2013). Once the ROI is selected, the code converts the image to greyscale. The echotexture analysis, based on the analysis of the GLCM, was conducted for each selected ROI. This analysis is derived from studying the angular relationship between the contiguous pixels, and its results have no unit.

2.11. Statistical analysis

An absolute frequency and a percentage were used to describe qualitative measures. Quantitative measures were reported using the mean and the standard deviation (SD). Distribution and normality were determined by one-sample Kolmogorov–Smirnov test (significance < 0.05). The Student's *t*-test (t-test) and the Chi-square test were used to compare the outcomes between men and women. Levene's test assessed the variance heterogeneity (significance < 0.15). The Pearson Correlation Coefficient (r) was used to assess the possible bivariate correlations between the echotexture biomarkers, age, BMI, muscle strength and physical function, stratified by sex. Spearman's rho (ρ) was used to assess the correlations between the echotexture biomarkers and self-reported outcomes (NYHA, Katz Index, and Lawton & Brody scale). Bivariate correlations were classified into three categories: poor ($r \leq 0.49$), moderate ($0.50 \leq r \leq 0.74$) and strong ($r \geq 0.75$). Multivariate linear regression analyses assessed the relationship between the echotexture

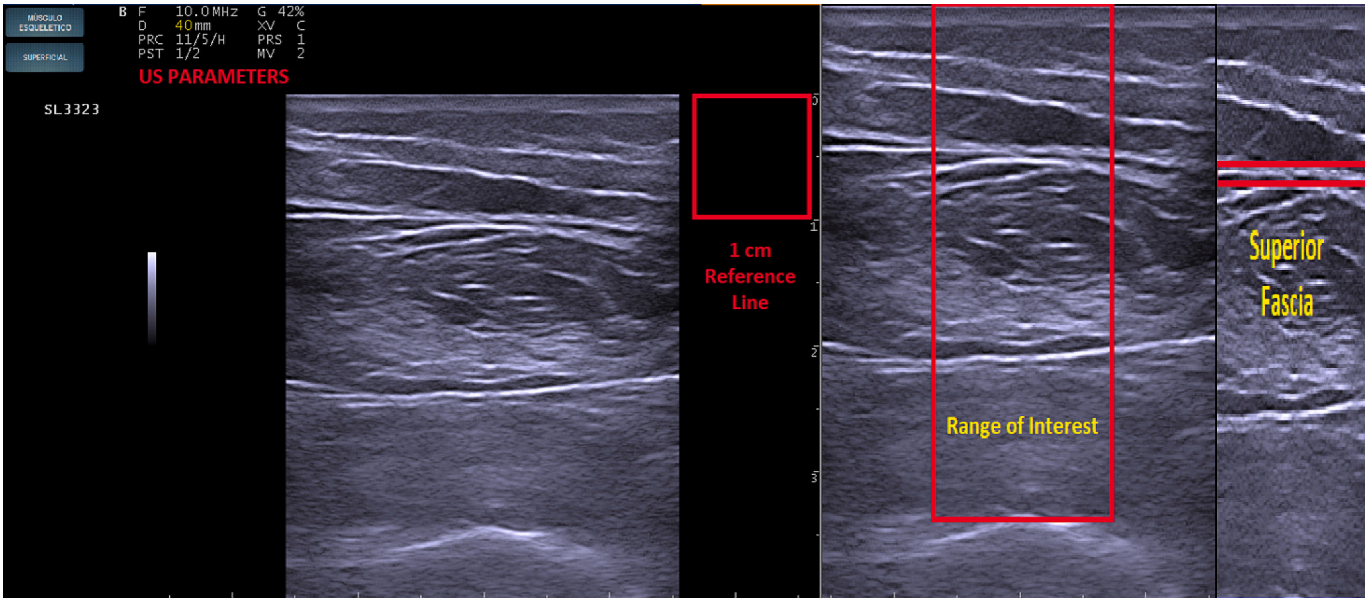

Fig. 1. Range of interest and selected areas.

biomarkers and muscle strength and physical function. Only the echotexture biomarkers that showed the most significant bivariate correlation with muscle strength or physical function were included in the model, adjusted by age and BMI, and stratified by sex. The contribution of the exposures to the model's predictability was assessed by the coefficient of determination (R2). A *p*-value of $p < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 22.0 for Windows.

3. Results

Seventy-six older adults with HFpEF were voluntarily recruited, but data for four older adults were lost when outcomes were collected. Thus, data from seventy-two older adults with HFpEF were included in the present study. Height and body weight were significantly lower in women than in men. However, there was no difference in BMI between the sexes. Relaxed and MVIC muscle contrast was greater in men than women, whereas relaxed and MVIC muscle energy and homogeneity were significantly greater in women than in men. Women also showed worse physical function (SPPB, TUG and 6MWT) and slower UGS and FGS than men. There was no difference in muscle strength, self-reported outcomes and age between the sexes (Table 1). Relaxed and MVIC subcutaneous fat tissue energy was greater in men than women. MVIC subcutaneous fat tissue homogeneity was also greater in men than women (Table 1). Other clinical-epidemiological variables and blood are shown in Supplementary Appendix C. In summary, the mean LVEF was 60.51%, and most older adults with HFpEF were overweight (43.10%) or obese (34.70%). Forty older adults with HFpEF (58.30%) had fallen last year. In addition, older adults with HFpEF had a mean of 8.36 comorbidities and were taking a mean of 10.18 drugs per day. The most frequent comorbidities were hypertension (97.20%), dyslipidemia (86.10%), valve disease (65.30%) and chronic kidney disease (65.30%). In addition, older adults with HFpEF showed a left atrial dimension of 42.37 mm, a left ventricular end-systolic dimension of 29.77 mm and a left ventricular end-diastolic dimension of 47.95 mm. The most prescribed drugs were loop diuretics (86.11%), beta-blockers (73.60%) and angiotensin II receptor antagonists (62.50%).

Relaxed muscle entropy significantly correlated with women's muscle strength and physical function, except with the 6MWT. MVIC muscle entropy significantly correlated with the SPPB, the TUG and the FGS in women. MVIC muscle energy is also correlated with women's muscle strength and physical function, except for the 6MWT. Relaxed muscle contrast and entropy also correlated with women's NYHA score. No relevant correlations between muscle echotexture biomarkers and muscle strength, physical function, and self-reported outcomes were shown in men (Table 2). In women, relaxed and MVIC muscle energy, relaxed muscle entropy and MVIC muscle homogeneity correlated with BMI. No subcutaneous fat tissue echotexture biomarkers correlated with women's muscle strength and physical function. Relaxed and MVIC subcutaneous fat tissue homogeneity showed the main correlations with the TUG and the 6MWT in men (Supplementary Appendix D). In women, relaxed and MVIC muscle energy and entropy explained 35.40% of the TUG variance, relaxed muscle entropy and MVIC muscle energy shared 24.00% of the UGS variance, while relaxed and MVIC muscle entropy, MVIC muscle contrast and MVIC muscle energy explained 32.60% of the FGS variance, adjusted all the models by age and BMI (Table 3). However, these muscle echotexture biomarkers did not reach the required value to explain the model, except for the MVIC muscle energy in the UGS model ($p < 0.05$) (Table 4). No muscle echotexture biomarker could explain the 5-STS and the SPPB variance (Table 3). Moreover, no subcutaneous fat tissue echotexture biomarker could explain the muscle strength and physical function variance in men (Supplementary Appendix E and F).

4. Discussion

As far as the authors know, this is the first study to describe the echotexture biomarkers and show their relationship with sex, age, BMI, self-reported outcomes, muscle strength and physical function in older adults with HFpEF. As a result of the study, there were differences between the sexes in some muscle and subcutaneous fat tissue echotexture biomarkers (Table 1). Women also showed worse physical function and slower UGS and FGS than men (Table 1). Moreover, some muscle echotexture biomarkers showed a significant statistical correlation with women's muscle strength and physical function, except with the 6MWT. These correlations were always poor ($r \leq 0.49$) (Table 2). Relaxed muscle contrast and entropy also correlated with women's NYHA score, and relaxed muscle entropy correlated with the women's Katz Index. These correlations also were poor ($r \leq 0.49$) (Table 2). No muscle echotexture biomarkers correlated with Lawton & Brody score in women with HFpEF. Relaxed and MVIC subcutaneous fat tissue homogeneity showed poor correlations ($r \leq 0.49$) with the TUG and the

Table 1
Descriptive statistics of the study outcomes and outcomes differences between sex ($n = 72$).

	All Older Adults (n = 72)	Men ($n = 32$, 44.40%)	Women ($n = 40$, 55.60%)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean Difference Between Sex (SE)	P Between Sex
Clinical					
Age (years)	81.06 (5.83)	80.06 (6.68)	81.95 (4.84)	1.89 (1.41)	0.185
Antropometric					
Height (m)	1.61 (0.08)	1.68 (0.06)	1.56 (0.06)	−0.12 (0.01)	<0.001**
Weight (Kg)	75.65 (14.13)	80.14 (11.99)	72.40 (15.26)	−7.74 (3.30)	0.022*
BMI (Kg/m^2)	29.13 (5.49)	28.52 (4.44)	29.91 (6.61)	1.39 (1.36)	0.313
Muscle Echotexture Biomarkers					
Relaxed					
Contrast	13,257.16 (6390.81)	16,318.76 (6620.85)	11,019.37 (4987.09)	−5299.39 (1411.26)	<0.001**
Correlation	−0.00005 (0.0027)	−0.00016 (0.0030)	−0.000005 (0.0025)	0.00016 (0.00064)	0.805
Energy	0.00004 (0.00002)	0.00003 (0.00001)	0.00004 (0.00002)	0.00001 (0.000003)	0.002*
Homogeneity	0.036 (0.0077)	0.033 (0.0065)	0.038 (0.0075)	0.0054 (0.0017)	0.002*
Entropy	6.55 (0.24)	6.51 (0.26)	6.58 (0.23)	0.064 (0.058)	0.273
MVIC					
Contrast	16,359.51 (7449.83)	19,670.09 (7834.27)	13,919.68 (5872.55)	−5750.40 (1667.38)	0.001**
Correlation	0.00008 (0.0020)	−0.0003 (0.0017)	0.0004 (0.0022)	0.0007 (0.0005)	0.169
Energy	0.00004 (0.00001)	0.00003 (0.000012)	0.00004 (0.000015)	0.000006 (0.000003)	0.050*
Homogeneity	0.034 (0.007)	0.031 (0.005)	0.035 (0.007)	0.0046 (0.0015)	0.003*
Entropy	6.32 (0.24)	6.35 (0.021)	6.31 (0.25)	−0.040 (0.055)	0.475
Difference					
Contrast	3102.35 (4511.36)	3351.33 (4753.70)	2900.31 (4359.91)	−451.02 (1076.40)	0.676
Correlation	0.0001 (0.003)	−0.00013 (0.0032)	0.00038 (0.0034)	0.0005 (0.0008)	0.525
Energy	−0.0000004 (0.000009)	0.000002 (0.000009)	−0.000002 (0.000009)	−0.000004 (0.000002)	0.041*
Homogeneity	−0.003 (0.004)	−0.002 (0.004)	−0.003 (0.005)	−0.0008 (0.001)	0.471
Entropy	−0.22 (0.26)	−0.16 (0.28)	−0.26 (0.24)	−0.10 (0.06)	0.097
Subcutaneous Fat Tissue Echotexture Biomarkers					
Relaxed					
Contrast	5144.45 (3110.15)	4859.22 (3566.61)	5372.63 (2716.32)	513.42 (740.35)	0.490
Correlation	−0.0011 (0.0069)	−0.0007 (0.005)	−0.0015 (0.008)	−0.0008 (0.0016)	0.620
Energy	0.000085 (0.000037)	0.0001 (0.00004)	0.00008 (0.00003)	−0.00002 (0.000009)	0.017*
Homogeneity	0.053 (0.010)	0.055 (0.01)	0.051 (0.01)	−0.004 (0.002)	0.115
Entropy	6.49 (0.31)	6.50 (0.30)	6.48 (0.32)	−0.019 (0.07)	0.800
MVIC					
Contrast	4288.42 (2627.15)	3754.33 (2880.57)	4715.68 (2355.45)	961.35 (616.91)	0.124
Correlation	−0.00041 (0.0056)	0.0003 (0.004)	−0.0009 (0.006)	−0.001 (0.001)	0.370
Energy	0.00011 (0.00006)	0.0001 (0.00008)	0.00009 (0.00003)	−0.00005 (0.00001)	0.002*
Homogeneity	0.057 (0.012)	0.061 (0.01)	0.053 (0.01)	−0.008 (0.003)	0.003*
Entropy	6.52 (0.34)	6.57 (0.35)	6.48 (0.33)	−0.09 (0.08)	0.261
Difference					
Contrast	−856.03 (1808.68)	−1104.88 (1824.20)	−656.95 (1794.13)	447.93 (428.69)	0.300
Correlation	0.00072 (0.0094)	0.0009 (0.007)	0.0005 (0.011)	−0.0004 (0.002)	0.864
Energy	0.00002 (0.00004)	0.00004 (0.00005)	0.00001 (0.00002)	−0.00003 (0.000009)	0.006*
Homogeneity	0.004 (0.007)	0.007 (0.007)	0.002 (0.005)	−0.0044 (0.0015)	0.006*
Entropy	0.027 (0.24)	0.07 (0.25)	−0.005 (0.22)	−0.072 (0.056)	0.204
Muscle Strength					
5-STS (sec)	15.90 (5.86)	15.28 (5.84)	16.74 (5.83)	1.46 (1.38)	0.296
Physical Function					
SPPB (0–12)	7.85 (2.64)	8.72 (2.68)	7.05 (2.34)	−1.67 (0.60)	0.008*
TUG (sec)	19.48 (8.88)	16.85 (9.45)	21.80 (7.81)	4.96 (2.03)	0.017*
6MWT (m)	244.72 (99.33)	275.47 (107.65)	216.00 (82.77)	−59.47 (23.10)	0.013*
UGS (m/s)	0.50 (0.22)	0.61 (0.26)	0.42 (0.13)	−0.19 (0.05)	<0.001**
FGS (m/s)	0.67 (0.28)	0.77 (0.32)	0.58 (0.21)	−0.19 (0.07)	0.005*
Self-reported questionnaires					
Katz Index (0–3)	0.97 (0.95)	0.78 (0.83)	1.13 (1.02)	0.34 (0.22)	0.128
Lawton & Brody (0–4)	1.83 (1.52)	1.72 (1.44)	1.93 (1.59)	0.21 (0.36)	0.571
NYHA	**n (%)**				
II	48 (66.67%)	19 (39.58%)	29 (60.42%)		0.240
III	24 (33.33%)	13 (54.17%)	11 (45.83%)		0.240

SD: Standard Deviation; SE: Standard Error; BMI: Body Mass Index; MVIC: Maximal Voluntary Isometric Contraction; 5-STS: Five-Repetitions Sit-to Stand; SPPB: Short Physical Performance Battery; TUG: Timed Up and Go test; 6MWT: 6 Minute Walking Test; UGS: Usual pace Gait Speed; FGS: Fast pace Gait Speed; NYHA: New York Heart Association class.

* $p < 0.05$.

** $p < 0.001$.

6MWT in men with HFpEF (Supplementary Appendix D). A previous study described the muscle and subcutaneous fat tissue thickness and echo-intensity and showed their relationship with muscle strength and physical function in older adults with HFpEF (Fuentes-Abolafio et al., 2022a). This study also reported differences between both sexes in muscle and subcutaneous fat tissue thickness, echo-intensity and muscle strength and physical function (Fuentes-Abolafio et al., 2022a). Body composition differences between both sexes have been reported

Table 2
Bivariate correlations (r, ρ) between the muscle echotexture biomarkers and age, BMI, self-reported outcomes, muscle strength and physical function, stratified by sex.

	Age	BMI	NYHA	Katz Index	Lawnton & Brody	5-STS	SPPB	TUG	6MWT	UGS	FGS
Muscle Echotexture Biomarkers											
Men (n = 32)											
Relaxed											
Contrast	**−0.416***	0.286	−0.038	−0.148	0.341	0.193	−0.274	0.181	−0.334	−0.207	−0.091
Correlation	−0.244	−0.074	−0.258	0.019	0.052	0.046	0.109	0.031	−0.070	0.118	0.062
Energy	0.300	0.247	0.065	0.047	−0.130	−0.126	0.225	0.022	0.010	0.080	0.085
Homogeneity	**0.430***	−0.086	0.024	0.215	−0.299	−0.236	0.264	−0.197	0.291	0.200	0.120
Entropy	−0.001	−0.163	−0.252	0.292	−0.268	−0.270	0.226	**−0.367***	0.346	0.257	0.295
MVIC											
Contrast	−0.284	0.136	−0.121	0.034	0.057	0.077	−0.170	0.081	−0.235	−0.180	0.085
Correlation	−0.066	0.133	0.196	−0.341	0.109	−0.036	0.124	−0.045	−0.073	0.140	−0.025
Energy	0.233	0.283	0.045	0.007	0.076	0.031	0.108	0.272	−0.092	−0.038	−0.119
Homogeneity	0.290	0.001	0.086	−0.022	−0.051	−0.136	0.188	−0.087	0.252	0.175	−0.026
Entropy	0.133	−0.177	−0.065	0.060	−0.009	−0.270	0.201	−0.260	0.246	0.088	0.050
Difference											
Contrast	0.110	−0.174	−0.196	0.277	−0.258	−0.142	0.101	−0.118	0.079	−0.008	0.268
Correlation	0.193	0.140	**0.355***	−0.190	0.118	−0.062	−0.035	−0.053	0.027	−0.035	−0.071
Energy	−0.108	0.034	0.045	−0.020	0.281	0.220	−0.171	0.338	−0.139	−0.166	−0.282
Homogeneity	−0.298	0.137	0.183	−0.284	0.273	0.193	−0.170	0.197	−0.128	−0.085	−0.223
Entropy	0.098	0.022	0.327	−0.268	0.180	0.054	−0.063	0.150	−0.141	−0.174	−0.236
Women (n = 40)											
Relaxed											
Contrast	0.104	−0.215	**0.361***	0.072	0.159	−0.073	0.169	−0.174	0.152	0.191	0.190
Correlation	−0.157	−0.034	0.065	0.213	−0.096	0.292	0.016	0.063	0.033	0.160	0.040
Energy	−0.293	**0.506****	−0.061	0.115	−0.181	0.226	−0.294	**0.321***	−0.171	−0.278	−0.271
Homogeneity	−0.196	0.329*	−0.308	−0.016	−0.175	0.011	−0.107	0.121	−0.097	−0.120	−0.121
Entropy	**0.335***	**−0.324***	**−0.429****	**−0.393***	0.038	**−0.348***	**0.366***	**−0.443****	0.291	**0.342***	**0.366***
MVIC											
Contrast	0.099	−0.196	0.303	0.120	0.153	−0.168	0.199	−0.234	0.245	0.263	**0.315***
Correlation	0.125	−0.001	−0.298	−0.295	0.170	0.006	−0.079	0.099	−0.006	−0.060	0.003
Energy	**−0.396***	**0.521****	−0.099	0.065	−0.204	**0.330***	**−0.321***	**0.370***	−0.275	**−0.417****	**−0.333***
Homogeneity	−0.236	**0.378***	−0.293	−0.118	−0.179	0.112	−0.082	0.171	−0.186	−0.203	−0.157
Entropy	0.153	−0.124	−0.133	−0.199	−0.024	−0.265	**0.345***	**−0.415****	0.217	0.284	**0.369***
Difference											
Contrast	0.014	−0.017	0.017	0.134	−0.048	−0.143	0.075	−0.116	0.156	0.137	0.206
Correlation	0.193	0.024	−0.245	−0.284	0.119	−0.205	−0.063	0.020	−0.028	−0.154	−0.026
Energy	−0.134	−0.024	0.002	−0.088	0.061	0.141	−0.015	0.045	−0.147	−0.191	−0.072
Homogeneity	−0.031	0.024	0.056	−0.098	0.043	0.146	0.052	0.055	−0.116	−0.103	−0.035
Entropy	−0.159	0.180	0.201	0.190	−0.144	0.052	0.015	−0.015	−0.049	−0.027	0.040

BMI: Body Mass Index; NYHA: New York Heart Association class; 5-STS: Five-Repetitions Sit-to Stand; SPPB: Short Physical Performance Battery; TUG: Timed Up and Go test; 6MWT: 6 Minute Walking Test; UGS: Usual pace Gait Speed; FGS: Fast pace Gait Speed; MVIC: Maximal Voluntary Isometric Contraction.
* $p < 0.05$.
** $p < 0.001$.

Table 3
Summary of muscle echotexture biomarkers models in women.

	R	R^2	Adjusted R^2	SE	F	p
5-STS	0.430	0.185	0.092	5.56	1.98	0.119
SPPB	0.491	0.241	0.129	2.22	2.16	0.082
TUG	0.595	0.354	0.236	6.82	3.01	0.019
UGS	0.490	0.240	0.154	0.12	2.77	0.042
FGS	0.571	0.326	0.203	0.19	2.66	0.033

(Kitamura et al., 2014; Bredella, 2017; Kanehisa et al., 2004). Ageing has been associated with a more significant increase in subcutaneous fat tissue in women than men (Kanehisa et al., 2004). Muscle mass loss is also more quickly in women than men (Kitamura et al., 2014). Despite higher muscle and lean mass, men showed higher visceral and inter- and intramuscular adipose tissue (Bredella, 2017). Women, on the other hand, showed more femoral subcutaneous fat tissue (Bredella, 2017). These changes in body composition between both sexes could explain the results of this study.

The second-order muscle and subcutaneous fat tissue echotexture biomarkers analysed in this study were proposed to provide additional information through grey-level patterns in healthy individuals, ALS patients or metastatic breast cancer women (Martínez-Payá et al., 2018; Escriche-Escuder et al., 2022; Molinari et al., 2015). Some of these second-order parameters have shown good discrimination capacity between the sexes and muscle type and a correlation (especially muscle entropy) with the physiologic muscle status in healthy individuals (Molinari et al., 2015). In ALS patients, a combination of muscle echotexture biomarkers, with muscle echo-variation and muscle echo-intensity showed an excellent discrimination capacity, correlated with clinical variables, and could detect lower motor neuron impairment or muscle changes (Martínez-Payá et al., 2018; Martínez-Payá et al., 2017a; Arts et al., 2008; Martínez-Payá et al., 2017b). Moreover, a pilot study suggested that echotexture biomarkers could be used to monitor disease progression by measuring muscle impairment in patients with ALS due to the loss of motor neurons (Martínez-Payá et al., 2018). Echotexture biomarkers also correlated with quality of life and fatigue in metastatic breast cancer women (Escriche-Escuder et al., 2022). In addition, echotexture biomarkers helped quantify therapeutic exercise programmes' effect in this oncological population (Escriche-Escuder et al., 2022). Other parameters, such as muscle thickness and echo-intensity, have shown a relationship with muscle strength and physical function in older adults with HFpEF (Fuentes-Abolafio et al., 2022a). Echo-intensity may also be a more objective parameter for diagnosing and following soleus muscle injuries in athletes (De-la-cruz-torres et al., 2021). Thus, US biomarkers such as muscle and subcutaneous thickness, echo-intensity and echotexture could be promising

Table 4
Multivariate linear regression muscle echotexture biomarkers models in women, adjusted by age and BMI.

Dependent Outcome	Predictor Variables	Non-standardised coefficients		Typified coefficients	t	p	95%CI
		B	SE	Beta			
	(Constant)	59.461	32.919		1.806	0.079	(−7.369, 126.290)
	Muscle Entropy (Relaxed)	−7.623	4.239	−0.298	−1.799	0.081	(−16.228, 0.981)
	Muscle Energy (MVIC)	114,417.42	72,535.61	0.287	1.577	0.124	(−32,837.69, 261,672.53)
5-STS	Age	0.051	0.223	0.042	0.228	0.821	(−0.402, 0.504)
	BMI	−0.035	0.174	−0.040	−0.202	0.841	(−0.389, 0.318)
	(Constant)	−13.215	13.667		−0.967	0.340	(−40.989, 14.559)
	Muscle Entropy (Relaxed)						(−1.903, 6.040)
		2.069	1.954	0.198	1.059	0.297	
	Muscle Energy (MVIC)	−45,698.29	28,989.65	−0.282	−1.576	0.124	(−104,612.34, 13,215.76)
SPPB	Muscle Entropy (MVIC)						
		2.250	1.652	0.238	1.362	0.182	(−1.107, 5.608)
	Age	−0.066	0.089	−0.134	−0.737	0.466	(−0.247, 0.115)
	BMI	−0.015	0.069	−0.042	−0.218	0.829	(−0.156, 0.126)
	(Constant)	119.767	42.505		2.818	0.008	(33.289, 206.245)
	Muscle Energy (Relaxed)	69,532.95	123,449.41	0.138	0.563	0.577	(−181,626.76, 320,692.66)
	Muscle Entropy (Relaxed)						
		−9.424	6.024	−0.275	−1.564	0.127	(−21.680, 2.832)
	Muscle Energy (MVIC)	144,037.48	134,770.19	0.270	1.069	0.293	(−130,154.5, 418,229.49)
TUG	Muscle Entropy (MVIC)						
		−8.824	5.092	−0.284	−1.733	0.092	(−19.185, 1.536)
	Age	0.191	0.276	0.118	0.690	0.495	(−0.371, 0.752)
	BMI	−0.136	0.219	−0.115	−0.621	0.539	(−0.582, 0.310)
	(Constant)	−0.341	0.725		−0.470	0.641	(−1.813, 1.132)
	Muscle Entropy (Relaxed)						
		0.163	0.093	0.278	1.742	0.090	(−0.027, 0.352)
UGS	Muscle Energy (MVIC)	−3640.97	1598.12	−0.401	−2.278	0.029	(−6885.32, −396.62)
	Age	−0.002	0.005	−0.090	−0.503	0.618	(−0.012, 0.008)
	BMI	0.001	0.004	0.044	0.232	0.818	(−0.007, 0.009)
	(Constant)	−2.852	1.396		−2.043	0.049	(−5.691, −0.012)
	Muscle Entropy (Relaxed)						
		0.280	0.180	0.298	1.556	0.129	(−0.086, 0.646)
	Muscle Contrast (MVIC)						
		1.766E-005	0.000	0.486	1.902	0.066	(0.000, 0.000)
FGS	Muscle Energy (MVIC)	2416.66	4284.01	0.166	0.564	0.576	(−6299.23, 11,132.55)
	Muscle Entropy (MVIC)						
		0.235	0.142	0.277	1.652	0.108	(−0.054, 0.524)
	Age	−0.002	0.008	−0.037	−0.211	0.834	(−0.017, 0.014)
	BMI	−0.003	0.006	−0.100	−0.528	0.601	(−0.016, 0.009)

US biomarkers (Martínez-Payá et al., 2017b).

Previous literature has found accentuated muscle dysfunction, reduced mitochondrial size in skeletal muscle, increased levels of atrophy genes and proteins and metabolic abnormalities in skeletal muscle in stable outpatients with HFpEF compared with older adults with HFrEF and healthy controls (Bekfani et al., 2020). A previous study also reported that older adults with HFpEF have limited aerobic capacity and poor physical function (Fuentes-Abolafio et al., 2022b). Physical function was related to prognosis in patients with HF (Fuentes-Abolafio et al., 2020). Older adults with HFpEF also showed reduced muscle strength, decreased physical function, and slowed gait speed in this study. In women of the present study, relaxed and MVIC muscle energy and entropy explained 35.40% of the TUG variance. Relaxed muscle entropy and MVIC muscle energy shared 24.00% of the UGS variance. Relaxed and MVIC muscle entropy, MVIC muscle contrast and MVIC muscle energy explained 32.60% of the FGS variance, adjusted all the models by age and BMI (Table 3). However, these muscle echotexture biomarkers did not reach the required value to explain the model, except for the MVIC muscle energy in the UGS model ($p < 0.05$) (Table 4). These results are consistent with previous studies performed in older adults with HFpEF (Fuentes-Abolafio et al., 2022a) and patients with ALS (Martínez-Payá et al., 2017a) where muscle or subcutaneous fat tissue thickness, echo-intensity and echo-variation could not explain >40% of the physical function or muscle strength variance. Physical function is a multidimensional construct which depends on fat mass, intermuscular and intramuscular fat infiltration, muscle mass, echo-intensity, echotexture, muscle contractile properties, muscle strength or nervous system (Bouchard et al., 2011; Reid et al., 2014). Thus, US biomarkers have difficulty independently explaining >40% of the physical function variance (Bouchard et al., 2011; Reid et al., 2014; Misic et al., 2007). However, the muscle and subcutaneous fat tissue echotexture, thickness, echo-intensity, and physical function assessments could help clinicians properly manage a complex and heterogeneous group of older adults with HFpEF. Therapeutic exercise improves physical function and muscle strength in older adults (Escriche-Escuder et al., 2021). Therapeutic exercise can improve muscle mass, reduce fat thickness, body fat mass, and intramuscular and intermuscular fat infiltration, improve muscle echo-intensity, and improve muscle echotexture, above all when performing a therapeutic exercise program of >12 weeks progressing toward high intensity (Radaelli et al., 2021; Beckweé et al., 2019). The US has all the advantages to be used in clinical practice to assess musculoskeletal structural biomarkers and monitor the effect of clinical interventions (Perkisas et al., 2021).

5. Implications for clinical practice

Our results showed a relationship between muscle echotexture and muscle strength and physical function in older adults with HFpEF, especially in women with HFpEF. Together with muscle and subcutaneous fat tissue thickness and echo-intensity (Fuentes-Abolafio et al., 2022a), clinicians could incorporate echotexture biomarkers assessment by the US into their clinical practice since US biomarkers assessment could allow them to monitor the effectiveness of clinical interventions and HFpEF progression.

6. Future research

Future studies should analyse echotexture biomarkers differences between older adults with HFpEF and older adults with HFrEF or healthy people. Future studies could assess the differences between echotexture biomarkers in both legs. Future studies should determine the responsiveness of all US biomarkers in longitudinal studies. Future studies should confirm the findings shown by the present study, including a larger sample size.

7. Strengths and limitations of the study

Our study was the first study assessing the relationship between echotexture biomarkers with sex, age, BMI, muscle strength and physical function in older adults with HFpEF. The author IJF-A also conducted all the US measurements and assessed all the US images to reduce the risk of bias among sonographers. All the US measurements were performed with the same US at the same point of the quadriceps femoris and using the same US parameters. The older adults were also placed in the same chair and posture to avoid biases when obtaining the echotexture biomarkers. The statistically significant and non-significant results were presented to avoid publication bias. However, several limitations must be considered when interpreting the results. The US image landmark and the older adults' position may have affected the echotexture biomarkers and the correlations shown in our study (Perkisas et al., 2018). The included patients' age may also have affected the magnitude of the correlation since older age was associated with a lower correlation (Overend et al., 1992). There could also be differences between both legs. The morphological and clinical characteristics of the included older adults with HFpEF could have affected the echotexture biomarkers, causing a detection bias in these outcomes. The sample size could be small.

8. Conclusions

Echotexture biomarkers statistically correlated with women's muscle strength and physical function, especially muscle energy, contrast, and entropy. Echotexture biomarkers assessed by the US could be relevant, as well as complementary biomarkers of muscle thickness and echointensity related to muscle strength and physical function in older adults with HFpEF. All these US biomarkers could also facilitate the management of older adults with HFpEF, monitor its progression and assess the effectiveness of treatments on the musculoskeletal structure.

Ethics and consent

Ethical approval for the study was granted by the Portal de Ética de la Investigación Biomédica de Andalucía Ethics Committee, Spain (26032020) and was registered on the ClinicalTrial.gov database as NCT03909919. The study complied with the principles laid out in the Declaration of Helsinki. Moreover, all participants in this study signed an informed consent form prior to inclusion, and their participation was voluntary.

Declaration of generative AI in scientific writing

No AI was used during the preparation of this work.

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CRediT authorship contribution statement

Iván José Fuentes-Abolafio: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Michele Ricci:** Writing – review & editing, Data curation. **María Rosa Bernal-López:** Writing – review & editing, Conceptualization. **Ricardo Gómez-Huelgas:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing. **Antonio Ignacio Cuesta-Vargas:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing. **Luis Miguel Pérez-Belmonte:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article. Authors, their immediate family, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

Data availability

The data that support the findings of this study are available from the corresponding author, [AICV], upon reasonable request.

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Appendix A. Supplementary data

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