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ORIGINAL ARTICLE

Frailty phenotype in heart failure: A condition that transcends age

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KEYWORDS
Heart failure;
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Hand grip strength;
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Type 2 diabetes mellitus

Abstract
Introduction and objectives: Studies on younger frail and pre-frail subjects suffering from heart failure (HF) are scarce, except for those focusing on the critically ill. This work aims to describe differences between younger (<65 years) and older (≥65 years) pre-frail and frail HF outpatients regarding their nutritional, functional and clinical statuses.
Methods: In this cross-sectional study, a sample of 99 HF frail and pre-frail patients (aged 24–81 years, 38.4% women, 21.2% frail, 59.6% <65 years) was recruited from an HF outpatients' clinic in northern Portugal. Muscle mass was estimated from mid-upper arm muscle circumference. Weight status was assessed using body mass index. Hand grip strength and gait speed were measured. Medical records were reviewed. Associations between participants' characteristics and age were calculated using binary logistic regression.
Results: Age was associated with hand grip strength (OR=0.90), gait speed (OR=0.01) and diabetes (OR=4.95). Obesity, muscle mass or heart failure functional classes were not associated with age categories.

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Conclusion: There is an overall lack of differentiation between younger and older HF patients with the frailty phenotype. Therefore, frailty phenotype should be assessed in all patients, regardless of age. Hand grip strength seems to be a good predictor for older age and more studies are needed to define age-specific hand grip strength cut-offs for HF populations.

PALAVRAS-CHAVE
Insuficiência cardíaca;
Fenótipo de fragilidade;
Força de preensão da mão;
Velocidade da marcha;
Diabetes *mellitus* tipo 2

O fenótipo de fragilidade na insuficiência cardíaca: uma condição que transcende idades

Resumo
Introdução e objetivos: Estudos em insuficientes cardíacos jovens com fragilidade e pré-fragilidade são escassos, à exceção de trabalhos focados em doentes críticos. Este trabalho tem como objetivo descrever diferenças entre pacientes externos adultos (<65 anos) e idosos (≥65 anos), com fragilidade e insuficiência cardíaca concomitantes, no respeitante ao seu estado nutricional, funcional e clínico.
Métodos: Neste estudo transversal, foi recrutada de uma consulta externa de um hospital do Norte de Portugal, uma amostra de 99 insuficientes cardíacos com fragilidade e pré-fragilidade (idade 24-81 anos, 38,4% mulheres, 21,2% frágeis, 59,6% < 65 anos). A massa muscular foi estimada a partir do perímetro muscular do braço. O estado ponderal foi classificado utilizando o Índice de Massa Corporal. Foi medida a força de preensão da mão. A associação entre as características preditivas dos participantes e as categorias de idade foi calculada através de regressão logística binária.
Resultados: A idade foi associada à força preensora da mão (OR=0,90), à velocidade da marcha (OR=0,01) e à diabetes (OR=4,95). A obesidade, a massa muscular ou as classes funcionais de insuficiência cardíaca não foram associadas às categorias de idade.
Conclusões: Verificou-se uma escassez generalizada de diferenças entre doentes adultos e idosos com insuficiência cardíaca e fenótipo de fragilidade concomitantes, justificando a avaliação da fragilidade mesmo em indivíduos mais jovens. A força de preensão da mão parece ser um bom preditor para a idade, mas são necessários mais estudos para definir pontos de corte específicos para populações de insuficientes cardíacos.

Introduction

The frailty phenotype (FP) is extremely common in heart failure (HF), with a prevalence ranging from 14% in the community to 77% in hospitalized patients.[1] Older adults with concomitant FP and HF are at increased risk of poor clinical outcomes, early disability, hospitalization and long-term mortality.[2,3]

Few works address FP in the non-elderly, with most of them focusing on the critically ill, such as chronic kidney disease patients,[4–6] or those admitted as surgical emergencies or to intensive care units.[7–9] Studies on FP that include younger samples of HF patients are also scarce and centered on advanced HF: Jha et al. studied patients referred for heart transplantation (n=120, aged 53±12 years, 32.5% frail),[10] and in another work, studied the addition of cognitive assessment to FP to improve the predictive validity of frailty for mortality in patients referred for heart transplantation (n=156, aged 53±13 years, 33% frail)[11]; Joseph et al. studied the association between frailty and adverse events in cardiac surgery, in a sample of end-stage HF patients undergoing the placement of a left ventricular assist device (LVAD) (n=75, aged 58±12 years, 59% frail)[12]; Chung et al. also evaluated HF patients undergoing LVAD placement (n=72, aged 59±2 years), with low hand grip strength (HGS), which the authors used as a proxy for frailty, associated with the worst outcomes after device implantation.[13] There is, therefore, a lack of evidence regarding FP younger outpatient HF patients. More studies focusing on these patients are needed in order to contribute to the improvement of their healthcare and quality of life.

The present study aims to compare age categories in a sample of frail and pre-frail HF outpatients which includes younger (<65 years) and older (≥65 years) individuals, regarding their nutritional, functional and clinical statuses.

Methods

This cross-sectional study uses data from the DeM Project (Symbiotic technology for societal efficiency gains: Deus ex

Machina) and the AdHeart Project (Engage with your heart: Improving therapeutic adherence with a telemonitoring system for chronic heart failure patients). Data collection took place from September 2017 to July 2018.

A sample of HF patients was recruited from an HF and transplantation outpatients' clinic in a university hospital in northern Portugal. Inclusion criteria were having a clinical validated diagnosis of HF according to the European Society of Cardiology,[14] being pre-frail or frail according to Fried et al. criteria,[15] being 18 years or older and being able to communicate in Portuguese. Individuals with severe visual acuity deficit were excluded, as well as patients within the New York Heart Association (NYHA) functional class IV, due to their limitations in participating in the study assessment procedures. Participants were randomly selected from the daily appointments lists according to inclusion and exclusion criteria.

Sociodemographic data included sex, age, marital and professional statuses, family income and education.

Clinical data were collected by a cardiologist during the appointment and medical records were reviewed. Data included HF etiology, left ventricular ejection fraction (LVEF) percentage, functional HF classification according to the NYHA,[16] incidental stroke, presence of atrial fibrillation, medication, presence of type 2 diabetes mellitus (T2DM) and smoking habits. Polypharmacy was defined as the use of five or more medicines per day.[17]

Nutritional status was assessed using anthropometric measurements, collected following standard procedures[18] as described elsewhere,[19] and included mid-upper arm, calf, waist and gluteal girths, triceps skinfold thickness (TST), weight and stature. Body mass index (BMI) was calculated using the standard formula [body weight (kg)/stature^2 (m)], and categorized according to the World Health Organization cut-offs.[20] Muscle mass was estimated using mid-upper arm muscle circumference (MAMC), calculated from mid-upper arm circumference (MUAC) and TST using the following formula[21]: MAMC=MUAC$-$(3.14$\times$TST).

Frailty was classified according to Fried et al.,[15] as the presence of three or more of the following criteria: weakness, assessed using HGS; slow gait speed (GS); low physical activity as low expenditure of energy per week; self-reported nonintentional weight loss in the last year and self-reported exhaustion. Pre-frail individuals were classified through the presence of one or two of the described criteria. FP criteria were accessed as described elsewhere.[19] For bivariate and multivariate analysis, the calculated GS was further adjusted for height (GSAH) using the following formula: GS/height.

Ethics

This research followed the guidelines established by the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Hospital Center in which the study was implemented and all participants gave their informed consent to the anonymous use of data for research purposes.

Statistical analysis

The sample was described according to the participants' age categories (<65 and $\geq$65 years). The distribution of quantitative variables was assessed using the Shapiro-Wilk test. Quantitative data were associated using parametric and non-parametric tests and categorical data were compared using the Chi-square test or Fisher's exact test as adequate. Results are presented as frequencies (percent) for categorical variables, mean (standard deviation) for normally-distributed continuous variables and median (lower and upper quartiles) for continuous variables with skewed distribution.

Binary logistic regressions were carried out and the crude and adjusted odds ratios (OR) and respective 95% confidence intervals (95% CI) were calculated as measures of association in models with age categories as dependent variables: <65 years old and $\geq$65 years old. Three models, which included both frail and pre-frail participants, were constructed regarding the overall sample and sex. Predictors in the models included: measures of physical functionality, using quantitative HGS and GSAH; surrogate measures of body composition, using BMI categorized as obese ($\geq$30 kg m^{-2}) and non-obese (<30 kg m^{-2}, reference), and quantitative MAMC; the presence of symptoms and tolerance for physical exercise, using NYHA functional classes categorized as symptomatic (NYHA classes II+III) and not symptomatic (NYHA class I, reference), and the presence or absence (reference) of type 2 diabetes mellitus (T2DM). Missing values for NYHA classes (n=2) were included in the models on the reference group. The level of statistical significance for all tests was defined by p<0.050.

All analyses were performed with IBM SPSS Statistics 27 (SPSS, Inc., an IBM Company, USA).

Results

Overall, 139 patients were enrolled in the study. A total of 40 were excluded (37 for not having FP and three with incomplete evaluation protocols), leading to a final number of 99 pre-frail and frail HF patients with full protocol evaluation.

The characteristics of the participants are described in Table 1. Women made up 38.4% of the sample. Age ranged from 24 to 81 years. Median age was 60.0 (lower quartile: 50.0; upper quartile: 69.0) years. Pre-frail and frail participants comprised 78.8% and 21.2% of the sample, respectively, and 59.6% of the sample were younger than 65 years.

Regarding the overall sample, apart from the expected differences in school attendance and professional activity, older ($\geq$65 years) and younger (<65 years) pre-frail and frail patients were rather similar in sociodemographic, clinical and nutritional characteristics. Notable differences were a higher frequency of T2DM (p=0.008) and polypharmacy (p=0.018) and a lower frequency of smoking habits (p=0.045) in older participants. Also, mean HGS and median GSAH were significantly higher in younger individuals (p=0.002 for both associations). Pre-frail participants generally maintained the same pattern as the overall sample regarding significant age differences.

Table 1 Characteristics of participants according to age categories.

Characteristics	Overall (n=99)			Pre-frail (n=78)			Frail (n=21)		
	<65 (n=59)	≥65 (n=40)	p-Value	<65 (n=48)	≥65 (n=30)	p-Value	<65 (n=11)	≥65 (n=10)	p-Value
Age, years	52.0 [44.0, 59.0]	70.0 [68.0, 72.0]	0.000	52.5 [44.3, 58.8]	69.0 [67.8, 71.3]	0.000	50.9, SD 9.5	72.4, SD 5.0	0.000
Women	21 (35.6)	17 (42.5)	0.488	16 (33.3)	9 (30.0)	0.759	5 (45.5)	8 (80.0)	0.183
School attendance			0.000			0.016			0.000
≤4 years	12 (20.3)	24 (60.0)		10 (20.8)	14 (46.7)		2 (18.2)	10 (100.0)	
>4 years	47 (79.7)	16 (40.0)		38 (79.2)	16 (53.3)		9 (81.8)	0 (0.0)	
Family income			0.490			0.967			0.387
<1000 €	20 (35.1)	16 (42.1)		15 (32.6)	9 (32.1)		5 (45.5)	7 (70.0)	
≥1000 €	37 (69.4)	22 (57.9)		31 (67.4)	19 (67.9)		6 (54.5)	3 (30.0)	
Professional status			0.004			0.019			0.214
Active	27 (45.8)	7 (17.5)		24 (50.0)	7 (23.3)		3 (27.3)	0 (0.0)	
Inactive	32 (54.2)	33 (82.5)		24 (50.0)	23 (76.7)		8 (72.7)	10 (100.0)	
Marital status			0.957			0.761			0.586
Married or in common law union	47 (79.7)	32 (80.0)		37 (77.1)	24 (80.0)		10 (90.9)	8 (80.0)	
Single, divorced, widower	12 (20.3)	8 (20.0)		11 (22.9)	6 (20.0)		1 (9.1)	2 (20.0)	
HF etiology			0.451			0.614			0.330
Dilated cardiomyopathy	26 (46.4)	22 (57.9)		25 (54.3)	17 (58.6)		1 (10.0)	5 (55.6)	
Ischemic	17 (30.4)	13 (34.2)		15 (32.6)	12 (41.4)		2 (20.0)	1 (11.1)	
Myocarditis	3 (5.4)	0 (0.0)		2 (4.3)	0 (0.0)		1 (10.0)	0 (0.0)	
Hypertrophic	6 (10.7)	2 (5.3)		2 (4.3)	0 (0.0)		4 (40.0)	2 (22.2)	
Others	4 (7.1)	1 (2.6)		2 (4.3)	0 (0.0)		2 (20.0)	1 (11.1)	
LVEF, %	37.0, SD 13.0	39.0, SD 15.6	0.521	36.3, SD 12.3	38.1, SD 14.2	0.554	41.1, SD 16.6	41.3, SD 20.1	0.971
NYHA classification			0.924			0.500			0.261
Class I	15 (26.3)	12 (30.0)		14 (30.4)	11 (36.7)		1 (9.1)	1 (10.0)	
Class II	30 (52.6)	20 (50.0)		26 (56.5)	13 (43.3)		4 (36.4)	7 (70.0)	
Class III	12 (21.1)	8 (20.0)		6 (13.0)	6 (20.0)		6 (54.5)	2 (20.0)	
Incidental stroke	13 (23.2)	11 (27.5)	0.633	11 (23.9)	10 (33.3)	0.369	2 (20.0)	1 (10.0)	0.998
Atrial fibrillation	9 (15.8)	9 (23.7)	0.336	6 (13.0)	6 (21.4)	0.343	3 (27.3)	3 (30.0)	0.999
Diabetes mellitus	14 (24.1)	20 (50.0)	0.008	13 (27.7)	16 (53.3)	0.023	1 (9.1)	4 (40.0)	0.149
Polypharmacy	42 (72.4)	37 (92.5)	0.018	34 (72.3)	28 (93.3)	0.037	8 (72.7)	9 (90.0)	0.453

Table 1 (*Continued*)

Characteristics	Overall (n=99)			Pre-frail (n=78)			Frail (n=21)		
	<65 (n=59)	≥65 (n=40)	p-Value	<65 (n=48)	≥65 (n=30)	p-Value	<65 (n=11)	≥65 (n=10)	p-Value
Smoking habits	26 (44.8)	10 (25.0)	0.045	22 (68.8)	10 (33.3)	0.242	4 (36.4)	0 (0.0)	0.090
Sitting time, min/day	300 [150,480]	240 [150,420]	0.666	255 [128,480]	270 [173,420]	0.922	374 [150,540]	261 [120,435]	0.255
Weight, kg	80.1, SD 16.4	74.5, SD 10.7	0.057	79.4 [71.6, 89.7]	74.3 [68.3, 81.9]	0.170	79.3, SD 15.2	70.9, SD 12.2	0.183
Standing height, cm	164.8, SD 10.0	159.9, SD 9.0	0.015	164.9, SD 9.2	161.9, SD 8.2	0.138	164.3, SD 13.5	154.2, SD 9.0	0.062
BMI, kg m^{-2}	29.4, SD 4.8	29.2, SD 4.0	0.824	29.4, SD 5.0	29.0, SD 3.8	0.673	29.3, SD 3.8	29.8, SD 4.7	0.764
BMI classes			0.888			0.489			0.630
Underweight+Normal	12 (20.3)	7 (17.5)		11 (22.9)	4 (13.3)		1 (9.1)	3 (30.0)	
Overweight	21 (35.6)	16 (40.0)		16 (33.3)	13 (43.3)		5 (45.5)	3 (30.0)	
Obese	26 (44.1)	17 (42.5)		21 (43.8)	13 (43.3)		5 (45.5)	4 (40.0)	
MUAC, cm	30.9, SD 3.8	29.7, SD 2.9	0.082	31.1, SD 3.9	29.6, SD 2.6	0.069	23.8, SD 3.4	23.2, SD 2.9	0.652
Waist circumference, cm	96.7, SD 14.2	96.5, SD 10.4	0.995	96.3, SD 14.5	98.1, SD 10.1	0.563	98.2, SD 13.3	91.9, SD 10.6	0.246
Hip circumference, cm	102.8, SD 9.8	102.0, SD 8.2	0.669	99.5 [95.6, 109.5]	101.9 [96.6, 106.2]	0.882	103.1, SD 9.0	103.2, SD 10.5	0.974
Waist-to-hip ratio	0.94, SD 0.10	0.95, SD 0.09	0.687	0.94, SD 0.10	0.97, SD 0.09	0.197	0.95, SD 0.11	0.89, SD 0.07	0.154
Calf circumference, cm	37.3, SD 3.0	36.4, SD 3.1	0.180	37.5, SD 3.0	36.3, SD 2.8	0.067	36.2, SD 3.2	36.9, SD 4.1	0.660
Triceps skinfold thickness, mm	18.8, SD 7.6	17.9, SD 7.2	0.544	16.7 [12.3, 24.9]	15.2 [11.2, 21.3]	0.295	20.1, SD 7.0	21.2, SD 7.6	0.738
MAMC, cm	25.0, SD 3.6	24.0, SD 2.5	0.149	25.3, SD 3.6	24.3, SD 2.3	0.211	23.8, SD 3.5	23.2, SD 2.9	0.662
HGS, kgf	30.1, SD 9.2	24.7, SD 7.1	0.002	31.1, SD 9.2	26.6, SD 6.8	0.021	25.4, SD 8.0	19.0, SD 5.1	0.043
GSAH, m/s	1.14 [0.56, 0.85]	0.90 [0.49, 0.67]	0.002	0.69 [0.59, 0.86]	0.58 [0.53, 0.76]	0.022	0.62 [0.42, 0.72]	0.50 [0.45, 0.53]	0.181

Values are indicated in number (percentage), median [lower, upper quartiles], or mean, SD standard deviation. BMI: body mass index; GSAH: gait speed adjusted for height; HF: heart failure; HGS: hand grip strength; LVEF: left ventricular ejection fraction; MAMC: mid-upper arm muscle circumference; MUAC: mid-upper arm circumference; NYHA: New York Heart Association. Missing values: atrial fibrillation: 4; etiology: 5; family income: 4; incidental stroke: 3; LVEF: 4; NYHA classes: 2.

Table 2 Distribution of positive frailty phenotype criteria according to age categories.

Frailty phenotype criteria	Age <65 years (n=59)	Age ≥65 years (n=40)	p-Value
Weakness	20 (33.9)	29 (72.5)	0.000
Slowness	8 (13.6)	7 (17.5)	0.592
Low physical activity	31 (52.5)	20 (50.0)	0.804
Exhaustion	32 (54.2)	16 (40.0)	0.164
Non-intentional weight loss	11 (18.6)	5 (12.5)	0.415

Values are indicated in number (percentage).

When observing frail individuals separately, there were no differences between younger and older patients, except for a higher HGS in the younger participants (p=0.043) and a lower frequency of school attendance in the older (p<0.001).

Table 2 depicts the age differences according to the Fried et al. criteria on classifying FP.[15] Being weak, having low HGS, was the only criterion with significant differences between younger and older participants (33.9% vs. 72.6%, respectively, p<0.001).

The results of the binary logistic regression analysis are shown in Table 3. HGS, GSAH and the presence of T2DM were the only significant age predictors.

Regarding the adjusted model, higher HGS was the most consistent predictor of younger age (overall: OR=0.90; 95% CI=0.83, 0.98; p=0.013. women: OR=0.69; 95% CI=0.52, 0.93; p=0.015), except for men, although with statistical indicators close to significant (OR=0.90; 95% CI=0.81, 1.00; p=0.060).

Gait speed adjusted for height did not have an effect in defining age categories in men (OR=0.03; 95% CI=0.00, 2.82; p=0.128), and women (OR=0.01; 95% CI=0.00, 1.24; p=0.059), but was significant in the overall sample, with higher gait speed associated with younger age (OR=0.01; 95% CI=0.00, 0.22; p=0.004).

Being diabetic was also associated with an increased likelihood of being older in the overall sample (OR=4.95; 95% CI=1.64, 14.93; p=0.004) but not when considering women and men separately.

Discussion

The most interesting results from the present study relate to a general lack of a significant effect of age of various characteristics in HF patients with FP. Taking into consideration that our study represented a wide range of ages and nearly 60% of participants were younger than 65 years old, age-related comorbidities would eventually play a major role in differentiating younger and older participants, if not for the fact the entire population in analysis was affected by frailty and pre-frailty. This alone is enough to recommend the assessment of FP in all HF patients, regardless of age.

Hand grip strength

Skeletal muscle function is an important component of aging and disease. Evidence toward the use of HGS as a biomarker for aging has been growing,[22,23] such as in its use as an outcome predictor of HF, being associated with incidence, hospitalization, readmission and mortality.[13,24–26]

Hand grip strength was the most consistent predictor for age differences in this sample. Also, low HGS as defined by Fried at al., was already present in a third of the younger participants. These results show that loss of muscle function with age is observable in younger HF patients and that HGS could be used to establish its onset.

The gradual loss of muscle strength with age in pre-frail and frail HF patients should be a focus for further longitudinal studies with larger samples. Age-specific HGS cut-offs are needed for the entire HF population, as HGS seems to be a good measure of global myopathy, thus reflecting critical changes in HF progression that need rapid attention and personalized interventions.

Gait speed

Slow gait is independently associated with HF mortality, all-cause mortality and hospitalization in older (≥70 years) HF patients, as shown by the IMAGE-HF Study.[27] During hospitalization, short term increments in GS are associated with reduced risks of death and readmission in older acute HF patients.[28] In the present study, lower GS was associated with older age, which was expected. However, only 15.2% of the participants were classified as being slow, according to the cut-offs established by Fried et al.,[15] which we attributed to the fact that this sample was comprised of community-dwelling individuals and not hospitalized patients. Moreover, there were no significant differences between younger and older patients in respect to this defining FP criterion.

Muscle mass and obesity

The association of lower functionality with older age, consubstantiated by our results regarding HGS and GSAH, was not accompanied by lower estimated muscle mass using MUAC. This means that either our method for estimating muscle mass could not predict age differences, or that functional decline could precede muscular decline in this sample. While these associations deserve further research, it is interesting to verify that functional assessment has been gaining traction in contrast with body composition: a recent position statement from the Sarcopenia Definition and Outcomes Consortium recommends the use of HGS to define and assess sarcopenia, with many consortium members agreeing that dual-energy X-ray absorptiometry (DEXA) derived

Table 3 Results from the binary logistic regression analysis regarding age categories (<65 years and ≥65 years) for pre-frail and frail individuals (n=99).

	Unadjusted						Adjusted					
	Women		Men		All		Women		Men		All	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
HGS	0.85 (0.73–0.99)	0.049	0.88 (0.80–0.96)	0.006	0.92 (0.88–0.97)	0.004	0.69 (0.52–0.93)	0.015	0.90 (0.81–1.00)	0.060	0.90 (0.83–0.98)	0.013
GSAH	0.01 (0.00–0.37)	0.018	0.05 (0.00–1.30)	0.071	0.02 (0.00–0.25)	0.003	0.01 (0.00–1.24)	0.059	0.03 (0.00–2.82)	0.128	0.01 (0.00–0.22)	0.004
MAMC	1.18 (0.91–1.51)	0.209	0.72 (0.56–0.93)	0.011	0.91 (0.80–1.04)	0.150	1.23 (0.77–1.96)	0.392	0.84 (0.59–1.18)	0.317	1.06 (0.86–1.31)	0.595
BMI												
<30 kg m^{-2}	1		1		1		1		1		1	
≥30 kg m^{-2}	0.64 (0.18–2.31)	0.493	1.66 (0.56–4.98)	0.364	1.07 (0.47–2.40)	0.877	5.8 (0.33–101.28)	0.226	0.82 (0.15–4.56)	0.824	0.73 (0.24–2.24)	0.577
Diabetes												
Non-diabetic	1		1		1		1		1		1	
Diabetic	14.00 (1.51–130.01)	0.020	2.40 (0.83–6.97)	0.107	3.14 (1.33–7.45)	0.009	16.19 (0.39–667.98)	0.142	2.89 (0.71–11.86)	0.140	4.95 (1.64–14.93)	0.004
NYHA classes												
Class I	1		1		1		1		1		1	
Classes II+III	1.46 (0.29–7.23)	0.644	0.72 (0.24–2.12)	0.548	0.94 (0.39–2.28)	0.899	0.81 (0.06–11.79)	0.880	0.32 (0.08–1.37)	0.125	0.40 (0.13–1.23)	0.110

BMI: body mass index; GSAH: gait speed adjusted for height; HGS: hand grip strength; MAMC: mid-upper arm muscle circumference; NYHA: New York Heart Association.

lean mass measures were not good predictors of health-related outcomes of sarcopenia.[29] Until recently, DEXA was the preferred method for accessing lean mass by the European Working Group on Sarcopenia in Older People, while the use of other methods, such as bioelectric impedance and anthropometric assessment, was being discouraged.[30]

Obesity coexisted with FP in this sample, with 43.4% of the individuals having a BMI $\geq$30 kg m^{-2}. There was, however, no association between obesity and age categories. Yet, 42% of the obese participants had concomitant low HGS, which raises important questions regarding the presence of sarcopenic obesity in this sample.

Diabetes

According to the Cardiovascular Health Study, the prevalence of T2DM is 18.8% in individuals without FP, 24.5% in pre-frail and 32.4% in frail individuals.[31] T2DM can also reduce the likelihood of improving pre-frailty.[32] Sarcopenia may play an important role in the pathophysiological mechanisms linking FP and T2DM, as muscle deterioration is often associated with insulin resistance, low-grade inflammation and mitochondrial alterations, typical of diabetes.[33]

Type 2 diabetes is an independent predictor for the development of HF.[34] Diabetes is highly prevalent in HF and patients with both conditions have a higher risk of mortality compared with patients with only HF or T2DM.[35]

The frequency of T2DM in this sample was 34.3%, being notably higher in pre-frail participants compared with the frail (37.0% vs. 23.8%, respectively). Our multivariate analysis has shown T2DM to be associated with older age in frail and pre-frail patients. The associations between aging, diabetes, frailty and HF deserve further study. Nonetheless, our results might indicate a need for better glycemic control on younger pre-frail and frail HF patients in order to prevent or mitigate T2DM at older ages.

Heart failure functional classes

In our multivariate analysis, NYHA functional classes, which were recoded as indicators of the presence vs. absence of symptoms and tolerance to physical exercise, were not a significant predictor of age. This shows that younger and older pre-frail and frail HF patients tended to be similar in terms of the severity of symptoms and the level of tolerance to physical activity.

Primary versus secondary frailty phenotype

The frailty phenotype is associated with both advanced age and HF. Goldwater et al. discuss the possibility that secondary FP, related with HF, is a separate entity to that of primary FP, associated with advanced age, although both share the propensity to a catabolic state fueled by inflammation, mitochondrial dysfunction, oxidative stress and hormonal dysregulations. Identifiable differences between both conditions are subtle at most. Muscle loss in HF seems to be associated with a higher percentage of fast-twitch glycolytic type II fibers, and HF frail patients seem to have a better response to physical therapy compared with those with primary frailty.[2] However, it is possible that age-related primary FP and HF-related secondary FP are not mutually exclusive, and the onset of FP occurs in younger ages in HF individuals than in the general population. Whether or not FP is a separate entity in HF or in aging, frailty seems to be a process of accelerated aging associated with chronic diseases such as HF,[36] thus disputing the utility of taking an HF patient's chronological age into consideration when addressing assessment methods or therapeutic strategies to prevent or revert FP.

Limitations

Some limitations should be acknowledged. First, this is a cross-sectional study, therefore it does not allow for causal associations. Secondly, the sample is rather small, which precluded its stratification in more than two age intervals; this stratification would eventually allow for a more thorough analysis. The effect of the small sample size was also felt in the frail (n=21) individuals, hampering the possibility of conducting a separate multivariate analysis on this group. For the same reason, the 37 participants who were excluded for not having FP could not be used to contrast our findings, as only six were 65 years or older. Also, body composition was assessed solely on the basis of anthropometric measurements, namely MAMC and BMI, as the conditions of the study setting, as well as the research logistics, did not allow for easy access to other assessment methods. However, the anthropometric measurements that led to the definition of MAMC and BMI were conducted by the same experienced registered nutritionist to avoid inter-observer errors. Finally, only the Fried phenotype was used to assess frailty. It would be interesting to study the effect of other frailty constructs, such as the multidimensional frailty classifications, as it is known that different measures can affect the proportion of HF individuals classified as frail and pre-frail.[1]

Despite the described limitations, this is, to our knowledge, the first study comparing older and younger individuals with concomitant FP and HF, and we hope it can contribute to broadening the view of FP in HF beyond the classical aspects of a geriatric syndrome.

Conclusions

The general scarcity of significant differences in nutritional and clinical statuses between younger and older HF patients with FP suggests that frailty should be assessed in all HF patients, regardless of their chronological age.

Low HGS is a good predictor of older age and can potentially help differentiate younger individuals with accelerated myopathy, but studies regarding HGS on HF populations are needed in order to establish cut-offs associated with the progression of FP, especially regarding the onset of impaired muscle strength at younger ages.

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Conflict of interest

The authors declare that there is no conflict of interest.

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