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DOUTORAMENTO

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Fragilidade e Sarcopenia em Insuficientes Cardíacos Portugueses – fatores nutricionais, funcionais e clínicos associados

Frailty and Sarcopenia in Portuguese Heart Failure Patients – nutritional, functional and clinical associated factors

Rui Valdiviesso

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Dissertação de candidatura ao grau de Doutor, apresentada à Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

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Artigos

Fazem parte desta dissertação os seguintes artigos e manuscritos, em forma publicada (1) ou submetida para publicação (2-5):

1. Valdiviesso R, Azevedo LF, Moreira E, Ataíde R, Martins S, Fernandes L, Silva-Cardoso J, Borges N. Frailty phenotype and associated nutritional factors in a sample of Portuguese heart failure outpatients. Nutr Metab Cardiovasc Dis. 2021 Jul 22;31(8):2391-2397.

2. Valdiviesso R, Moreira E, Martins S, Azevedo LF, Ataíde R, Fernandes L, Silva-Cardoso J, Borges N. Frailty phenotype in heart failure: a condition that transcends age [*accepted for publication, Rev Port Cardiol*].

3. Valdiviesso R, Sousa-Santos AR, Azevedo LF, Moreira E, Amaral TF, Silva-Cardoso J, Borges N. Statins are associated with reduced likelihood of sarcopenia in a sample of heart failure outpatients [*accepted for publication, BMC Cardiovasc Disord*].

4. Valdiviesso R, Amaral TF, Moreira E, Sousa-Santos AR, Fernandes M, Aguiar MJV, Martins S, Azevedo LF, Fernandes L, Silva-Cardoso J, Borges N. The associations between medicine use and ejection fraction with the coexistence of frailty and sarcopenia in a sample of Portuguese heart failure outpatients [*submitted for publication*].

5. Valdiviesso R, Aguiar MJV, Azevedo LF, Fernandes M, Moreira E, Sousa-Santos AR, Amaral TF, Azevedo LF, Silva-Cardoso J, Borges N. Hand grip strength cross-sectional association with clinical, nutritional, and physical activity variables in heart failure outpatients [*submitted for publication*].

Participei na definição de objetivos, no desenho do estudo, na definição do protocolo do estudo e na recolha dos dados. Fui responsável pela organização, análise e interpretação dos dados, pela definição de objetivos específicos e pela redação das versões iniciais de todos os manuscritos. Colaborei nas revisões subsequentes dos artigos.

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Resumo / Abstract

Resumo

Introdução:

A insuficiência cardíaca (IC) é uma síndrome causada por anomalias cardíacas estruturais e/ou funcionais que resultam num débito cardíaco desadequado às funções do organismo. A prevalência mundial da IC tem aumentado, resultando em elevada pressão sobre os sistemas de saúde.

A fragilidade é uma síndrome que resulta da perda de homeostasia devido ao declínio cumulativo de vários sistemas fisiológicos, causando uma redução das reservas corporais e a perda de capacidade para lidar com agressões quotidianas. A sarcopenia é uma doença muscular caracterizada pela perda de força e de massa musculares.

A fragilidade e a sarcopenia são muito comuns em doentes com IC, sendo que estas três condições partilham importantes componentes fisiopatológicos e interferem mutuamente no sentido de piores resultados clínicos. A fragilidade e a sarcopenia estão associadas, assim, a maior mortalidade e hospitalizações na IC, mas apesar disto, permanecem desconhecidas nestes doentes em Portugal, bem como os fatores que estão associados a estas duas condições, quer isoladamente, quem em concomitância.

Objetivos:

Esta dissertação tem como objetivos: avaliar a fragilidade e fatores clínicos e nutricionais associados (Artigo 1); comparar doentes de IC pré-frágeis e frágeis, com menos de 65 anos e com 65 anos ou mais, relativamente aos fatores associados com as diferenças de idade (Artigo 2); avaliar o efeito das estatinas na presença de sarcopenia em doentes com IC, bem como os fatores associados à sarcopenia nesta população (Artigo 3); estudar a coexistência de fragilidade e sarcopenia e os fatores associados, nomeadamente o uso de medicamentos e a fração de ejeção (Artigo 4), e estudar as associações entre variáveis do estado clínico e nutricional e atividade física com a força de preensão da mão (Artigo 5).

Métodos:

Os participantes neste estudo transversal foram recrutados numa consulta externa de insuficiência cardíaca e selecionados aleatoriamente das listas de consulta. Os dados clínicos utilizados incluem a severidade da doença, avaliada

a partir das classes funcionais da *New York Heart Association*, a fração de ejeção do ventrículo esquerdo e os fenótipos de IC (fração de ejeção reduzida, ligeiramente reduzida e preservada), a medicação, os fatores de risco e as comorbilidades. O fenótipo de fragilidade foi avaliado de acordo com Fried et al. A sarcopenia foi diagnosticada de acordo com o consenso revisto do *European Working Group on Sarcopenia in Older People*.

Resultados:

Todos os resultados são relativos à mesma amostra de 136 insuficientes cardíacos (33,8% mulheres, idades entre 24 e 81 anos, mediana (Md) de idades de 59,0 anos, (intervalo interquartil (IIQ) = 49,0 – 68,0 anos), exceto os resultados do Artigo 2, que se referem a uma subamostra de 99 participantes com pré-fragilidade e fragilidade (38,4% mulheres, idades entre 24 e 81 anos, 59,6% < 65 anos).

Os resultados do Artigo 1 mostraram uma frequência de fragilidade e de pré-fragilidade de 15,4% e 57,4%, respetivamente. O critério mais frequente na definição de fragilidade foi a exaustão (90,5%), seguido da baixa atividade física (81,0%). A análise multivariada (regressão logística ordinal) relativamente à variável dependente ordinal "robusto / pré-frágil / frágil", mostrou que as mulheres com mais de 70 anos tinham mais probabilidade de serem pré-frágeis e/ou frágeis (razão de possibilidades, *odds ratio* (OR) = 16,85; intervalo de confiança a 95% (IC 95%) = 2,89 – 98,07). Homens em classe I de NYHA e obesos tinham maiores probabilidades de serem classificados como pré-frágeis e/ou frágeis (OR = 0,07; IC 95% = 0,02 - 0,33 e OR = 3,62; IC 95% = 1,15 – 11,39, respetivamente). Em ambos os sexos, por cada unidade de incremento do perímetro muscular do braço (PMB), diminuíram as probabilidades de transitar para categorias de fragilidade mais elevadas (homens: OR = 0,71; IC 95% = 0,53 – 0,96; mulheres: OR = 0,67; IC 95% = 0,53 – 0,83).

No Artigo 2 foram comparados participantes com fragilidade e pré-fragilidade relativamente à idade, categorizada como maior ou igual que 65 anos, ou menos que 65 anos. Os participantes pré-frágeis e frágeis constituíram 78,8% e 21,2% da amostra, respetivamente, sendo que 59.6% dos indivíduos tinham 65 ou menos anos. Em análise multivariada, em que a variável de resultado era a categoria de idades (regressão logística binária), a força de preensão da mão

(FPM) foi associada a ter idade menor que 65 anos (amostra total: OR = 0,90; IC 95% = 0,83 – 0,98; mulheres: OR = 0,69; IC 95% = 0,52 – 0,93), exceto em homens. Na amostra total, ter diabetes e apresentar menor velocidade da marcha foram associados a maior probabilidade de ter 65 ou mais anos na amostra total (OR = 4,95; IC 95% = 1,64 – 14,93 e OR = 0,01; IC 95% = 0,00 – 0,22, respetivamente), mas não em homens ou mulheres isoladamente.

O Artigo 3 reportou uma frequência de sarcopenia de 18,4%. Esta frequência variou entre 12,2% em menores de 65 anos e 30,4% nos mais velhos, e entre 3,3% em homens e 47,8% em mulheres. A sarcopenia severa estava presente em 7,4% da amostra, e a obesidade sarcopénica em 5,1%. Um total de 89 participantes estava medicado com estatinas. A análise multivariada (regressão logística binária) demonstrou que as estatinas estavam associadas a uma menor probabilidade de ser sarcopénico (OR = 0,06; IC 95% = 0,01 – 0,40). Por cada aumento de um ano de idade, houve um aumento de 9% da probabilidade de ter sarcopenia (OR = 1,09; IC 95% = 1,01 – 1,17) e por cada aumento de índice de massa corporal (IMC) de 1 Kg/m^2, verificou-se uma diminuição de 19% da probabilidade de ter sarcopenia (OR = 0,81; IC 95% = 0,67 – 0,97). A polifarmácia e ter cardiomiopatia hipertrófica como diagnóstico etiológico da IC, foram também fatores associados ao aumento de probabilidade de ser sarcopénico (OR = 24,09; IC 95% = 1,82 – 318,52 e OR = 19,67; IC 95% = 1,25 – 310,26, respetivamente).

O estudo da coexistência da fragilidade e da sarcopenia foi feito no Artigo 4. No total, 8,1% da amostra tinha ambas as condições em simultâneo. Entre os sarcopénicos, 44% eram frágeis, e 52% dos frágeis eram sarcopénicos. A regressão logística ordinal foi feita relativamente à variável de resultado “não ter nenhuma das condições / ter uma das condições / ter ambas as condições concomitantemente”. Os resultados multivariados mostraram que as mulheres tinham muito maior probabilidade de acumular fragilidade e sarcopenia que os homens (OR = 60,53; IC 95% = 13,11 – 279,56). Por cada aumento de um ano de idade, a probabilidade de ter um número maior de condições aumentou 12% (OR = 1,12; IC 95% = 1,05 – 1,18). Os indivíduos com insuficiência cardíaca com fração de ejeção preservada (ICFEP) tinham maior probabilidade de acumular condições do que os outros fenótipos de IC (OR = 6,34; IC 95% = 1,45 – 27,69).

Relativamente à medicação, os utilizadores de estatinas tinham menor probabilidade de serem alocados em categorias mais altas de coexistência (OR = 0,07; IC 95% = 0,02 – 0,33), enquanto que os utilizadores de anticoagulantes e antidepressivos tinham maior probabilidade de transitar em direção à coexistência (OR = 6,80; IC 95% = 1,90 – 24,31 e OR = 10,73; IC 95% = 2,56 – 44,94, respetivamente).

No artigo 5 foi reportada uma mediana de FPM de 28,9 Kgf (IIQ = 23,2 – 37,3 Kgf), sendo mais alta em homens (Md = 34,6 Kgf; IIQ = 28,7 – 40,9 Kgf) que em mulheres (Md = 21,3 Kgf; IIQ = 17,4 – 24,6 Kgf). Um total de 41,9% dos participantes tinham baixa FPM. Os resultados da análise multivariada (regressão logística binária) mostraram que os homens tinham muito menor probabilidade de apresentar FPM baixa que as mulheres (OR = 0,11; IC 95% = 0,02 – 0,49). Ser fisicamente ativo ou ter maior PMB foi associado a uma menor probabilidade de ter baixa FPM (OR = 0,21; IC 95% = 0,06 – 0,71 e OR = 0,63; IC 95% = 0,45 – 0,88, respetivamente). Em sentido contrário, um IMC elevado foi associado a maior probabilidade de ter baixa FPM (OR = 1,28; IC 95% = 1,05 – 1,57). A idade, a polifarmácia, as classes de NYHA e a fração de ejeção não foram associadas à FPM.

Conclusões:

A fragilidade e a pré-fragilidade foram frequentes nesta amostra de doentes de IC, inclusivamente numa grande proporção de indivíduos mais jovens. A baixa massa muscular foi um preditor consistente de pré-fragilidade e/ou fragilidade, devendo ser considerada em intervenções que visem modificar esta condição.

Em doentes de ambulatório frágeis e pré-frágeis, a escassez de diferenças entre pacientes com menos ou mais de 65 anos confirmou que todos os pacientes com IC devem ser avaliados para a presença de fragilidade, independentemente da sua idade. A FPM foi um preditor de idade mais avançada. Esta medida pode ser potencialmente utilizada para discriminar indivíduos jovens em maior risco de sofrer miopatia acelerada.

A sarcopenia foi também frequente entre os indivíduos estudados. A sarcopenia grave e a obesidade sarcopénica foram diagnosticadas na amostra. Ao contrário do esperado, o uso de estatinas foi associado a uma menor probabilidade de ter sarcopenia, independentemente da idade, sexo, polifarmácia, atividade física e

etiologia da IC. Pode-se levantar a hipótese de que os efeitos pleiotrópicos das estatinas exerçam benefícios na função endotelial, contribuindo para uma melhor aptidão neuromuscular. Esta associação justifica um estudo mais aprofundado.
A frequência da coexistência de fragilidade e sarcopenia foi baixa, o que evidencia a necessidade de atenção individualizada a estas condições. No entanto, o estudo da sua coocorrência permitiu isolar os indivíduos que podem estar em maior risco de resultados clínicos desfavoráveis, como os mais velhos, as mulheres, os que estavam medicados com antidepressivos e/ou anticoagulantes e os pacientes com ICFEP. A ICFEP compartilha a inexistência de terapias farmacológicas com a fragilidade e a sarcopenia, portanto o exercício físico e intervenções nutricionais e de saúde mental podem contribuir para o aumento da qualidade de vida destes indivíduos.
A baixa FPM foi particularmente associada a um pior estado nutricional e à baixa atividade física, mas não a variáveis do estado clínico da IC, como a FEVE, as classes de NYHA ou a polifarmácia. Isto confirma a relevância da FPM como um marcador da saúde muscular geral e reforça a importância das intervenções nutricionais e de exercício físico em pacientes com IC, independentemente do seu estado clínico.
Os resultados do presente estudo contribuem para aumentar as evidências que suportam a necessidade de avaliação da fragilidade e sarcopenia em dentes com IC, o que continua a ser uma carência na prática clínica em Portugal. É reforçada, também, a importância de olhar para estas condições e para os seus fatores funcionais e nutricionais no sentido de estabelecer planos de intervenção que possam contribuir para melhores resultados clínicos na IC.

Palavras-chave:
Insuficiência Cardíaca; Fragilidade; Sarcopenia; Força de Preensão da Mão; Estado Nutricional.

Abstract

Background:

Heart failure (HF) is a syndrome caused by structural and/or functional cardiac anomalies that result in inadequate cardiac output. The worldwide prevalence of HF has been increasing, with an immense burden on health systems.

Frailty is a syndrome that results from the loss of homeostasis due to a cumulative decline across multiple physiologic systems, causing a reduction in reserves and a lack of capacity to cope with stressors. Sarcopenia is a muscle disease characterised by the loss of muscle strength and muscle mass.

Frailty and sarcopenia are very common in patients with HF, and these three conditions share important pathophysiological components, mutually interfering with each other towards worse clinical outcomes. Frailty and sarcopenia are thus associated with higher mortality and hospitalizations in HF. Despite this, they remain unknown in Portuguese HF patients, as well as the factors that are associated with them, either alone or concomitantly.

Aims:

The present dissertation aims to evaluate the frequency of frailty and its associated nutritional and clinical factors (Paper 1), the comparison between younger and older HF patients with frailty and pre-frailty and the factors associated with age differences (Paper 2), the frequency of sarcopenia and its association with the use of statins (Paper 3), the overlapping between frailty and sarcopenia, and the association between medication and ejection fraction and the coexistence of these conditions (Paper 4) and the association between clinical, nutritional and physical activity variables and hand grip strength (Paper 5).

Methods:

Participants in this cross-sectional study were recruited from a clinic for HF outpatients. A random selection of the appointments lists was performed. Clinical data included the severity of the disease, classified according to the New York Heart Association (NYHA), left ventricular ejection fraction (LFEF) and HF phenotypes (reduced, mildly reduced and preserved ejection fractions), medication, risk factors and comorbidities. Frailty phenotype was assessed

according to Fried et al. Sarcopenia was defined according to the revised consensus of the European Working Group on Sarcopenia in Older People.

Results:

All results refer to the same sample of 136 patients (33.8% women, age range 24-81 years, median (Md) age 59.0 years, interquartile range (IQR) = 49.0, 68.0 years, except for Paper 2, which analysed a subsample of 99 frail and pre-frail patients (aged 24-81 years, 38.4% women, 59.6% < 65 years).

The results from Paper 1 showed a frequency of frailty and pre-frailty of 15.4% and 57.4%, respectively. Most frequent frailty criterion was exhaustion (90.5%), followed by low physical activity (81.0%). Multivariable analysis (ordinal logistic regression), in regard to the result variable categories “normal / pre-frail / frail”, showed that women with 70 years or older had higher odds of being allocated in higher frailty phenotype categories (odds ratio (OR) = 16.85; 95% confidence interval (95% CI) = 2.89, 98.07). Men at NYHA class I and obese had higher odds of being classified from normal towards frail (OR = 0.07; 95% CI = 0.02, 0.33 and OR = 3.62; 95% CI = 1.15, 11.39, respectively). Both men and women had diminishing odds of being allocated in higher frailty phenotype categories with every unit increase of mid-upper arm muscle circumference (MAMC), (OR = 0.71; 95% CI = 0.53, 0.96 and OR = 0.67; 95% CI = 0.53, 0.83, respectively).

In Paper 2, pre-frail and frail participants comprised 78.8% and 21.2% of the sample, respectively, and 59.6% of the sample was younger than 65 years. Multivariate results (logistic regression) showed that higher hand grip strength (HGS) was the most consistent predictor of younger age (Overall: OR = 0.90; 95% CI = 0.83, 0.98. Women: OR = 0.69; 95% CI = 0.52, 0.93), except in men. In the overall sample, being diabetic and having lower gait speed were associated with being 65 years or older (OR = 4.95; 95% CI = 1.64, 14.93 and OR = 0.01; 95% CI = 0.00, 0.22, respectively), but not in women or men alone.

Paper 3 reports a frequency of sarcopenia of 18.4%, ranging from 12.2% in younger (< 65 years) participants vs. 30.4% in older ones and from 3.3% in men vs. 47.8% in women. Severe sarcopenia accounted for 7.4% of the sample and sarcopenic obesity was present in 5.1% of the participants. A total of 89 patients were medicated with statins. Multivariate results (binary logistic regression) showed that the use of statins was inversely associated with sarcopenia (OR =

0.06; 95% CI = 0.01, 0.40). Each additional age year was associated with a 9% increase in the likelihood of being sarcopenic (OR = 1.09; 95% CI = 1.01, 1.17), and each body mass index (BMI) Kg/m increment was associated with a 19% decrease in the likelihood of sarcopenia (OR = 0.81; 95% CI = 0.67, 0.97). The daily use of 5 or more medicines and having hypertrophic cardiomyopathy as aetiological HF diagnosis were also directly associated with sarcopenia (OR = 24.09; 95% CI = 1.82, 318.52 and OR = 19.67; 95% CI = 1.25, 310.26, respectively). Being a man and being physically active were inversely associated with sarcopenia (OR = 0.01; 95% CI = 0.00, 0.08 and OR = 0.16; 95% CI = 0.03, 0.97, respectively).

Results from Paper 4 showed that the frequency of patients with concomitant frailty and sarcopenia was 8.1%. Within sarcopenic participants, 44% were frail; 52% of frail participants were sarcopenic. Multivariable results (ordinal logistic regression) for the dependent variable categorised as “no condition / frail or sarcopenic / both conditions”, showed that, for every year increase in age, the odds of having more conditions increased by 12% (OR = 1.12; 95% CI = 1.05, 1.18). Women were much more likely to be allocated in higher categories of coexistence of frailty and sarcopenia than men (OR = 60.53; 95% CI = 13.11, 279.56). Patients with heart failure with preserved ejection fraction (HFpEF) were more likely to have an accumulation of conditions than those with reduced or mildly reduced LVEF (OR = 6.34; 95% CI = 1.45, 27.69). Regarding medication, the participants who used statins were less likely to be allocated in higher categories of co-occurrence of frailty and sarcopenia than those who were not statin users (OR = 0.07; 95% CI = 0.02, 0.33), while patients who were prescribed anticoagulants and antidepressants were more likely to accumulate conditions (OR = 6.80; 95% CI = 1.90, 24.31 and OR = 10.73; 95% CI = 2.56, 44.94, respectively).

Paper 5 reports an overall median HGS of 28.9 Kgf (IQR = 23.2, 37.3 Kgf), which was higher in men (Md = 34.6 Kgf; IQR = 28.7, 40.9 Kgf) than in women (Md = 21.3 Kgf; IQR = 17.4, 24.6 Kgf). A total of 41.9% of the participants had low HGS. Multivariable results (binary logistic regression) showed that men had much lower odds of having low HGS than women (OR = 0.11, 95% CI = 0.02, 0.49). Being physically active and having higher MAMC were inversely associated with low

hand grip strength (OR = 0.21, 95% CI = 0.06, 0.71 and OR = 0.63, 95% CI = 0.45, 0.88, respectively). Contrariwise, higher BMI was a predictor of lower HGS (OR = 1.28, 95% CI = 1.05, 1.57). Age, polypharmacy, functional classes, and ejection fraction were not associated with categories of HGS in this sample.

Conclusions:

Frailty and pre-frailty were frequent in this sample, inclusively in a large percentage of younger patients. Low muscle mass was a consistent predictor of having pre-frailty and/or frailty and should be considered in interventions aimed at modifying frailty.

In frail and pre-frail outpatients, differences between the younger and the older individuals were very scarce, which confirms that all HF patients should be screened for frailty, irrespective of chronologic age. Lower HGS predicted older age, therefore, this measure could be potentially used to discriminate younger individuals with accelerated myopathy.

Sarcopenia was frequent among the studied patients. Severe sarcopenia and sarcopenic obesity were also diagnosed. Contrarily to what was expected, statin use was associated with a lower likelihood of being sarcopenic, irrespectively of age, sex, polypharmacy, physical activity and HF aetiology. It can be hypothesised that the pleiotropic effects of statins may exert benefits in endothelial function, thus contributing to better neuromuscular fitness. This warrants further study.

The frequency of the coexistence of frailty and sarcopenia was low, which highlights the need for individualised attention to these conditions. However, studying their co-occurrence allowed for isolating the individuals who may be at a higher risk of poor outcomes, such as the older, the women, those who are prescribed antidepressants and/or anticoagulants, and patients with HFpEF. The latter share the inexistence of pharmacological therapies with frailty and sarcopenia, thus may benefit from exercise training, nutrition and mental health interventions.

Low HGS was particularly associated with a poorer nutritional status and with low physical activity, but was not predicted by HF clinical status variables, such as LVEF, NYHA classes or polypharmacy. This confirms the relevance of HGS as a

marker of general muscle health and reinforces the importance of nutrition and exercise interventions in HF patients.
The present work's results contribute to increasing the evidence regarding these conditions and to reinforce the necessity of assessing physical frailty and sarcopenia in HF patients, which remains an unmet need in Portuguese clinical practice, as well as the importance of looking at these conditions and their clinical, functional and nutritional factors in regard to establishing intervention plans that can contribute to better HF outcomes.

Keywords: Heart Failure; Frailty; Sarcopenia; Hand Grip Strength; Nutritional Status.

List of Abbreviations

ASM: Appendicular Skeletal Mass

AWGS: Asian Working Group for Sarcopenia

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CC: Calf Circumference

CT: Computerised Tomography

DEXA: dual-energy x-ray absorptiometry

ESC: European Society of Cardiology

EWGSOP: European Working Group on Sarcopenia in Older People

EWGSOP2: Revised Consensus of the European Working Group on Sarcopenia in Older People

GS: Gait Speed

HF: Heart Failure

HFA: Heart Failure Association of the European Society of Cardiology

HFmrEF: Heart Failure with mildly reduced Ejection Fraction

HFpEF: Heart Failure with preserved Ejection Fraction

HFrEF: Heart Failure with reduced Ejection Fraction

HGS: Hand Grip Strength

IWGS: International Working Group on Sarcopenia

LVAD: Left Ventricular Assist Device

LVEF: Left-Ventricular Ejection Fraction

MAMC: Mid-upper Arm Muscle Circumference

MRI: Magnetic Resonance Imaging

MUAC: Mid-Upper Arm Circumference

NYHA: New York Heart Association

RCT: Randomised Controlled Trial

SPPB: Short Physical Performance Battery

TST: Triceps Skinfold Thickness

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Introduction

Introduction

1. Heart Failure

1.1. Definition

Definitions of heart failure (HF) have been evolving to accommodate for the complexity of its pathophysiology and the multitude of aetiological factors, as well as the growing awareness of the clinical and research professionals for the specificity of its symptoms and signs. Rather than a disease, HF is a clinical syndrome with diverse manifestations, which makes it difficult to define in a consensual manner[1].

In the 2021 guidelines for the diagnosis and treatment of acute and chronic heart failure, the European Society of Cardiology (ESC) defines HF as "*a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise*"[2].

Also recently, a committee composed of various international cardiology societies reached a consensus on a universal definition of HF. The committee focused mainly on the importance of the haemodynamic aspects of HF, the biomarkers that define this syndrome and the clinician's perspectives on diagnosing it. The following definition was proposed: "*HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac*

abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion"[1].

1.2. Classification and Terminology

The left-ventricular ejection fraction (LVEF), which is the percentage of chamber volume ejected during systolic contraction in relation to the volume of the blood in the ventricle at the end of a diastole[3], is central to the classification of the phenotypes of HF. Heart failure with reduced ejection fraction (HFrEF) characterizes those who have a significant reduction of left-ventricular systolic function (LVEF ≤ 40%). An LVEF between 41% and 49% is designated as heart failure with mildly reduced ejection fraction (HFmrEF). The patients with LVEF ≥ 50% but with evidence of structural and/or functional cardiac abnormalities and/or raised natriuretic peptide levels are classified as having heart failure with preserved ejection fraction (HFpEF)[2].

Regarding the severity of the disease, classification of HF is usually done according to the New York Heart Association (NYHA), which places the patients in four categories concerning the presence of symptoms and the tolerance to physical activity. NYHA Class I classifies an asymptomatic patient with no limitation to physical activity, while NYHA Class II refers to patients that are asymptomatic at rest but present slight dyspnoea, palpitations and fatigue with ordinary physical activity. Patients within NYHA Class III are comfortable at rest but become fatigued and dyspnoeic with light physical activity. Finally, NYHA Class IV characterises patients who present HF symptoms even at rest, which increase with any physical activity[4].

1.3. Epidemiology

The global prevalence of HF seems to be 1% - 2%, varying in age from 1% in people younger than 55 years to 10% in patients older than 70 years[5,6]. The incidence of HF in the European adult population is around 5/1,000 person-year[7]. While the global incidence of HF is rising, mainly due to population ageing, age-adjusted incidence seems to be lowering, which may be a result of better management of cardiovascular diseases[8].

Mortality related to HF has a similar or even higher incidence than cancer mortality, with a comparable number of expected life-years lost[9]. For all types of HF patients, 5-year mortality rates after diagnosis are between 53% and 67%[10,11]. Globally, women seem to have lower mortality rates than men[12].

Usually, following initial diagnosis patients are hospitalised once every year on average[13]. In France, age-standardized rates for HF admission reached 246.2 per 100,000 inhabitants in 2012[14]. Hospitalisation seems to be an important predictor of HF outcomes, as patients not requiring hospital admission around the time of the HF diagnosis have improved survival when compared to those who have to be hospitalised[15].

Temporal trends in incidence, prevalence, mortality, and hospitalisation for HF present interesting fluctuations that reflect the therapeutic advances from the last decades, as well as the age structure of the populations. Demographic ageing in developed countries seems to be contributing to an accumulation of comorbidities, contributing to worse HF prognosis[2] and to modest improvements

in survival rates over the last years[15], which seems to be offsetting the evolution and improvement of HF treatments.

1.3.1. Heart Failure in Portugal

In Portugal, the prevalence of chronic HF was estimated by the EPIC study (1998-2000) at 4.4% in the adult population, rising to 12.7% in older adults from 70-79 years and to 16.1% in patients older than 80 years[16]. While the current incidence is around 1 - 2/1,000 person-year[7], population projections estimate HF prevalence to increase by 30% by 2035 and by 33% in 2060, accounting for nearly half a million individuals affected by this disease[17]. This poses a major public health issue and a tremendous burden for the public health system, as HF accounts for around 2% of direct health costs in developed countries[18]. Direct estimated costs amounted to 2.6% of the total expenditure of the Portuguese public health in 2014. Costs are expected to increase by 24% in 2036[19].

According to a report by the Portuguese Directorate General of Health, HF patients accounted for 182,512 hospitalisation days in 2014, with a mean hospital length of stay of 9.8 days. Hospital death rates for HF during the 2010-2014 period were 12.5%, which places HF as the leading cause of in-hospital mortality among all other cardiovascular and cerebral diseases[20]. The number of hospital admissions for HF rose by 33% between 2004 and 2012[21] and every HF patient had an average of 1.44 readmission episodes[19].

The risk of developing HF among the Portuguese population seems to be particularly worrying, as many cardiovascular disease risk factors have a very

high prevalence. All-age national prevalence of obesity is 22.3%, being much higher in older adults (39.2%). Pre-obesity accounts for 34.8% of the Portuguese population and abdominal obesity has even higher numbers: 50.5% in adults and 80.2% in the elderly[22]. Overall hypertension prevalence is 36.0%, rising to 71.3% in those aged 65-75 years old[23]. Smokers amount to 20.9% of the population[24]. Diabetes has a prevalence of 11.7%[25]. The prevalence of metabolic syndrome, according to the International Diabetes Federation classification, is 49.6%[26].

1.4. Aetiology

The aetiology of HF is complex and, in many cases, difficult to investigate. In developed countries, coronary artery disease and hypertension seem to be the most important contributors to the onset of HF. Valve disease, heart muscle disease (e.g. dilated cardiomyopathy, hypertrophic cardiomyopathy), congenital heart disease or infections such as viral myocarditis are also important aetiologies. In Latin America, Chagas disease is the leading cause of non-ischaemic cardiomyopathy. In resume, any condition that chronically affects heart function or structure can, over time, result in heart failure[2,27].

1.5. Diagnosis

According to the ESC guidelines, suspicion of HF is deemed by abnormal electrocardiogram, the presence of symptoms and signs and/or the presence of risk factors. High natriuretic peptide values and cardiac abnormalities detected by echocardiography confirm a diagnosis of HF. The HF phenotype is then

assessed based on LVEF and the comorbidities are evaluated prior to the initiation of treatments[2].

1.6. Congestion

Congestion is common in HF and is the most frequent complication in acute or decompensated phases of the disease. Congestion can be defined as signs and symptoms of extracellular fluid accumulation as a result of an increase in left-side cardiac filling pressure. These symptoms and signs can include dyspnoea, orthopnoea, pulmonary crackles, third heart sound, jugular venous distention, and pulmonary or peripheral oedema. Congestion progresses slowly, starting asymptomatically as a result of small pressure increases at the right side of the heart, and quickly shifting to a life-threatening clinical congestion, that is usually characterised by pulmonary oedema, myocardial ischaemia, decline in kidney function, increased risk of arrhythmia and cerebral changes[28]. Congestion often requires urgent hospitalisation and is one of the main predictors of poor HF outcomes[29].

1.7. Treatment

Treatment of HF varies accordingly to LVEF and comorbidities. Most research in HF was classically oriented for patients with HFrEF, who have access to a higher number of therapies based on evidence, namely on randomised controlled trials (RCT). Pharmacotherapy is the cornerstone of HFrEF treatment. As per the latest ESC guidelines, a combination of angiotensin-converting

enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists and sodium-glucose cotransporter 2 inhibitors is the current recommendation, as it is associated with reduced mortality, hospitalisation and symptomatology. Sacubitril/valsartan, a combination of a neprilysin inhibitor and an angiotensin receptor antagonist, is recommended as a substitute for angiotensin-converting enzyme inhibitors in patients that are able to tolerate it. Diuretics are recommended to alleviate symptoms and signs of congestion whenever present. Implantable cardiac electronic devices are also usually considered in elected patients[2].

The phenotype of HFmrEF has a rather recent definition and still lacks therapeutically-oriented evidence. This category was previously called HF with mid-range ejection fraction, but the many common characteristics with HFrEF justified the redefinition to “mildly reduced”[30]. Classically, patients with HFmrEF were studied along those with HFpEF, and most evidence regarding the response to treatments are based on analyses on subgroups with LVEF 41-49% within cohorts of patients with LVEF ≥ 50%. Diuretics are commonly prescribed to congestive patients, and the same tetrad of drugs that are usually recommended to patients with HFrEF may be considered in HFmrEF patients[2].

Treating HFpEF remains one of the most unmet needs in cardiology, as no pharmacological therapies have shown efficacy in reducing hospitalization and mortality, despite several trials aimed at medicines successfully used in HFrEF. Therefore, the treatment of HFpEF is centred on the alleviation of symptoms and the control of comorbidities[2].

In end-stage or advanced HF, the use of a left ventricular assist device (LVAD) can be contemplated as long-term therapy for patients who are not candidates for transplantation or as a bridge-to-transplant therapy. However, the gold standard treatment for advanced HF is heart transplantation, as it is the only treatment available that can obviate the chronic functional and structural abnormalities of the heart[2].

Physical exercise can be regarded as a treatment for HF. Cardiac rehabilitation using exercise training can contribute to a better quality of life[31]. Benefits of exercise can be found both in patients with HFrEF[32] and HFpEF[33,34].

1.8. Comorbidities Related to the Nutritional Status

Diabetes is both a risk factor and a major comorbidity of HF. Diabetic patients have more than twice the risk of developing HF than those who are not diabetic[35], and patients with both HF and diabetes have a higher risk of mortality compared with patients with only one of the conditions[36]. In the US, 44% of the patients hospitalised for HF had diabetes[37]. Glycaemia by itself may not be enough to explain the increased risk of diabetic patients to develop HF, and a complex and interrelated pathophysiology may exist between diabetes mellitus and HF[38].

The impact of obesity as a determinant of HF was first described by the Framingham Heart Study, which showed an increase in the risk of developing HF of 7% in women and 5% in men for every unit increase in body mass index (BMI)[39]. Excess adiposity is a cause of poor cardiac performance through

mechanisms that encompass haemodynamic changes, metabolic adaptations, cardiac remodelling and inflammation, among others[40]. However, overweight and mildly obese HF patients seem to have a better prognosis than non-obese ones, a phenomenon that became known as the obesity paradox of heart failure[41]. Factors such as higher metabolic reserve, less likeability to develop cardiac cachexia, increased concentration of tumour necrosis factor receptors or attenuated response to the renin-angiotensin-aldosterone system have been suggested as probable mechanisms for the obesity paradox[42]. Better evidence is needed regarding the obesity paradox. Studies centred in components of adiposity and different distributions of fat mass are warranted, as well as clinical trials regarding intentional weight loss and improvement of cardiorespiratory fitness. Also, studies in different HF phenotypes are needed in order to evaluate the impact of obesity on these very different manifestations of HF[43]. It is also not completely clear why the obesity paradox is not present in diabetic HF patients[44]. The ESC guidelines seem to reflect this haze around the evidence regarding the obesity paradox. In 2016, weight loss for HF patients below 35 $Kg.m^{-2}$ was not recommended[45], while the 2021 ESC guidelines do not convey specific recommendations regarding weight management of patients with an already established diagnosis of HF[2].

Iron deficiency and anaemia are very common in HF patients and are associated with increased mortality and hospitalisation[46]. Iron deficiency may be caused by impaired iron metabolism due to the chronic inflammatory activation of HF, but also by reduced intake or absorption, or increased loss. Iron deficiency affects skeletal muscle function, hence is associated with functional impairment

and lower exercise capacity[47]. The co-occurrence of anaemia and frailty is prevalent in HF patients (39.3%) and has a negative impact on mortality[48].

Malnutrition is frequently present in HF patients and is associated with worst outcomes, mainly in advanced HF, but is yet to be thoroughly studied[49]. The prevalence of malnutrition in HF may vary between 6% - 60%, depending on the assessment method[50]. In a cohort of 4,021 HF patients, studied by Sze et al., those with malnutrition, evaluated by various scores, had increased mortality when compared with patients with mild malnutrition or normal nutritional status[51].

Frailty and sarcopenia are also important comorbidities of HF which will be addressed over the following sections.

2. Frailty

2.1. Definition

Frailty results from a cumulative decline across multiple physiologic systems, causing a decrease in reserves and a lack of ability to cope with everyday stressors. This state of increased vulnerability contributes to a higher risk of disability, falls, institutionalisation and death[52,53].

The first operationalised definition of frailty was proposed by Linda Fried and collaborators, within the Cardiovascular Health Study, and uses five criteria: weakness as measured by low grip strength, slowness by low walking speed, low level of physical activity, low energy or self-reported exhaustion, and unintentional weight loss. A frail individual presents three or more of the aforementioned criteria, while pre-frailty is classified by the presence of one or two[53].

Despite the Fried et al. operationalisation, frailty still lacks a wide consensus regarding its definition and diagnosis criteria. Some efforts have been attained towards that objective, such as a consensus meeting of six major international societies (International Association of Gerontology and Geriatrics; Society on Sarcopenia, Cachexia, and Wasting Diseases; International Academy of Nutrition and Aging; European Union Geriatric Medicine Society; American Medical Directors Association and American Federation for Aging Research), where the following definition of frailty was suggested: "*a medical syndrome with multiple causes and contributors that is characterized by diminished strength,*

endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death"[54].

2.2. Prevalence

Prevalence of frailty is highly dependent on the assessment method that is chosen to diagnose this syndrome. The most recent data regarding the global prevalence of frailty was based on a meta-analysis published by O'Caoimh et al., that included 240 studies from 62 countries: pooled prevalence of frailty and pre-frailty was 12% and 46%, respectively, when using physical frailty measurements, and 24% and 49% when using the frailty index model[55].

In Portugal, the only data available on frailty was conveyed by the Nutrition UP 65 study, which enrolled 1,500 older adults (≥65 years) representative of the Portuguese older population[56,57]. The frequency of physical frailty and pre-frailty among Portuguese older adults was 21.5% and 54.3%, respectively. Weakness (low HGS) accounted for the most frequent criterion (76.7%), followed by exhaustion[58].

2.3. Pathology

Frailty is characterised by a multisystem dysregulation that leads to a loss of homeostasis and to augmented spending of physiologic reserves. This creates a vicious cycle of functional decline. Chronic inflammation is a crucial mechanism of frailty and may be caused by acute or chronic disease, environmental factors

or genetic factors[59]. The immune activation relies mainly on interleukin-6[60], a pro-inflammatory cytokine, but other molecules, like tumour necrosis factor-α and c-reactive protein, may also play a role in establishing a state of chronic inflammation which affects multiple systems, mainly the musculoskeletal, endocrine, hematologic and cardiovascular[59].

Immune dysfunctions in frail patients are beyond those that are associated with age-senescent immune remodelling. These alterations are present both in the innate and in the adaptive immune systems and include increased number of white blood cells, increased monocyte expression of stress-response genes, increased CD8 T-cells, and decreased ratio of CD4/CD8 T-cells[61].

Dysregulations in the stress response system, namely in the hypothalamic-pituitary-adrenal axis and in diurnal cortisol secretions also seem to be part of the pathophysiology of frailty[62,63], as well as the glucose metabolism, as insulin resistance is associated with increased risk of frailty[64].

Sarcopenia is considered one of the main causes of physical frailty and these conditions share many pathophysiologic features[65]. This will be addressed in the corresponding section, along with some considerations regarding the impairment of the muscle-skeletal system that occurs in sarcopenic and in many frail individuals.

Behavioural maladaptation to changes that occur with ageing can be important precursors to frailty. These changes can be environmental, such as reduction in physical living space, obstacles in the living environment and low social or familial support, or intra-individual, such as increasing disease burden,

need for assistive devices and mental health limitations. The reduction in living space, i.e., the lack of ability to leave home, or to roam around in one's neighbourhood, may lead to a reduction in physical activity and social engagement, which can predispose to frailty[66].

Frailty is indeed a syndrome associated with ageing but can be present in younger adults, such as the critically ill[67–69], patients with chronic or end-stage renal disease[70–72], and patients infected with the human immunodeficiency virus[73–75]. Recently, a study from Hanlon et al., using the UK BIOBANK database, reported a prevalence of physical frailty of 3 – 4% in younger adults aged 37 – 65 years and positive associations between frailty and multimorbidity in those with four or more chronic conditions such as multiple sclerosis, chronic obstructive pulmonary disease, connective tissue disease, and diabetes[76]. This seems to show that some severe acute and chronic states contribute to the heightened vulnerability that is associated with the risk of frailty, even in the absence of the chronologic ageing process.

2.4. Assessment

Two main classes of models to measure frailty have been used throughout the years: the physical frailty model, which centres its operationalisation mostly on biological criteria, and the multidimensional model, which, on top of some physical assessment or biologic measures, uses criteria related to cognitive, psychological and social functions and/or quality of life, among other aspects.

The most recurrently used model for assessing physical frailty is the Fried's phenotype, also known as the frailty phenotype and less frequently referred to as the Cardiovascular Health Study Frailty Screening. Rationale and measurements were thoroughly defined in the aforementioned Fried et al. work from 2001, which was based on a sample of 5,317 older adults (65-101 years)[53]. In a recent review, Fried et al. integrated new evidence towards the confirmation of the frailty phenotype as a clinical syndrome that is distinct from the undermentioned frailty index and other constructs of frailty, such as cognitive, emotional or psychosocial frailty, bringing to the forefront the impairment of physiologic responsiveness and the weakening of interaction between key systems that contributes to the loss of homeostasis[77].

Rockwood and Mitnitsky proposed a model of frailty based on the accumulation of deficits, the Frailty Index, a flexible multidimensional score that can comprise a variable number of measures and thus reflect the individual's proportion of deficits[78,79]. The typical number of deficits to include in the score is 80, although is usual to count around 30-70 deficits[80].

2.4.1. Assessment of the Frailty Phenotype

As previously mentioned, the syndrome of phenotypical frailty, or physical frailty, is characterized by the presentation of three or more of five key clinical symptoms and signs: weakness or low strength; slow walking speed; exhaustion or fatigue; low physical activity and unintentional weight loss.

Low strength is evaluated by hand grip strength (HGS). Fried et al. selected the lowest quintile for defining sex and body mass index specific cut-offs. In women, a low strength was defined as HGS ≤ 17 Kgf for BMI ≤ 23 Kg/m^2, HGS ≤ 18 Kgf for BMI 26.1 – 29 Kg/m^2 and HGS ≤ 21 Kgf for BMI > 29 Kg/m^2. In men, low strength is classified as HGS ≤ 29 Kgf for BMI ≤ 24 Kg/m^2, HGS ≤ 30 Kgf for BMI 24.1 - 28 Kg/m^2 and HGS ≤ 32 Kgf for BMI > 28 Kg/m^2[53].

Slowness can be assessed by measuring usual gait speed (GS), with the lowest quintile serving as a threshold for defining GS by sex and height, based on the time the subjects took to walk 4.6 m at usual gait. Therefore, a slow gait was defined as a time ≥ 6 s for women > 159 cm or men > 173 cm, or as a time ≥ 7 s for women ≤ 159 cm or men ≤ 173 cm[53].

For assessing low physical activity, Fried et al. used the Minnesota Leisure Time Physical Activity Questionnaire[81], but other self-reporting methods that can estimate the energetic expenditure per week may be used. Such is the case of the International Physical Activity Questionnaire, which has the advantages of being a much more recent tool and of being validated for the Portuguese population in either short or long versions[82]. Cut-off points for classifying low physical activity were defined as < 270 Kcal/week for women and < 383 Kcal/week for men[53].

Self-report of exhaustion is done using two questions taken from the Center for Epidemiologic Studies Depression Scale, namely "*I felt that everything I did was an effort*" and "*I could not get going*"[53,83].

Unintentional weight loss is self-reported as the involuntary reduction in weight of at least 4.5Kg over the previous year[53].

2.5. Frailty in Heart Failure

The growing evidence regarding the poor outcomes in HF patients associated with frailty has been granting increased attention by the clinical professionals and researchers. International guidelines for the management of HF have been reflecting this augmented interest while emphasising the importance of the awareness of frailty in the treatment of HF[2,45,84–88].

Indeed, frailty is an independent risk factor for incident HF among older adults[43] and is associated with HF progression, mortality, hospitalisation, readmission and increased utilization of healthcare resources[89–93]. Compared to the non-frail, frail HF patients have an increased hazard for death and hospitalisation by around 1.5 fold[94]. Even pre-frailty, by itself, is a determinant of cardiovascular disease. In a large cohort study by Sergi et al., community-dwelling older adults with 1 or 2 frailty phenotype criteria had higher risks of developing cardiovascular disease, with HF accounting for more than half of the incidents in pre-frail individuals[95].

In analogy to what was described regarding general populations, the prevalence of frailty in HF varies accordingly to the assessment method used and the study setting. In a meta-analysis by Denfeld et al., the global prevalence of frailty was estimated at 44.5%, being lower when only studies using physical frailty were accounted for, and slightly higher when multidimensional models

were used (42.9% vs. 47.4%, respectively). The prevalence of frailty reported in the selected papers for the meta-analysis ranged from 77% in hospitalised patients to 14% in the community[96]. It is estimated that the prevalence of frailty in HF patients is up to six times higher than in the general population[97].

Frailty and HF worsen each other through multiple and complex pathogenic mechanisms that are not fully elucidated yet. These mechanisms include DNA damage, impaired autophagy and mitochondrial dysfunction[98]. The resulting disrupted homeostasis leads to augmented levels of stress hormones and cytokines[99] and to metabolic dysregulations conducting to an overall catabolic state that leads to wasting[100]. Moreover, frailty and HF are both associated with low exercise capacity, which fuels a vicious circle of reciprocal worsening.

Another interesting approach regarding the relations between frailty and HF is the study of the role of the autonomous nervous system in maintaining homeostasis. Augmented sympathetic activation is a common trait in frailty and HF[77,101] and is closely related to cardiovascular performance. In a systematic review by Parvaneh et al., it was discussed that frail individuals present cardiac autonomous nervous system impairments compared to non-frail ones, that are observable in the form of lower responses in heart rate dynamics[102]. Also, a sustained sympathetic activation stimulates the renin-angiotensin-aldosterone axis, which can accelerate muscle wasting through many mechanisms[103], and thus contribute to frailty and sarcopenia.

As previously discussed, frailty can be a result of ageing or can be secondary to a chronic disease such as HF. Goldwater and Pinney postulate that

frailty secondary to HF is a different entity of that of age-related primary frailty, although both share the same pathophysiologic framework of a catabolic state driven by inflammation, oxidative stress, mitochondrial dysfunction and endocrine unbalance. The authors identify subtle differences, such as the higher proportion of fast-twitch glycolytic type II fibres during muscle loss in HF, and that HF patients seem to have a better response to physical exercise compared to frail patients who do not have HF[104].

In a similar way to other chronic or severely acute diseases, frailty can be present in younger HF patients. However, all studies reporting frailty in younger adults are based on samples of end-stage HF patients, such as those undergoing LVAD placement and/or heart transplantation[105–108]. Frailty phenotype in younger ambulatory or non-critical HF patients remains undocumented, as well as possible differences between younger and older HF patients with concomitant frailty or pre-frailty.

2.5.1. Assessing Frailty in Heart Failure

The Heart Failure Association (HFA) of the ESC has recently proposed a new operationalisation of frailty for use in HF settings: the HFA frailty score. This score focus on four main dimensions: clinical; psycho-cognitive; functional and social[97]. This multidimensional tool is yet to be validated.

Denfeld et al. recommend the use of Fried's frailty phenotype to measure physical frailty in HF populations, as it can easily be used across research and clinical practice. Moreover, it is the most widely used measurement of frailty

applied to HF patients[96], allowing for a more uniform comparison with already published works.

3. Sarcopenia

3.1. Definition

The term “sarcopenia” was first proposed by Irwin H. Rosenberg in 1988 to describe the decline of muscle mass with age, through the aggregation of two Greek words, *sarx*, flesh, and *penia*, loss[109]. Later on, in 2010, muscle strength and function were added to the definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP). This consensus group defined sarcopenia as “*a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with risk of adverse outcomes such as physical disability, poor quality of life and death*”[110]. As of 2016, sarcopenia is classified as a muscle disease (M62.84, according to the International Classification of Diseases, Tenth Revision, Clinical Modification)[111].

In 2018, a revised consensus of the European Working Group on Sarcopenia in Older People (EWGSOP2) updated the definition and operationalisation of sarcopenia[112]. This revision was based on recent evidence regarding the predominance of muscle strength in predicting adverse outcomes[113–116]. Therefore, the operational definition of sarcopenia relies on the detection of low muscle strength as a criterion for probable sarcopenia. The diagnosis is confirmed by the presence of low muscle quantity or quality. According to the revised consensus, severe sarcopenia is accounted for when low physical performance is present[112], whereas, in the 2010 consensus, low physical performance was at the core of the definition and diagnosis of sarcopenia[110].

3.2. Prevalence

Notwithstanding to the fact that the EWGSOP2 consensus defines a set of procedures that are thoroughly based on relevant evidence towards the definition and diagnosis of sarcopenia, there is still a lack of standardisation of the methods for measuring sarcopenia. Moreover, as this revised consensus is still recent, most works report epidemiological data on sarcopenia based on the 2010 operationalisation or in other methodologies. Therefore, and similarly to what was previously described regarding frailty, the prevalence of sarcopenia varies broadly as a result of the methods used.

A meta-analysis of prevalence by Shafiee et al., including 58,404 healthy individuals aged ≥ 60 years, is a good testimony of the variation between standards and methods. The selected studies used EWGSOP, International Working Group on Sarcopenia (IWGS) and Asian Working Group for Sarcopenia (AWGS) definitions, which have different cut-off values for muscle mass and function. The overall estimated prevalence of sarcopenia was 10% in both sexes. However, the prevalence was 13% and 8% when bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DEXA) were used to estimate muscle mass, respectively. Moreover, there were inconsistencies between populations when using different methods: in Asian vs. non-Asian men, the prevalence was 10% vs. 19% when using BIA, but when DEXA was used, the reported prevalence was 9% vs. 6%[117]. A joint study by EWGSOP and IWGS reported a prevalence of sarcopenia of 1-29% in community-dwelling populations and of 14-33% in long-term care populations[118].

In Portugal, Sousa-Santos et al. described a frequency of sarcopenia of 11.6% in a cross-sectional sample of 1,500 older adults (mostly community-dwelling), using the EWGSOP criteria and mid-upper arm muscle circumference (MAMC) as an anthropometric estimator of muscle mass[119]. In a following paper on the same sample, the authors reported a frequency of 4.4% using the EWGSOP2 criteria and MAMC and calf circumference (CC) as estimators of muscle mass[120]. These differences between the proportion of sarcopenic individuals classified according to EWGSOP vs. EWGSOP2 are partially in line with a recent study by Van Ancum et al., that found a significant reduction in diagnosed cases in men when the most recent criteria were applied. Contrariwise, women had slightly higher frequencies of sarcopenia when diagnosed according to the EWGSOP2[121].

In Portuguese hospitalised patients, Sousa et al. described a frequency of sarcopenia of 25.3% using the EWGSOP criteria and BIA. Frequencies were much lower, at 7.7%, when using MAMC to estimate muscle mass. Another interesting result of this study was the rather high frequency of sarcopenia in hospitalized younger patients (≤ 65 years), at 18.6%[122].

3.3. Pathology

Sarcopenia occurs physiologically with ageing. After the age of 50 years old, the annual decline in leg muscle mass is around 1 – 2%, with a corresponding reduction in muscle strength of about 1.5 - 5%[123]. This mismatch between loss of mass and strength suggests a decline in muscle quality[124].

There are several factors underlying the onset and progression of sarcopenia. Among others, these mechanisms include genetic and epigenetic aspects[125], anatomical and physiological alterations in the neuromuscular system[126], lower endocrine stimulation of skeletal muscle growth due to age-associated male hypogonadism[127], lower growth hormone and insulin-like growth factor levels[128], abnormal thyroidal regulation[129], insulin resistance[130], anorexia, malnutrition or malabsorption[131–133], endothelial dysfunction[134], low physical activity, immobilization or lack of gravity[135–138], mitochondrial dysfunction[139], cellular apoptosis[140] and chronic inflammation[141].

Sarcopenia can be categorised as primary or age-related, or secondary to a chronic disease[110], such as chronic obstructive pulmonary disease[142], diabetes[143], male hypogonadism[127], chronic kidney disease[144], and heart failure[145].

The mechanisms of primary sarcopenia are mainly related to changes in the myocyte structure and metabolism. With advancing age, there is a reduction of the number and size of type 2 fibres (glycolytic, fast-twitching) while type 1 (slow-twitching) fibres are less affected. The lost muscle tissue is then replaced by fat and connective tissues[146]. This is thought to be caused by age-related denervation of the motor units and a reduced anabolic capacity, due to a decrease in anabolic hormones such as growth hormone, insulin-like growth factor 1 and testosterone. Conversely, there is an increase in catabolic agents, particularly interleukin-6, that further intensifies muscle wasting[147]. A crosstalk between mitochondria dysfunction and cellular senescence in the ageing muscle also plays a role in sarcopenia, along with the aforementioned processes. The

accumulation of mitochondrial DNA mutations with age may result in the synthesis of defective components of the electron transport chain, which leads to the production of radical oxygen species. The resulting oxidative stress further increases DNA, mitochondrial and cellular damages, leading to cellular senescence, which in turn enhances the pro-inflammatory state through the expression of cytokines[148].

Sarcopenic obesity has been commonly defined as the coexistence of sarcopenia with increased adipose tissue[149]. Criteria for defining the component of obesity may vary, but generally, BMI or waist circumference is used[150]. Obesity and sarcopenia may act synergistically towards worsening each other, as both share common pathophysiologic mechanisms, such as sedentary behaviour, insulin resistance, low-grade inflammation and increased oxidative stress. Sarcopenic obesity is generally associated with worst outcomes than sarcopenia or obesity alone[150], such as disability[151,152], osteoporosis and fractures[153], depression[154], and mortality[155].

3.4. Diagnosis

The EWGSOP2 provided for a useful set of guidelines and an algorithm for diagnosing sarcopenia, as well as appropriate cut-points for defining low muscle strength, mass and function[112].

According to the EWGSOP2 algorithm, suspicion of sarcopenia or a score ≥ 4 in the SARC-F questionnaire[156] signalise the risk of having sarcopenia. Assessment of probable sarcopenia is then evaluated measuring muscle

strength, which can be made by HGS or sit-and-stand test. If low muscle strength is detected, sarcopenia is confirmed by the presence of low muscle quantity or quality. Muscle mass can be estimated using BIA, DEXA, computerised tomography (CT) or magnetic resonance imaging (MRI). Severe sarcopenia is then diagnosed if low physical performance is present. This is assessed using gait speed, short physical performance battery (SPPB), time up and go test or 400m walking test[112].

Hand grip strength is the most commonly used method for assessing muscle strength, as it is simple, inexpensive and correlates well with strength in other body compartments. The EWGSOP2 recommends the use of calibrated dynamometers and specifically endorses the Jamar hand dynamometer, as it is validated and widely used for measuring HGS[112]. The recommended cut-off points for HGS result from normative values produced by Dodds et al. and are defined as < 27 Kgf for men and < 16 Kgf for women[157].

The EWGSOP2 recommends using DEXA for measuring muscle quantity in research and in clinical settings, as it provides for a reasonably accurate estimation of body composition and, contrarily to MRI or CT scan, has well defined cut-off values, namely for the quantity of appendicular skeletal muscle mass (ASM)[112,158,159].

The use of anthropometry to estimate muscle mass is not recommended by the EWGSOP and EWGSOP2, except when no other methods are available[110,112], which is frequently the case in most clinical settings. Methods such as MRI, CT and DEXA are extremely costly, time-consuming and demand technical expertise. Also, CT may expose patients to radiation[160,161]. Moreover,

portability may be a great concern in clinical settings[112]. BIA, when performed under standardised conditions, is considered to be a valid alternative to the other methods[110,112,162]. Contrasting evidence regarding both good agreement between DEXA and BIA and misclassification of sarcopenia when these techniques are compared[162,163], support the need for new validated prediction equations of different populations. BIA measurements can also be influenced by hydration status[164] and by abnormal fluid distribution, which is the case for congestive HF patients. Due to this fact, the bioelectrical analysis of the phase angle can be used as a predictor of congestion in HF patients[165]. The risk of interference between BIA and cardiac implantable electronic devices - which are very common in HF patients - has been reported, mainly by manufacturers of BIA apparatus, but no evidence of adverse effects was found so far[166–168]. Also, the presence of cardiac electronic implantable devices does not seem to affect BIA, at least in regard to the phase angle[165]. However, some caution is recommended, as samples used in the safety studies were generally small and not every implantable device or BIA system has been tested.

Anthropometric measurements for estimating muscle quantity and that have been used to diagnose sarcopenia, include the MAMC and the calf circumference. The latter is the elected measurement by the EWGSOP2, in case no other method is available[112]. These methods are extremely simple to perform, do not demand expensive material, can be put to practice on-site and are well accepted by the patients.

Calf circumference has a well-defined cut-off point (≤ 31 cm) that is associated with disability, performance and survival in older adults[169,170]. Mid-

upper arm muscle circumference is an indirect anthropometric measurement. It results from the combination of mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST), using the Jelliffe formula: MAMC = MUAC – (3.14 x TST)[171]. Sex-specific cut-off points for MAMC were proposed by Landi et al., as < 21.1 cm for men and < 19.2 cm for women[172]. The use of MAMC for estimating muscle mass seems to be of particular interest for HF patients as it is performed in a body part that is usually free from oedema[173]. Recently, a Portuguese study including 159 older adults reported that CC and MAMC can be valid measurements to classify sarcopenia when compared with DEXA[162].

Regarding low physical performance, the SPPB is considered the reference method. However, the SPPB is somewhat time-consuming to perform, and the use of a gait speed ≤ 0.8 m/s, which is one of the individual measurements of the SPPB, is used as a more simple but still appropriate and valid alternative[110,112]. Gait speed is, by itself, a good predictor of survival in older adults[174] and is associated with overweight, obesity and undernutrition risk[175].

3.5. Sarcopenia in Heart Failure

Sarcopenia is a leading cause of low physical performance and reduced cardiorespiratory fitness in HF patients[176], and contributes to mortality in older HF patients, irrespective of LVEF[177].

The prevalence of sarcopenia in HF patients can be nearly 20% higher than in healthy individuals[178]. The pooled prevalence of sarcopenia in HF

patients ranges from 55% in hospitalised patients to 26% in community-dwelling ones, with an overall pooled prevalence of 34%[179].

Heart failure can promote the development of sarcopenia through multiple pathophysiological mechanisms. Interestingly, many of the mechanisms that characterise HF are shared with sarcopenia, such as physical inactivity, malnutrition, malabsorption, inflammation, endothelial dysfunctions, endocrine dysfunctions, oxidative stress and apoptosis[180].

The mechanisms that contribute to the myocardial remodelling are an elucidative example of the shared pathophysiology between sarcopenia and HF, namely through mitochondrial dysfunction. In HF patients, the unbalance in metabolic and neuro-hormonal homeostasis poses greater demands in mitochondrial phosphorylation, with the consequent increase in the production of reactive oxygen species that damage mitochondrial DNA, proteins and lipids and leads to further production of oxygen radicals. This causes cellular damage in the myocytes, which include hypertrophy, apoptosis, and interstitial fibrosis[181].

Sarcopenia and cachexia are often confounded. Both share some pathophysiologic features but are distinct conditions. Cachexic patients present a different inflammatory profile, with higher levels of cytokines and elevated levels of pro-catabolic hormones, which result in a metabolic unbalance affecting not only muscle mass but also fat and bone mass[182]. Cachexia is a serious metabolic syndrome consequential to chronic illnesses such as cancer, end-stage renal disease, chronic obstructive pulmonary disease, neurological disease or rheumatoid arthritis[100]. Prevalence of cachexia in end-stage HF patients ranges from 5% to 15%[183], and is associated with very poor outcomes, including

an elevated mortality risk[184], lower quality of life and more severe symptoms[185] and increased lengths of hospital stay with elevated financial costs[186].

4. Hand Grip Strength

As previously mentioned, HGS is central to the diagnosis of sarcopenia and the assessment of physical frailty. Moreover, HGS has been gaining recognition as a biomarker for ageing[187], an indicator of nutritional status[188] and an end-point for treatments destined at patients with cardiovascular diseases[189].

Low muscle strength, measured by HGS, is indeed a preponderant measure for ascertaining the risk of developing frailty, as it is the most frequent first manifestation of this syndrome[190]. Low HGS is also associated with recurrent falls[116], increased risk of osteoporosis and fractures[191], coronary heart disease and stroke[192], reduced quality of life[193] and all-cause mortality[113,194].

The recent evidence regarding the independent associations of HGS with HF outcomes puts this useful measure at the forefront of the functional evaluation of HF patients: a meta-analysis conducted by Pavasini et al. concluded that low HGS predicted all-cause death, cardiac death and hospitalisation in HF patients[195]. Moreover, HGS is associated with HF incidence[196,197].

An interesting example of the use of HGS as a therapeutic end-point in HF patients comes from a prospective cohort study by Warriner et al., who showed that a positive response to cardiac resynchronisation therapy was significantly associated with gains in HGS[198]. Chung et al. found an association between low HGS and worst outcomes in HF patients that underwent LVAD placement[108]. Also, when combined with cognitive assessment, HGS predicted lower readmission of HF patients[199]. In a cohort of Brazilian decompensated HF

patients, HGS was a good indicator of malnutrition and was able to predict mortality[200].

A recent prospective cohort study, using UK Biobank data on 4,654 patients, showed an association between higher HGS and lower cardiac hypertrophy and remodelling, which are associated with worse cardiovascular outcomes[201]. This seems to demonstrate that the mechanisms promoting both cardiac and skeletal muscle dysfunction may be closely related.

Despite all these relevant advances concerning the predictive significance of HGS in HF patients, studies regarding the association of this muscle strength indicator with other variables such as LVEF and NYHA classes are still rare and HGS values remain undocumented in Portuguese HF patients.

Aims

Aims

The present work aims at:

1. Studying the frailty phenotype in Portuguese HF patients (Chapter 1), namely:
    1.1. Describing frailty phenotype in Portuguese HF outpatients, its frequency and associated nutritional, clinical and functional factors (Chapter 1.a.);
    1.2. Describing differences between younger (< 65 years) and older frail and pre-frail HF patients and factors associated with the age differences (Chapter 1.b.);
2. Studying sarcopenia in Portuguese HF patients (Chapter 2), namely:
    2.1. Describing the frequency of sarcopenia, severe sarcopenia and sarcopenic obesity;
    2.2. Describing the associations between clinical and nutritional statuses of HF patients and sarcopenia;
    2.3. Exploring the association of the use of statins with sarcopenia.
3. Studying the coexistence of frailty and sarcopenia in HF patients (Chapter 3), namely:
    3.1. Describing the frequency of the overlapping between frailty and sarcopenia;
    3.2. Studying the association of clinical and nutritional factors with the growing degree of accumulation of frailty and sarcopenia.
4. Studying the association between hand grip strength and clinical, nutritional and physical activity variables in HF patients (Chapter 4).

Included Papers

Included Papers

The following papers this dissertation was based upon are presented within the next chapters:

1. Valdiviesso R, Azevedo LF, Moreira E, Ataíde R, Martins S, Fernandes L, Silva-Cardoso J, Borges N. Frailty phenotype and associated nutritional factors in a sample of Portuguese heart failure outpatients. Nutr Metab Cardiovasc Dis. 2021 Jul 22;31(8):2391-2397.

2. Valdiviesso R, Moreira E, Martins S, Azevedo LF, Ataíde R, Fernandes L, Silva-Cardoso J, Borges N. Frailty phenotype in heart failure: a condition that transcends age [*submitted for publication*].

3. Valdiviesso R, Sousa-Santos AR, Azevedo LF, Moreira E, Amaral TF, Silva-Cardoso J, Borges N. Statins are associated with reduced likelihood of sarcopenia in a sample of heart failure outpatients [*submitted for publication*].

4. Valdiviesso R, Amaral TF, Moreira E, Sousa-Santos AR, Fernandes M, Aguiar MJV, Martins S, Azevedo LF, Fernandes L, Silva-Cardoso J, Borges N. The associations between medicine use and ejection fraction with the coexistence of frailty and sarcopenia in a sample of Portuguese heart failure outpatients [*submitted for publication*].

5. Valdiviesso R, Aguiar MJV, Azevedo LF, Fernandes M, Moreira E, Sousa-Santos AR, Amaral TF, Azevedo LF, Silva-Cardoso J, Borges N. Hand grip strength cross-sectional association with clinical, nutritional, and physical activity variables in heart failure outpatients [*submitted for publication*].

Paper 1 is presented as published. Papers 2-5 are depicted as facsimiles of the submitted manuscripts. The first author collaborated in the definition of objectives, in the study design, in defining the protocol and in the collection of data; was responsible for the organisation, analysis and interpretation of data, for the definition of specific objectives for each paper and the drafting of the original versions of the manuscripts; participated in the subsequent revision of the papers.

Chapter 1. - Frailty

Chapter 1.a.

Frailty phenotype and associated nutritional factors in a sample of Portuguese heart failure outpatients.

Valdiviesso R, Azevedo LF, Moreira E, Ataíde R, Martins S, Fernandes L, Silva-Cardoso J, Borges N.

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Frailty phenotype and associated nutritional factors in a sample of Portuguese outpatients with heart failure

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KEYWORDS
Frailty phenotype;
Heart failure;
Nutritional status;
Muscle mass;
Obesity

Abstract *Background and aim:* Frailty phenotype (FP) is very common in heart failure (HF) and both syndromes worsen one another. The aim of this study is to first describe FP in a sample of Portuguese patients with HF, and to analyse its association with nutritional and clinical statuses, namely, muscle mass, obesity and functional class.
Methods and results: In this cross-sectional study, a sample of 136 outpatients with HF (24–81 years, 33.8% women) were randomly selected from the appointments' listings of a HF and Transplant clinic in a Portuguese University Hospital. FP was assessed according to Fried et al. muscle mass was estimated from the mid-upper arm muscle circumference; weight status was assessed using the body mass index; HF functional classes were registered. The association between participants' characteristics and FP categories was analysed using logistic ordinal regression. The frequency of pre-frailty and frailty is 57.4% and 15.4%, respectively. Within frail individuals, 52.4% were under the age of 65. In multivariable analysis, frailty was positively associated with age 70 or older (OR = 3.44) and obesity (OR = 2.66), and negatively associated with muscle mass (OR = 0.77) and HF functional classes I (OR = 0.14) or II (OR = 0.29).
Conclusion: Muscle mass seems to be an important predictor of frailty in patients with HF and should be taken into account when designing intervention plans that allow for reverting or modifying frailty and pre-frailty. Younger patients should be monitored for the presence and evolution of FP.

Abbreviations: HF, Heart Failure; FP, Frailty Phenotype; NYHA, New York Heart Association; LVEF, Left-Ventricular Ejection Fraction; HGS, Hand Grip Strength; BMI, Body Mass Index; GS, Gait Speed; IPAQ-SF, International Physical Activity Questionnaire – Short Form; MET-min, Metabolic Equivalents of Tasks per minute; MAMC, Mid-upper Arm Muscle Circumference; MUAC, Mid-upper Arm Circumference; TST, Triceps Skinfold Thickness; LVAD, Left Ventricular Assist Device.

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Introduction

Frailty phenotype (FP) is a clinical recognisable state of increased vulnerability, very common in older adults, mainly due to the decline of function and reserve across multiple physiologic systems, compromising the ability to cope with everyday stressors [1]. It was described for the first time by Linda Fried and collaborators as a meeting of three of more of the following phenotypical criteria: low handgrip strength, or weakness; slow gait speed (GS); lack of physical activity; low energy, or exhaustion and unintentional weight loss [2]. Most of what is known about frailty in Portugal results from the Nutrition UP 65 study (n = 1500, ≥65 years): the frequency of pre-frailty and frailty is 54.3% and 21.5%, respectively, with weakness being the most frequent criterion (76.7%), followed by exhaustion (48.6%) [3].

FP is extremely common in patients with Heart Failure (HF) and portends a worse prognosis. The two syndromes worsen one another via complex molecular and cellular mechanisms which are not fully understood but include increased levels of stress hormones and cytokines [4]. FP and HF also share cellular senescence, increased oxidative stress, reduced autophagy or mitophagy, increased DNA damage, or mitochondrial dysfunction [5]. Additionally, both conditions may be associated due to common biological mechanisms that conduct to a state of catabolic imbalance and muscle inflammation, leading to the loss of muscle mass [6].

Several studies demonstrated that frailty is associated with increased utilization of healthcare resources by patients with HF [7] and with HF progression, mortality and hospital readmission [8–10]. Prevalence of frailty in patients with HF ranges from 14% in the community to 77% in hospitalized patients, with an overall prevalence estimation of 44.5% [11].

The objective of this cross-sectional study is to first describe FP in a sample of Portuguese HF outpatients, and its associations with nutritional and clinical statuses, namely, obesity, estimated muscle mass, and HF functional class.

Methods

This study was implemented between September 2017 and July 2018, in a HF Clinic at a University Hospital in northern Portugal.

Defined inclusion criteria were having a clinical validated diagnosis of HF according to the European Society of Cardiology [12] and age 18 years or older. Patients were excluded if they were not able to communicate in the Portuguese language or with severe visual acuity deficit. Patients at New York Heart Association (NYHA) functional class IV were also excluded, as the severity of their symptoms would hamper their participation in the demanding multidisciplinary data collection activities programmed. Patients meeting inclusion and exclusion criteria were randomly selected from the outpatient list and invited to participate in the study during the appointment with the cardiologist. Those who agreed were invited to sign an informed consent and to participate in the study protocol evaluation.

This cross-sectional study uses data from the DeM Project (Symbiotic technology for societal efficiency gains: Deus ex Machina), further studied within the AdHeart Project (Engage with your heart: Improving therapeutic adherence with a telemonitoring system for patients with chronic HF).

Sociodemographic data were collected regarding sex, age, education, family income, marital and professional status.

Clinical data were collected during an appointment with the cardiologist and medical records were reviewed. The collected information included HF aetiology, incidental stroke, presence of atrial fibrillation, systolic and diastolic blood pressures, functional classification according to the NYHA [13], left-ventricular ejection fraction (LVEF) percentage, medication, smoking habits and diabetes.

Frailty phenotype, as described by Fried et al. [2], was assessed through the presence of three or more of the following criteria: weakness [low muscle strength evaluated by hand grip strength (HGS), adjusted for sex and body mass index (BMI)]; slowness (GS, adjusted for sex and standing height); physical activity (low expenditure of energy per week, adjusted for sex); non-intentional weight loss in the last year; exhaustion (poor endurance, evaluated by self-report). Pre-frail individuals are classified through the presence of one or two of the described criteria.

HGS was measured according to the instructions of the American Society of Hand Therapists [14], using a calibrated hand dynamometer (Jamar Plus+, Sammons Preston, Bolingbrook, IL, USA) with 0,1kgf resolution. Physical activity was assessed using the International Physical Activity Questionnaire – Short Form (IPAQ-SF), validated for the Portuguese population [15]. Data collected within the IPAQ-SF were converted into metabolic equivalents of tasks per minute (MET-min), as described elsewhere [16], and cut-offs were defined according to Fried et al. [2]. Exhaustion was assessed using two questions taken from the Center for Epidemiologic Studies Depression Scale [17], namely, "I felt that everything I did was an effort" and "I could not get going". GS was measured regarding the time participants take to walk 4.6 m, adjusted for sex and height [2]. Patients who were not able to perform the walking test were considered positive. Finally, non-intentional weight loss was assessed by self-report of losing 4.5 kg or more over the past year [2].

Assessment of participants' nutritional status encompassed the collection of the following anthropometric data, according to standard procedures [18]: standing height, obtained with a calibrated stadiometer (Seca 213, Hamburg, Germany) with 0.1 cm resolution; body weight, measured with a calibrated electronic scale (Seca 803, Hamburg, Germany) with 0.1 kg resolution, with the participants wearing light clothes, and mid-upper arm, calf, waist and gluteal girths, measured with a metal tape (Lufkin W606PM, Sparks, Maryland, USA), with 0.1 cm resolution. BMI was calculated using the standard formula [body weight (kg)/stature^2(m)], and categorized using the World Health Organization criteria [19]. Muscle mass was estimated using mid-arm muscle circumference (MAMC), calculated from mid-upper arm circumference (MUAC) and triceps skinfold thickness

(TST) using the following formula [20]: MAMC = MUAC-(3.14 x TST). TST was measured using a calibrated Holtain skinfold calliper (Tanner/Whitehouse, Pembrokeshire, United Kingdom), with a 0.2 mm resolution.

Anthropometric data were collected by a registered nutritionist. Prior to the collection, a technical error of measurement study was conducted for all anthropometric measurements, with average intra-observer and inter-observer errors of 0.6% and 1.4%, respectively.

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the University Hospital Centre in which the study was implemented. All participants signed an informed consent form.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 24 (SPSS, Inc., an IBM Company, Chicago, IL). Descriptive analyses were conducted to show the characteristics of the study sample according to the categories of FP. The distribution of quantitative variables was assessed using the Shapiro–Wilk normality test. Parametric and non-parametric tests were conducted, and the results are presented as mean (M) and standard deviation (SD) for normal data and median (Md) and lower and upper quartiles for non-normal data. For categorical variables, the results are expressed as the number of participants (percentage). Categorical data were compared using the chi-square test or Fisher's exact test as adequate.

Ordinal logistic regression models were carried out with the three categories of FP as dependent variable: "Normal", "Pre-Frail" and "Frail" (reference category). Predictors in the model included age, categorized as $< \geq$ 70 years (reference $<$ 70), NYHA classes I to III (reference NYHA class III), BMI, categorized as obese ($\geq$30 kg.m^{-2}) and non-obese (reference), and quantitative MAMC.

With these models, we intended to study the associations between FP categories and: body composition, including muscular mass and the presence of obesity; HF severity of symptoms and tolerance to physical activity using NYHA classes; and age, namely, the associative effects concerning the oldest ($\geq$70 years) participants.

Three different proportional odds models were computed (women, men, and all) and the results are expressed as cumulative odds ratios (OR) and respective 95% confidence intervals (CI). The assumption of proportional odds (parallel lines) was tested in all ordinal logistic regression models. 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 $p < 0.050$.

Results

Overall, 139 patients were enrolled in the study. A total of 3 patients were excluded due to incomplete data and 136 participated in the full protocol evaluation. Participants' main characteristics are presented in Table 1. Age ranged from 24 to 81 years and the median age was 59.0 (lower quartile: 49.0; upper quartile: 68.0) years. Women represented 33.8% of the sample. Regarding frailty status, 78 (57.4%) were classified as pre-frail and 21 (15.4%) as frail, with the most relevant frailty criterion within frail individuals being exhaustion (90.5%), followed by low physical activity (81.0%). Figure 1 depicts the distribution of the percentage of frail and pre-frail individuals according to each FP criterion.

The results of the ordinal regression models are presented in Table 2. Women with 70 years or older had higher odds of being allocated in higher FP categories. Men at NYHA class 1 and obese had higher odds of being classified from normal towards frailty. Both men and women had diminishing odds of being allocated in higher FP categories with every unit increase of MAMC. The overall model presented significant associations for all parameters.

Discussion

One of the most interesting findings of this study is the rather high prevalence of frailty on younger patients with HF, at 8.1% below 65 years old. This frequency is, in fact, higher than that for the oldest participants, at 7.4%.

FP in non-elderly patients has been scarcely studied, and the exceptions are the critically ill, such as those admitted as surgical emergencies [21,22], to intensive care units [23] or suffering from chronic kidney disease [24–26]. The same exceptions seem to apply to studies that include younger HF samples: Jha et al. focussed on patients with advanced HF referred for heart transplantation (n = 120, aged 53 ± 12 years, 32.5% frail), with nearly 90% of the frail individuals in NYHA class IV [27]; in another work, Jha et al. studied the addition of cognitive assessment to Fried's FP in order to improve the predictive validity of frailty for mortality in patients referred for heart transplantation (n = 156, aged 53 ± 13 years, 33% frail) [28]; Joseph et al. studied the association between frailty and cardiac surgery adverse events in end-stage patients with HF undergoing left ventricular assist device (LVAD) placement (n = 75, aged 58 ± 12 years, 59% frail) [29]; Chung et al. used HGS, and not Fried's FP, as a marker of frailty in patients with HF also undergoing LVAD placement (n = 72, aged 59 ± 2 years), with low HGS associated with higher post-operative complication rates and increased risk of mortality after device implantation [30]. Therefore, the focus on FP in HF younger patients seems to be exclusively centred on the critically ill, in whom frailty is indeed much more apparent. As FP has always been considered a geriatric syndrome, the non-elderly community dwelling patients with HF could be overlooked. This may contribute to worse HF outcomes and deserves further research. This particularity of the study should be noted when comparing the discussed data with other works on frailty and HF, as they are mostly based on subjects over at least 60 years old.

In this study, we did not find a bivariate association between ordinal age and FP. This is in line with a systematic

Table 1 Characteristics of participants according to FP categories.

Characteristics	Normal (n = 37)	Pre-frail (n = 78)	Frail (n = 21)	*p*-value
Age, years	55 [44.0, 64.0]	60 [50.8, 68.3]	64 [49.5, 71.5]	0.060
Age categories				0.020
<70 years	34 (91.9)	65 (83.3)	13 (61.9)	
≥70 years	3 (8.1)	13 (16.7)	8 (38.1)	
Female	8 (21.6)	25 (32.1)	13 (61.9)	0.007
School years	9 [4.0, 12.0]	9 [4.0, 12.0]	4 [4.0, 9.0]	0.073
Family Income				0.019
<1000€	20 (57.1)	24 (32.4)	12 (57.1)	
≥1000€	15 (42.9)	50 (67.6)	9 (42.9)	
Professional status				0.010
Inactive	17 (45.9)	47 (60.3)	18 (85.7)	
Active	20 (54.1)	31 (39.7)	3 (14.3)	
Marital status				0.151
Married or common law union	24 (64.9)	61 (78.2)	18 (85.7)	
Single, divorced or widower	13 (35.1)	17 (21.8)	3 (14.3)	
HF Aetiology				0.001
Dilated cardiomyopathy	24 (64.9)	42 (56.0)	6 (31.6)	
Ischaemic	8 (21.6)	27 (36.0)	3 (15.8)	
Myocarditis	2 (5.4)	2 (2.7)	1 (5.3)	
Hypertrophic	1 (2.7)	2 (2.7)	6 (31.6)	
Others	2 (5.4)	2 (2.7)	3 (15.8)	
LVEF, %	37.9 ± 13.2	37.0 ± 13.0	41.2 ± 18.0	0.529
LVEF categories				0.333
Reduced LVEF (<40%)	18 (48.6)	40 (52.6)	8 (40.0)	
Intermediate LVEF (40–49%)	10 (27.0)	23 (30.3)	4 (20.0)	
Preserved LVEF (≥50%)	9 (24.3)	13 (17.1)	8 (40.0)	
NYHA classification				0.002
Class I	20 (54.1)	25 (32.9)	2 (9.5)	
Class II	15 (40.5)	39 (51.3)	11 (52.5)	
Class III	2 (5.4)	12 (15.8)	8 (38.1)	
Incidental stroke	8 (21.6)	21 (27.6)	3 (15.0)	0.461
Atrial fibrillation	1 (2.8)	12 (16.2)	6 (28.6)	0.015
Systolic BP, mmHg	115 [107.5, 126.5]	113 [106.5, 131.0]	114 [100.0, 127.0]	0.738
Diastolic BP, mmHg	69 [64.5, 73.5]	67 [60.0, 74.0]	60 [56.5, 70.5]	0.032
Diabetes mellitus	5 (13.5)	29 (37.7)	5 (23.8)	0.025
Polypharmacy (≥5 medicines/day)	22 (59.5)	62 (80.5)	17 (81.0)	0.059
Smoking habits (past and present)	13 (38.2)	32 (41.6)	4 (19.0)	0.165
Sitting time, min/day	180 [85.0, 330.0]	270 [150.0, 480.0]	270 [120.0, 480.0]	0.019
Weight, Kg	82.6 [74.2, 91.7]	76.8 [69.7, 84.9]	76.1 [62.5, 84.2]	0.076
Standing height, cm	168.9 ± 9.1	163.8 ± 8.9	159.5 ± 12.5	0.001
BMI, $Kg.m^{-2}$	29.2 ± 4.1	29.2 ± 4.5	29.5 ± 4.2	0.953
BMI classes				0.698
Underweight + Normal	6 (16.2)	15 (19.2)	4 (19.0)	
Overweight	19 (51.4)	29 (37.2)	8 (38.1)	
Obese	12 (32.4)	34 (43.6)	9 (42.9)	
Mid-upper arm circumference, cm	31.7 ± 2.9	30.5 ± 3.5	30.0 ± 3.5	0.119
Waist circumference, cm	98.2 ± 10.5	97.0 ± 12.9	95.2 ± 12.2	0.666
Hip circumference, cm	101.9 [97.8, 104.8]	101.1 [95.8, 106.8]	102.5 [95.5, 110.1]	0.907
Waist-to-hip ratio	0.96 ± 0.07	0.95 ± 0.10	0.92 ± 0.10	0.314
Calf circumference, cm	38.1 ± 3.2	37.5 ± 2.9	36.5 ± 3.6	0.123
Triceps Skinfold, mm	14.2 [10.3, 19.1]	16.2 [11.6, 23.5]	19.0 [14.2, 26.8]	0.014
MAMC, cm	27.0 ± 3.1	24.9 ± 3.2	23.5 ± 3.2	0.000

Categorical values are number (percentage) of patients; continuous values with normal distribution are Mean ± SD; continuous values with non-normal distribution are Median [lower quartile, upper quartile]. LVEF = Left Ventricular Ejection Fraction; NYHA = New York Heart Association functional classes; BP = Blood Pressure; BMI = Body Mass Index; MAMC = Mid Arm Muscle Circumference. Missing values: aetiology (n = 131); LVEF (n = 133); NYHA (n = 134); Atrial fibrillation (n = 131); Blood Pressure (n = 135); Diabetes mellitus (n = 135); Polypharmacy (n = 135); Smoking habits (n = 132).

review by Denfeld et al. [11]. It is known, however, that FP prevalence increases with age [5,31], thus being expectable that older patients with HF would be at higher odds of being frail. This was confirmed in our multivariable analysis for the 70 years or older women but not for men.

Obesity is usually viewed as a protector factor in terms of mortality in HP patients, a phenomenon which is known as the obesity paradox [32]. Our sample shows a direct association between obesity and the participants' odds of being allocated into higher FP categories, which raises questions

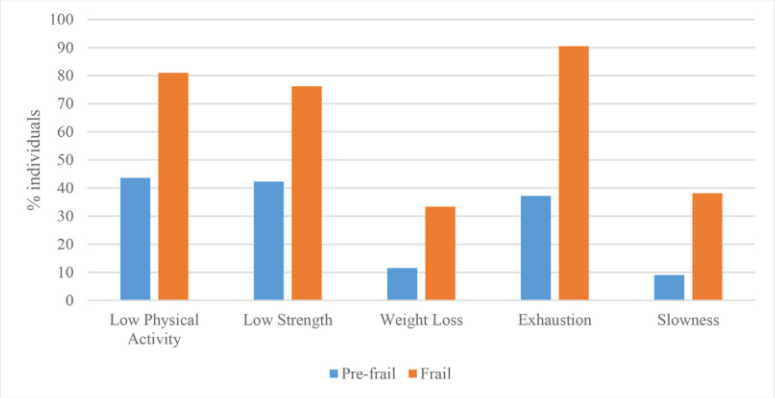

Figure 1 Percentage of individuals for each FP criterion within pre-frail and frail individuals.

Table 2 Results from the ordinal logistic regression analysis (proportional odds model) regarding FP ordinal categories [Normal, Pre-frail, Frail (reference category)].

	Women (n = 46)		Men (n = 90)		All (n = 136)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age						
<70 years	1		1		1	
≥70 years	16.85 (2.89–98.07)	0.002	1.26 (0.34–4.58)	0.729	3.44 (1.33–8.88)	0.011
NYHA functional classes						
Class III	1		1		1	
Class II	0.27 (0.05–1.31)	0.104	0.28 (0.06–1.20)	0.087	0.29 (0.11–0.80)	0.016
Class I	0.45 (0.07–3.04)	0.415	0.07 (0.02–0.33)	<0.001	0.14 (0.05–0.41)	<0.001
BMI						
<30 Kg.m^{-2}	1		1		1	
≥30 Kg.m^{-2}	3.77 (0.88–16.20)	0.074	3.62 (1.15–11.39)	0.028	2.66 (1.22–5.78)	0.014
MAMC (cm)	0.71 (0.53–0.96)	0.029	0.67 (0.53–0.83)	<0.001	0.77 (0.68–0.87)	<0.001

OR = Cumulative Odds Ratio; CI = Confidence Intervals; NYHA = New York Heart Association; BMI = Body Mass Index; MAMC = Mid Arm Muscle Circumference. Missing data regarding NYHA classes (n = 2): respondents were included in the reference category. Test of parallel lines to check the proportional odds assumption for each model: women $p = 0.882$; men $p = 0.453$; all $p = 0.924$.

regarding the role of frailty on the obesity paradox, considering frailty is an independent risk factor for HF mortality [10]. However, classifying obesity and overweight using BMI might unreliably predict adiposity in patients with HF and may better depict lean mass [33], which might be part of a reasonable explanation for the obesity paradox [34].

In this sample, patients with higher estimated muscle mass are less prone to be frail: for every unit increase in MAMC, the odds of being allocated in a higher FP category decreased in both genders. This expectable association could be related with the mechanisms that, in HF, conduct to a state of catabolic imbalance, mitochondrial dysfunction and muscle inflammation leading to the loss of muscle mass thus concurring to the installation of frailty [6]. The occurrence of low muscle mass, which is associated with various HF co-morbidities [35], becomes more worrying when we observe the frequency of participants from this study that were classified as weak by low HGS (36.0%, 76.2% within frail individuals). Considering this loss on muscle mass and function, we should admit the presence of sarcopenia in this sample, which is worth evaluating on further research.

HGS is, by itself, deemed as a useful outcome predictor in HF, being associated with incidence [36], hospitalization [37] and mortality [38].

In our study, slowness was not a frequent frailty criterion. This might be due to the rather young and active sample. In fact, GS seems to play a more important role on older patients with HF, being positively associated with death and hospitalization [39]. Exhaustion was the most frequent criterion. This is understandable, taking into account that exhaustion is a defining symptom in HF [40].

Contrary to that described by Denfeld et al. [11], in this sample, FP is positively associated with NYHA functional class. This is strongly observed in men but not in women. This result deserves further investigation.

This study has limitations. First, the cross-sectional design provides associative, not causal evidence. Second, we were not able to use methods of body composition assessment other than anthropometric ones. Methods such

as bioelectrical impedance analysis, dual energy X-ray absorptiometry, computed tomography and magnetic resonance imaging, as they may be more accurate to assess body composition, are not readily available, are time-consuming and expensive, require technical expertise and may expose patients to radiation [41,42]. However, the use of upper-arm anthropometry allowed us to estimate muscle mass, with the added advantages of being a simple and non-invasive method, performed in a body part that is usually free from oedema [43,44]. Moreover, measurements were performed by the same trained registered nutritionist, to avoid intra-observer error. Despite the described limitations, this article is, to our knowledge, the first in Portugal to describe frailty in patients with HF, in relation to their nutritional status, and may provide valuable insight for further research.

In conclusion, muscle mass seems to be an important predictor of FP in patients with HF and should be taken into account when designing intervention plans that allow for reverting or modifying frailty and pre-frailty. The onset of FP in younger patients with HF and the association of FP with NYHA classes deserve further research.

Declaration of competing interest

The authors have nothing to disclose.

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Chapter 1.b.

Frailty phenotype in heart failure: a condition that transcends age

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Abstract

Introduction and objectives: Studies on younger frail and pre-frail subjects suffering from heart failure are scarce, exception made to the critically ill. This work aims to describe differences between younger (<65 years) and older (≥65 years) pre-frail and frail heart failure outpatients in regard to their nutritional, functional and clinical statuses.
Methods: In this cross-sectional study, a sample of 99 heart failure frail and pre-frail patients (aged 24-81 years, 38.4% women, 21.2% frail, 59.6% < 65 years) was recruited from a 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. Association between participants' characteristics and age was calculated using binary logistic regression.
Results: Younger 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.
Conclusion: There is an overall lack of differentiation between younger and older heart failure patients with frailty phenotype, hence 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 heart failure populations.

Keywords: Heart Failure; Frailty Phenotype; Hand Grip Strength; Gait Speed; Type 2 Diabetes Mellitus

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.

Palavras-chave: Insuficiência Cardíaca; Fenótipo de Fragilidade; Força de Preensão da Mão; Velocidade da Marcha; Diabetes Mellitus tipo 2.

Introduction

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 nonelderly, 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]. The same applies to 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 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 of frailty, associated with worst outcomes after device implantation [13].

Studies regarding younger HF patients with FP are scarce, exceptions made to the critically ill. More studies focusing on these patients are needed in order to contribute to the improvement of their health care 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, in respect to 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 a 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 at 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 was collected by a cardiologist during the appointment and medical records were reviewed. Data included HF aetiology, 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 5 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 x TST).

Frailty was classified according to Fried et al. [15], as the presence of three or more of the following criteria: weakness, assessed using Hand Grip Strength (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 the purpose of 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 Centre 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 ≥ 65 years). Distribution of quantitative variables was assessed using Shapiro-Wilk normality test. Quantitative data was associated using parametric and non-parametric tests and categorical data was compared using 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 (CI) were calculated as measures of association in models with age categories as dependent variables: <65 years old and ≥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; 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 3 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 amount to 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 comprise 78.8% and 21.2% of the sample, respectively, and 59.6% of the sample is younger than 65 years.

Regarding the overall sample, apart from the expected differences in school attendance and professional activity, older (≥65 years) and younger (<65 years) pre-frail and frail patients were rather similar in sociodemographic, clinical and nutritional characteristics. Notable differences regard 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 maintain the same pattern as the overall sample regarding significant age differences.

When observing frail individuals separately, there were no differences between younger and older patients, with the exceptions of 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, as per 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; $p = 0.060$).

GSAH 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 in women or men.

Table 1. Characteristics of participants according to age categories

	Overall (n=99)			**Pre-frail** (n=78)			**Frail** (n=21)		
Characteristics	**<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 Aetiology			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)	
Ischaemic	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
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. HF = Heart Failure; NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; BMI = Body Mass Index; MUAC = Mid-upper Arm Circumference; MAMC = Mid-upper Arm Muscle Circumference; HGS = Hand Grip Strength; GSAH = Gait Speed Adjusted for Height. Missing values: Family income = 4; Aetiology = 5; LVEF = 3; NYHA classes = 2; Incidental Stroke = 3; Atrial fibrillation = 4.

Table 2. Distribution of positive FP 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).

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

HGS= Hand Grip Strenght; GSAH=Gait Speed Adjusted for Height; MAMC=Mid-upper Arm Muscle Circumference; BMI=Body Mass Index; NYHA=New York Heart Association.

Discussion

The most interesting results from the present study regard a general lack of significant effect of age on various characteristics in HF patients with FP. Taking into consideration that our study portrays a wide range of ages and nearly 60% of participants are 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 is 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 ageing and disease. Evidence towards the use of HGS as a biomarker for ageing has been growing [22,23], such as its use as an outcome predictor of HF, being associated with incidence, hospitalization, readmission and mortality [13,24–26].

HGS was the most consistent predictor for age differences in this sample. Also, low HGS as defined by Fried at al., is already present in a third of the younger participants. These results show that the 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 on 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 personalised 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 gait speed are associated with reduced risks of death and readmission in older acute HF patients [28]. In the present study, lower gait speed was associated with older age, which is expectable. 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 attribute to the fact that this sample is formed by 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 hand grip strength and gait speed to define and assess sarcopenia, with many consortium members agreeing that dual-energy x-ray absorptiometry (DEXA) derived 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 coexists 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, prevalence of T2DM is 18.8% in individuals without FP, 24.5% in pre-frail and 32.4% in frail [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].

T2DM 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 is 34.3%, being particularly higher in the pre-frail than in frail participants (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 ageing, diabetes, frailty and heart failure deserve further study. Nonetheless, our results might indicate a need for a better glycaemic control on younger pre-frail and frail HF patients in order to prevent or mitigate T2DM at older ages.

HF 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 tend to be similar in terms of the severity of symptoms and the level of tolerance to physical activity.

Primary vs. Secondary FP

Frailty phenotype is associated with both advanced age and HF. Goldwater and Pinney discuss the possibility that secondary FP, related with HF, is a separate entity to that of primary FP, associated with advanced age, albeit both share the propensity to a catabolic state fuelled 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 higher percentage of fast-twitch glycolytic type II fibres, and HF frail patients seem to have a better response to physical therapy as 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 ageing, frailty seems to be a process of accelerated ageing associated with chronic diseases such as HF [36], thus disputing the utility of taking a 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, thus not allowing for causal associations. Secondly, the sample is rather small; this effect is particularly felt on 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, only estimated and indirect measures of body composition were used, such as 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 in order to avoid inter-observer errors.

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 broaden 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 hand grip strength 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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Disclosures

The Authors declare that there is no conflict of interest.

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Chapter 2 - Sarcopenia

Statins are associated with reduced likelihood of sarcopenia in a sample of heart failure outpatients

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Title

Statins are associated with reduced likelihood of sarcopenia in a sample of heart failure outpatients

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List of Acronyms (in alphabetical order)

BMI: Body Mass Index
EWGSOP2: European Working Group on Sarcopenia in Older People 2
HCM: Hypertrophic Cardiomyopathy
HF: Heart Failure
LVEF: Left-Ventricular Ejection Fraction
MAMC: Mid-upper Arm Muscle Circumference
MUAC: Mid-Upper Arm Circumference
NYHA: New York Heart Association
TST: Triceps Skinfold Thickness

Abstract

Background and aim: Sarcopenia is prevalent in heart failure (HF) patients, contributing to its poor prognosis. Statin use is postulated as a probable risk for developing sarcopenia, but little is known regarding this association in HF patients. This work aims at classifying and characterising sarcopenia and at describing the association of statin use with sarcopenia in a sample of Portuguese HF outpatients.

Methods and results: In this cross-sectional study, a sample of 136 HF patients (median age: 59 years, 33.8% women) was recruited from an HF outpatients' clinic of a University Hospital in Portugal. Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People 2. Clinical, nutritional, and dietary data was collected. A total of 25 (18.4%) individuals were categorised as sarcopenic, ranging from 12.2% in younger (< 65 years) participants vs. 30.4% in older ones and from 3.3% in men vs. 47.8% in women. Severe sarcopenia accounted for 7.4% of the sample. In multivariable analysis, the use of statins (OR = 0.06), being a man (OR = 0.01), having higher body mass index (OR = 0.81) and being physically active (OR = 0.16) were inversely associated with sarcopenia, while older age (OR = 1.09), polypharmacy (OR = 24.09) and having hypertrophic cardiomyopathy as aetiological HF diagnosis (OR = 19.67) were directly associated with sarcopenia.

Conclusion: Patients medicated with statins were less likely to be sarcopenic. We hypothesise that this might be related with pleiotropic effects of statins on endothelial function. This association deserves further research.

Keywords

Heart Failure; Sarcopenia; Statins; Endothelial Dysfunction; Polypharmacy; Nutritional Status

Introduction

Sarcopenia can be defined as a progressive skeletal muscle disorder that increases the likelihood of adverse outcomes such as disability, falls, fractures and mortality. It is characterised by the loss of muscle strength and of muscle quantity or quality. Low physical performance further classifies sarcopenia as severe [1].

Heart failure (HF) and sarcopenia share pathophysiological pathways involving muscle dysfunction that include alterations in mitochondrial density and activity, fibre distribution and oxidative stress. Both diseases contribute to physical inactivity, which in turn aggravates both cardiac and muscular status [2]. Sarcopenia is considered one of the leading causes of reduced cardiorespiratory fitness and poor physical performance in HF patients [3], and contributes to mortality in older HF patients [4]. The pooled prevalence of sarcopenia in HF patients ranges from 55% in hospitalised patients to 26% in community-dwelling ones, with an overall pooled prevalence of 34% [5].

Statin use is often designated as a probable risk for developing sarcopenia [6]. Statins are competitive inhibitors to the 3-Hydroxy-3-methylglutaryl-coenzyme A reductase, a hepatic converter of an early phase cholesterol precursor, thus contributing to lower serum cholesterol levels [7]. Until recently, the prescription of statins to HF patients remained controversial, as studies evaluating cardiovascular outcomes show conflicting results [8]. However, a recent meta-analysis by Bielecka-Dabrowa et al. including 17 clinical trials and cohort studies showed a reduction in cardiovascular mortality, all-cause mortality and hospitalisation in patients undergoing statin therapy when compared with non-statin users. This effect was independent from HF aetiology and ejection fraction levels. The same study concluded that lipophilic statins seem to be more favourable than hydrophilic ones [9].

The 2021 guidelines of the European Society of Cardiology for treatment of HF do not recommend initiating statin therapy in patients with HF with reduced ejection fraction and only supports continuation of statin use in HF patients with coronary artery disease and/or hyperlipidaemia [10], a reason why most clinicians do not suspend statins in patients with these conditions that further develop HF [11].

The potential prosarcopenic properties of statins are related with statin-mediated mechanisms of muscle dysfunction involving inflammation, apoptosis, the ubiquitin–proteasome system, insulin-like growth factor 1 and myostatin [8]. Muscle complications such as myalgia, myopathy and rhabdomyolysis are the most described side-effects of statin use [12] and are the main reasons for suspending statin therapy [13]. It has also been postulated that the potential prosarcopenic effects of statins could limit their effectiveness in HF patients [8].

Despite the described potential risks, the effect of statins in the muscular mass and function in HF patients, and namely in their sarcopenia status, remains controversial. With this

study, we aim at classifying and characterising sarcopenia and at describing the association of statin use with sarcopenia in a sample of Portuguese HF outpatients.

Methods

Participants in this cross-sectional study were randomly recruited from the appointments' lists of an outpatients HF and transplantation clinic of a Portuguese university hospital. Inclusion and exclusion criteria were applied at recruitment. Patients were included if they were 18 years or older and had a clinically validated diagnostic of HF [10]. Patients with severe visual impairment were excluded, as well as patients within the New York Heart Association (NYHA) functional class IV, due to their limitations in complying to the study protocol. Collection of data was carried on from September 2017 to July 2018.

All anthropometric measurements were performed by a registered nutritionist according to standard procedures and are thoroughly described elsewhere [14]. These measurements include standing height, weight, calf circumference, mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST). Mid-upper arm muscle circumference (MAMC) was calculated using the Jelliffe equation [15]: MAMC=MUAC-(3.14 x TST). Body mass index (BMI), in $Kg.m^{-2}$ was calculated using the standard formula: Weight (Kg) / standing height $(m)^2$.

Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) guidelines and algorithm for diagnosis [1]. The average of three dynamometer compressions at the non-dominant hand was used to assess muscle strength, using a calibrated electronic hand dynamometer (Jamar Plus+) and following the measurement procedures of the American Society of Hand Therapists [16]. Cut points for classifying low hand grip strength were defined as < 27 Kgf for men and < 16 Kgf for women [17]. Low muscle quantity was defined as calf circumference < 31 cm [18], or MAMC < 21.1 cm for men and < 19.2 cm for women [19]. Usual gait speed ≤ 0.8 $m.s^{-1}$ was used to classify the severity of sarcopenia [1]. Sarcopenic obesity was defined as the coexistence of sarcopenia with BMI ≥ 30 $Kg.m^{-2}$ [20].

HF clinical status was assessed by cardiologists. Medical records were also consulted. Data included left-ventricular ejection fraction (FVEF) percentage and phenotypes of heart failure defined as heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) [10], functional HF classes according to the New York Heart Association (NYHA) [21], HF aetiology, atrial fibrillation, incidental stroke and medication. Polypharmacy was classified as the daily concurrent use of five or more different medicines [22].

Physical activity was evaluated using the International Physical Activity Questionnaire – Short Form, validated for the Portuguese population [23], and categories were defined as inactive, minimally active and active [24].

Daily energy and macronutrients intake was estimated using a 24 hour dietary recall [25] conducted by trained nutritionists, with visual aids for tableware and food portions [26]. Missing portion information was complemented with usual portions or product brand names using normative tables of food weights and portions [27]. The recall registers were converted into nutrients using the Portuguese Food Composition Table [28].

Statistical analysis

The sample was described according to the sarcopenia status and to the use of statins. Quantitative variables were tested for distribution using Shapiro-Wilk test, and associated with the outcome categories using parametric and non-parametric tests. Categorical data was compared using chi-square of Fisher's exact tests as adequate. Bonferroni adjustment was used to assess significant differences in categorical subsets. Results are presented as number and percentage [n (%)] for categorical variables, mean and standard deviation [M (SD)] for normally-distributed variables and median and inter-quartile range [Md (IQR)] for variables with skewed distribution.

A logistic regression was carried out with the use of statins as a predictor for having sarcopenia, further adjusted for age, sex, total fat intake, polypharmacy, physical activity, BMI and HF aetiology. Linearity between continuous variables was assessed using Box-Tidwell test. Model performance was evaluated using Omnibus likelihood ratio chi-square test, Hosmer and Lemeshow test and Nagelkerke R-square. As having hypertrophic cardiomyopathy (HCM) was the only significant aetiological factor, this dummy-encoded predictor (having HCM vs. all the others) was the only aetiology included in the model, further contributing to its strength. Odds ratios (OR) and respective 95% confidence intervals (95% CI) were calculated. All tests were performed for a level of statistical significance of $p < 0.050$.

Ethics

This work abides by the Declaration of Helsinki. All participants gave their informed consent to the anonymous use of data for research purposes. The study protocol was reviewed and approved by the Ethics Committee of the Hospital Centre where the study was conducted (reference 57/17 of the Ethics Committee of the *Centro Hospitalar Universitário de São João*).

Results

Overall, 136 patients (median age 59 years, 33.8% women) integrated this study. The sample is characterized in **Table 1**: a total of 25 (18.4%) individuals were categorized as sarcopenic, ranging from 12.2% in younger (< 65 years) participants vs. 30.4% in older ones (*p*

= 0.009) and from 3.3% in men vs. 47.8% in women ($p < 0.001$). Severe sarcopenia accounted for 7.4% of the sample and sarcopenic obesity was present in 5.1% of the participants. Participants with an aetiological diagnosis of HCM were more likely to be sarcopenic ($p = 0.040$), as well as physically inactive ($p = 0.017$) individuals. Estimated total energy and fat intakes were also lower in sarcopenic participants ($p = 0.008$ and $p = 0.020$ respectively).

The use of statins in this sample is described in **Table 2**, including the variables entered in the multivariable model. As expected, ischaemia and stroke were related to statin medication ($p < 0.001$). The proportion of older HF patients medicated with statins was higher than those that were not statin users (40.4% vs. 21.3%, $p = 0.025$). Statin users are also those who used more daily medication ($p < 0.001$).

The multivariable model was able to correctly classify 88.9% of the cases and to explain 71.4% of the variance (Nagelkerke R-square) in sarcopenia. **Table 3** depicts the results of the logistic regression. The use of statins was inversely associated with sarcopenia (OR = 0.06; 95% CI = 0.01, 0.40). Each additional age year was associated with a 9% increase in the likelihood of being sarcopenic (OR = 1.09; 95% CI = 1.01, 1.17), and each $Kg.m^{-2}$ increment was associated with a 19% decrease in the likelihood of sarcopenia (OR = 0.81; 95% CI = 0.67, 0.97). The daily use of 5 or more medicines and having HCM as aetiological HF diagnosis were also directly associated with sarcopenia (OR = 24.09; 95% CI = 1.82, 318.52 and OR = 19.67; 95% CI = 1.25, 310.26, respectively). On the other hand, being a man and being physically active were inversely associated with sarcopenia (OR = 0.01; 95% CI = 0.00, 0.08 and OR = 0.16; 95% CI = 0.03, 0.97, respectively).

Table 1. Characteristics of the sample according to the presence of sarcopenia

	Normal (n = 111)	**Sarcopenic** (n = 25)	***p*-value**
Sex, n (%)			< 0.001
Women	24 (21.6)	22 (88.0)	
Men	87 (78.4)	3 (12.0)	
Age, Md (IQR)	58.0 (49.0, 67.0)	67.0 (52.0, 70.5)	0.038
Age intervals, n (%)			0.009
<65	79 (71.2)	11 (44.0)	
≥65	32 (28.8)	14 (56.0)	
HF aetiology , n (%)			0.040
Dilated cardiomyopathy	59 (54.6)	13 (56.5)	
Ischaemic	33 (30.6)	5 (21.7)	
Myocarditis	5 (4.6)	0 (0.0)	
Hypertrophic*	4 (3.7)	5 (21.7)	
Others	7 (6.5)	0 (0.0)	
LVEF, %, M (SD)	36.8 (12.9)	42.3 (16.5)	0.080
LVEF categories, n (%)			0.202
HFrEF (<40%)	56 (51.9)	10 (40.0)	
HFmrEF (40-50%)	31 (28.7)	6 (24.0)	
HFpEF (≥50%)	21 (19.4)	9 (36.0)	
NYHA classification, n (%)			0.189
Class I	42 (38.5)	5 (20.0)	
Class II	49 (45.0)	16 (64.0)	
Class III	18 (16.5)	4 (16.0)	
Medications, n (%)			
ACE inhibitors	87 (79.1)	19 (76.0)	0.734
Beta blockers	106 (96.4)	23 (92.0)	0.339
Aldosterone antagonists	77 (70.0)	14 (56.0)	0.178
Statins	77 (69.4)	12 (48.0)	0.042
Furosemide	37 (33.6)	14 (56.0)	0.037
Incidental stroke, n (%)	28 (25.7)	4 (16.7)	0.436
Atrial fibrillation, n (%)	16 (15.1)	3 (12.0)	0.999
Polypharmacy, n (%)	79 (71.8)	22 (88.0)	0.092
Smoking habits, n (%)	46 (43.0)	3 (12.0)	0.005
Physical activity, n (%)			0.017
Inactive*	56 (50.5)	20 (80.0)	
Minimally active	41 (36.9)	5 (20.0)	
Active	14 (12.6)	0 (0.0)	
Weight, Kg, Md (IQR)	80.8 (73.5, 89.6)	67.2 (56.7, 73.9)	< 0.001
Standing height, cm, M (SD)	166.9 (8.6)	153.8 (8.8)	< 0.001
BMI, $Kg.m^{-2}$, M (SD)	29.5 (4.2)	28.0 (4.7)	0.120
BMI classes, n (%)			0.118
Underweight + Normal	17 (15.3)	8 (32.0)	
Overweight	46 (41.4)	10 (40.0)	
Obese	48 (43.2)	7 (28.0)	
Hand grip strength, Kgf, Md (IQR)	32.7 (26.5, 39.5)	18.0 (16.2, 22.9)	<0.001
Gait speed, $m.s^{-1}$, Md (IQR)	1.13 (0.93, 1.31)	0.83 (0.73, 1.07)	<0.001
Gait speed ≤ 0.8 $m.s^{-1}$, n (%)	5 (4.5)	10 (40.0)	<0.001
Dietary assessment			
Energy, Kcal/day, Md (IQR)	1765 (1500, 2227)	1533 (1151, 1792)	0.008
Total fat, g/day, Md (IQR)	56.9 (42.5, 86.2)	48.2 (31.2, 61.6)	0.020
Carbohydrates, g/day, Md (IQR)	198.1 (158.5, 245.8)	183.5 (118.8, 212.3)	0.069
Protein, g/day, Md (IQR)	85.9 (60.4, 106.3)	70.9 (59.1, 99.5)	0.134

Values are presented as: n (%) = number (percentage); M (SD) = Mean (Standard Deviation); Md (IQR) = Median (Lower quartile, Upper quartile). HF = Heart Failure; LVEF = Left Ventricular Ejection Fraction; ; HFrEF = Heart Failure with reduced Ejection Fraction; HFmrEF = Heart Failure with mildly reduced Ejection Fraction; HFpEF = Heart Failure with preserved Ejection Fraction; NYHA = New York Heart Association functional HF classes. ACE = Angiotensin-conversion Enzyme; BMI = Body Mass Index. Missing values: LVEF n = 3; NYHA n = 2; Incidental stroke n = 2; Atrial fibrillation n = 5; Smoking habits n = 2. *Results differ significantly between subsets of dependent variable, as per Bonferroni adjusted *p*-values.

Table 2. Characteristics of the sample according to the use of statins

	Not medicated with statins (n = 47)	**Statin users** (n = 89)	***p*-value**
Sex, n (%)			0.237
Women	19 (40.4)	27 (30.3)	
Men	28 (56.9)	62 (67.7)	
Age, years, Md (IQR)	51.0 (39.0, 64.0)	62.0 (54.0, 69.0)	< 0.001
Age categories, n (%)			0.025
< 65 years	37 (78.7)	53 (59.6)	
≥ 65 years	10 (21.3)	36 (40.4)	
HF aetiology , n (%)			< 0.001
Dilated cardiomyopathy	29 (61.7)	43 (48.3)	
Ischaemic*	4 (8.5)	34 (38.2)	
Myocarditis*	4 (8.5)	1 (1.1)	
Hypertrophic cardiomyopathy	4 (8.5)	5 (5.6)	
Others	6 (12.8)	6 (6.7)	
LVEF categories, n (%)			0.404
HFrEF + HFmrEF	36 (78.3)	63 (71.6)	
HFpEF	10 (21.7)	25 (28.4)	
NYHA classification, n (%)			0.455
Class I	16 (34.8)	31 (35.2)	
Class II	20 (43.5)	45 (51.1)	
Class III	10 821.7)	12 (13.6)	
Incidental stroke, n (%)	2 (4.5)	30 (33.7)	< 0.001
Polypharmacy, n (%)	25 (54.3)	76 (85.4)	< 0.001
Number of medicines/day, Md (IQR)	5.0 (3.8, 8.0)	7.0 (5.5, 9.5)	< 0.001
Physical activity, n (%)			0.175
Inactive	30 (63.8)	46 (51.7)	
Minimally active + active	17 (36.2)	43 (48.3)	
Body Mass Index, $Kg.m^{-2}$, M (SD)	28.9 (4.7)	29.4 (4.2)	0.526
Fat intake, g/day, Md (IQR)	59.7 (47.5, 86.4)	54.1 (37.0, 74.4)	0.149
Prescribed statin daily dose, n (%)			
10 mg	-	8 (9.2)	
20 mg	-	43 (49.4)	
40 mg	-	34 (39.1)	
80 mg	-	2 (2.3)	

HF = Heart Failure; LVEF = Left Ventricular Ejection Fraction; HFrEF = Heart Failure with reduced Ejection Fraction; HFmrEF = Heart Failure with mildly reduced Ejection Fraction; HFpEF = Heart Failure with preserved Ejection Fraction. Missing values: LVEF n = 3; NYHA n = 2; Incidental stroke n = 2; Statin dose n = 2. *Results differ significantly between subsets of dependent variable, as per Bonferroni adjusted *p*-values.

Table 3. Bivariable and multivariable results from the logistic regression analysis regarding sarcopenia status

		Unadjusted			**Adjusted**	
		OR (95% CI)	***p*-value**		**OR (95% CI)**	***p*-value**
Statin						
No		1			1	
Yes		0.41 (0.17, 0.99)	0.046		0.06 (0.01, 0.40)	0.004
Age, years		1.04 (0.99, 1.08)	0.070		1.09 (1.01, 1.17)	0.024
Sex						
Women		1			1	
Men		0.04 (0.01, 0.14)	< 0.001		0.01 (0.00, 0.08)	< 0.001
Total fat intake, g/day		0.98 (0.96, 0.99)	0.024		0.98 (0.94, 1.01)	0.210
Polypharmacy						
< 5 medicines/day		1			1	
≥ 5 medicines/day		2.88 (0.80, 10.31)	0.104		24.09 (1.82, 318.52)	0.016
Physical activity						
Inactive		1			1	
Minimally active + active		0.26 (0.09, 0.73)	0.011		0.16 (0.03, 0.97)	0.046
Body mass index, $Kg.m^{-2}$		0.92 (0.82, 1.02)	0.122		0.81 (0.67, 0.97)	0.022
Heart failure aetiology						
Others		1			1	
Hypertrophic cardiomyopathy		6.69 (1.65, 27.09)	0.008		19.67 (1.25, 310.26)	0.034

Values are expressed in Odds Ratio (OR) and 95% Confidence Intervals (95% CI). Omnibus test: $p < 0.001$; Nagelkerke R-square = 0.714; Hosmer and Lemeshow test: $p = 0.847$. Model sensitivity: 64.0%; Model specificity: 94.5%. Model accuracy: 88.9%.

Discussion

The frequency of sarcopenia in this sample is in line with the global prevalence for HF ambulatory patients [5], when considering the mean age of our population. As no works are known regarding sarcopenia in HF populations from Portugal, we can only contrast our results with healthy populations, namely with older adults: Sousa-Santos et al., reports a frequency of sarcopenia of 4.4% in a population-based cross-sectional study (Nutrition UP 65, n = 1500) [29], which is significantly lower than our sample's frequency.

It is worth noticing that 44% of all sarcopenic patients in our sample were younger than 65 years, which highlights the fact that sarcopenia secondary to HF cannot be considered a geriatric syndrome. This reality demands a more thorough attention to younger HF patients regarding their muscular mass and function.

Statins

Contrary to what was expected, in this sample statins were consistently associated with not being sarcopenic. A possible explanation for this probable protective factor might lie on the fact that the benefits of statins at a circulatory level could positively impact the neuromuscular function, thus contributing to the preservation of muscle strength, quantity, and quality. This cardiovascular pleiotropic effect of statins results in an anti-atherogenic state that goes beyond the effects on plasmatic lipids, inhibiting the proliferation of cytokines, c-reactive protein and cellular adhesion molecules and decreasing the adhesion of monocytes to the endothelium [30]. Contributing to the endothelial health, statins also indirectly promote nitric oxide release and bioavailability [31]. As HF patients with sarcopenia have impaired endothelial function, with lower vasodilation impacting exercise capacity [32], the use of statins could, potentially, improve their endothelial function, which may lead to a better muscle perfusion, thus contributing to a better neuromuscular fitness.

In fact, the link between endothelial dysfunction and sarcopenia has been gaining traction in the light of recent evidence. A study with 236 rural elderly women showed significant correlation between endothelial dysfunction and low hand grip strength [33]. A systematic review of publications (n = 18) reported that endothelial dysfunction may be an early predictor of frailty and sarcopenia [34]. In a cohort of chronic kidney disease patients (n = 77), sarcopenia was also more frequent in those with markers of atherosclerosis and endothelial dysfunction [35].

Alcalde-Estévez et al. suggest a probable mechanism for the association of endothelial dysfunction and sarcopenia, using cultured murine myoblasts incubated with endothelin-1, a peptide with augmented expression in endothelial dysfunction, resulting in myoblast senescence and fibrosis [36]. It is known that statins reduce significantly the concentrations of endothelin-1, as

demonstrated by a meta-analysis of 15 randomized controlled trials by Sahebkar et al. [37]. These findings contribute to the biological plausibility of our hypothesis that statins may have a pleiotropic protective effect on sarcopenia.

Physical activity, weight status and fat intake

As expected, active participants had lower odds of being sarcopenic. Exercise is an important factor for primary and secondary prevention of HF and for better prognosis of the disease [38]. Aerobic and resistance exercise is associated with better quality of life and reduced hospitalisation in HF patients [39]. Similarly, combination exercise has the best prevention and therapeutic effects on age-related sarcopenia [40]. Our results show that physical inactivity is highly frequent in this HF sample, being significantly higher in sarcopenic individuals, which calls for action regarding the recommendation of adequate and tailored exercise training.

The HF-ACTION controlled trial is the only known work studying the influence of statins on exercise training response in HF patients (n = 2331, with LVEF ≤ 35%). This study found no interaction between statin use and changes in exercise capacity or quality of life [41].

Regarding weight status, after adjusting for covariates, BMI was associated with lower odds of being sarcopenic. We attribute this association to the loss of lean body mass typical of sarcopenia.

Together with physical activity, changes in dietary habits are usually recommended to patients initiating statin use. Regardless of these recommendations, total fat intake has significantly increased over time in US statin users but not in non-users [42] and diet and lifestyle of Australian statin users were not significantly different than those of non-users, albeit statin users had lower saturated fat intake [43]. In this sample's bivariable analysis regarding total fat intake, no differences were found between statin vs. non-statin users but sarcopenic patients had significantly lower fat intake. After adjusting for covariates, fat intake lost its ability to predict sarcopenia.

Hypertrophic cardiomyopathy

In this study, having HCM as aetiological diagnosis for HF was a strong predictor for being sarcopenic. Neuromuscular disorders, particularly inherited ones, are the main causes of HCM [44], and within the plethora of genetic factors associated with HCM, many are also responsible for phenotypical abnormalities in skeletal muscle [45], but there are no studies associating sarcopenia to patients with HCM as the main contributor to their HF condition. However, a prospective study by Beyer et al., using BIOBANK data, concluded that higher hand grip strength was associated with cardiovascular magnetic resonance measures indicative of less hypertrophy and remodelling [46]. As for the effects of statins on HCM, the evidence is

also insufficient and contradicting: statins may prevent and ameliorate HCM in animal models [47,48], but a clinical trial by Hersi et al. did not show this effect in humans [49].

Polypharmacy

HF treatment demands prescribing multiple medications, in accordance to international guidelines [50], leading to a very high prevalence of polypharmacy. The management of multiple comorbidities associated with HF further increase the number of medicines needed, particularly in older patients [51], which makes polypharmacy an universal condition in HF populations [52]. While medication that contributes to maintain haemodynamic stability in HF patients is indispensable, patients could potentially benefit from reducing the use of other medicines that were not directly related to the maintenance or improvement of cardiovascular function or the management of comorbidities. Such is the case of non-prescription drugs, which seem to be of extremely common use by HF patients [52].

Evolution in pharmacological interventions in HF has contributed to reduce mortality and/or hospitalisations in recent past [53,54], but may also impose some challenges regarding many clinical aspects and, namely, in sarcopenia: in general, polypharmacy is associated with lower physical function in older adults [55]; polypharmacy was independently associated with sarcopenia in a cross-sectional study with German community-dwelling older adults [56] and with sarcopenia, disability and mortality in a cohort of community-dwelling Japanese older adults [57].

In our sample, the daily use of 5 or more medicines was associated with being sarcopenic, whereas the use of statins had the opposite association. Much more evidence is needed regarding the role of statins in HF and either if they should be withheld or withdrawn in the context of reducing polypharmacy or having an effect on neuromuscular fitness.

Limitations and strengths

This study has some limitations that the authors would like to acknowledge, starting with the cross-sectional design, that does not allow for causal associations, and the small sample size, which may limit the interpretation of the results.

Regarding the classification of sarcopenia, the EWGSOP2 does not recommend the use of anthropometry to assess muscular quantity and quality criteria for diagnosing this condition, except when other methods are not available, such as dual energy X-ray absorptiometry or bioimpedance analysis. In this case the recommended anthropometric method is the calf circumference [1], that we used to estimate muscle quantity. We decided to additionally use MAMC, as this estimator is based on upper-arm anthropometry, an area that is usually free from oedema, with clear benefits when evaluating HF patients [58,59], and with the added advantages of having defined and validated sex-specific cut-offs [19] and of being a fast, simple and inexpensive

method. Moreover, all anthropometric measurements were performed by the same trained nutritionist, in order to avoid inter-observer error.

This study uses dietary intake data produced by a single 24 dietary recall, which does not account for day-to-day variations and can underestimate energetic intake [60]. However, all interviews were made by trained nutritionists who put a special care in the registry of the dietary recalls and used ancillary tools to estimate food portions and to undertake the complex conversion of food records into nutritional information.

The type of statins was not registered and the prescribed dose was not analysed. Our sample size would not allow a stratification of statin users for type and dose, but it is still worth mentioning that, as lipophilic statins seem to be associated with better HF outcomes when compared with hydrophilic ones and low doses seem to be more beneficial to HF patients [8,61], dose and lipophility of statins should be important factors on future study designs.

Lastly, some bivariate analysis in this sample might suggest a possible survival bias underlying the relations between particular clinical conditions, sex, statin use and sarcopenia. As previously mentioned, prescription of statins is significantly higher in ischaemic patients, who account for 60.5% of individuals below 65 years vs. 39.5% in older ones. Also, the proportion of ischaemic men is much higher than that of women's (73.7% vs. 26.3%). As 88.0% of all participants classified with sarcopenia were women, and considering that coronary heart disease and stroke are the main causes of cardiovascular death in HF patients and, mainly, in male HF patients [62], this might mean that women were more likely to survive and to develop sarcopenia.

Despite the aforementioned limitations, this study is, to our knowledge, the first to describe sarcopenia in HF Portuguese patients in regard to their clinical and nutritional status, and the first to quantify the association between the use of statins and a reduced likelihood of sarcopenia in patients with HF. We are not, however, in a position to recommend or advocate for a change of medication towards HF patients. More evidence is needed, especially prospective studies and specifically randomized clinical trials, in order to clarify the complex relations of pharmacological intervention in HF patients, namely those affected by comorbidities associated with nutritional status and, specifically, skeletal muscle, such as sarcopenia and frailty.

Finally, we would like to stress that screening for sarcopenia is not a usually recommended clinical practice, despite its association with worst prognosis both in ageing and in many chronic diseases. Sarcopenia is preventable, manageable, treatable and, in some cases, reversible, and assessing sarcopenia in clinical settings is easy and inexpensive. The EWGSOP2 provides a simple algorithm for case-finding, diagnosis and severity determination [1]. We claim that clinical suspicion of sarcopenia exists in all patients with HF, hence all should be screened,

including the younger, and a low hand grip strength value (< 27 Kgf for men and < 16 Kgf for women) should be enough to classify sarcopenia as probable and to start intervention.

Conclusions

In summary, all HF patients, including the younger, should be screened and monitored for the onset and evolution of sarcopenia. In this HF sample, statin users were less likely to be sarcopenic than non-users, even when adjusting for age, sex, dietary fat intake, polypharmacy, physical activity, weight status and HF aetiology. Although this finding deserves further research, we hypothesise that this association might possibly be attributable to the pleiotropic effects of statins on endothelial function, contributing to a better neuromuscular fitness.

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Competing Interests

The authors have nothing to disclose.

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Chapter 3 - Coexistence of Frailty and Sarcopenia

The associations between medicine use and ejection fraction with the coexistence of frailty and sarcopenia in a sample of Portuguese heart failure outpatients

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Title

The associations between medicine use and ejection fraction with the coexistence of frailty and sarcopenia in a sample of Portuguese heart failure outpatients

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List of Acronyms

HF: Heart Failure
NYHA: New York Heart Association
LVEF: Left-Ventricular Ejection Fraction
HFrEF: Heart Failure with reduced Ejection Fraction
HFmrEF: Heart Failure with mildly reduced Ejection Fraction
HFpEF: Heart Failure with preserved Ejection Fraction
EWGSOP2: European Working Group on Sarcopenia in Older People 2
DEXA: dual-energy x-ray absorptiometry

Abstract

Aim: Frailty and sarcopenia have been extensively studied in heart failure (HF) patients, but their coexistence is unknown. This work aims to describe the coexistence of these conditions in a sample of HF outpatients and its association with the use of medication and left-ventricular ejection fraction.

Methods and Results: Participants in this cross-sectional study were recruited from an HF outpatients' clinic in northern Portugal. Frailty phenotype was assessed according to Fried et al. Sarcopenia was evaluated according to the European Working Group on Sarcopenia in Older People 2. Clinical data was collected. A total of 136 HF outpatients (33.8% women, median age 59 years) integrated this study. Frailty and sarcopenia accounted for 15.4% and 18.4% of the sample, respectively. Coexistence of frailty and sarcopenia was found in 8.1% of the participants, while 17.6% had only one of the conditions. In multivariable analysis, increasing age (OR = 1.12; 95% CI = 1.05, 1.18), being a woman (OR = 60.53; 95% CI = 13.11, 279.69), having heart failure with preserved ejection fraction (HFpEF) (OR = 6.34; 95% CI = 1.45, 27.69) and using antidepressants (OR = 6.80; 95% CI = 2.56, 44.94) and anticoagulants (OR = 10.73; 95% CI = 1.90, 24.31) were associated with increased likelihood of having coexistence of frailty and sarcopenia, while using statins showed the inverse effect (OR = 0.07; 95% CI = 0.02, 0.33).

Conclusion: The low frequency of coexistence of frailty and sarcopenia means that these conditions still deserve individual attention. Being a woman, older age, having HFpEF, using anticoagulants and antidepressants and not using statins were associated with having concomitant frailty and sarcopenia. These patients can potentially benefit from interventions that impact their quality of life such as nutritional and mental health interventions and exercise training.

Keywords: Heart Failure; Frailty; Sarcopenia; Coexistence; Left-Ventricular Ejection Fraction; HFpEF.

Introduction

Physical frailty is a state of vulnerability caused by the decline of reserve and function across multiple systems, which compromises the ability to cope with external stressors [1]. As described by Fried et al., frailty is present when three or more of the following criteria are met: low muscle strength; low physical performance; low physical activity; exhaustion and involuntary weight loss. Individuals are classified as pre-frail if one or two of the aforementioned criteria are present [2]. Sarcopenia is a systemic muscle disease, characterized by low muscle strength and quantity or quality. The presence of low physical performance adds to the severity of the disease [3].

Even though frailty and sarcopenia are two separate entities, they share common grounds: undernutrition, inactivity and inflammation are contributors to both conditions and, in many cases, frail individuals are also sarcopenic, as low muscle strength and physical performance are shared definitions. Notwithstanding this, frailty remains a much wider concept that can encompass sarcopenia to a partial degree, but also components of mental state, changes in body weight and usual physical activity [2,3].

Frailty and sarcopenia are very common in heart failure (HF) patients, with an overall estimated prevalence of 44.5% and 34.0%, respectively [4,5]. Both conditions are associated with increased mortality and/or hospitalisation in HF patients [5–7]. Despite this, the coexistence of frailty and sarcopenia is yet to be described in this population. Thus, studying their concomitance and its associated factors should allow for identifying which individuals are at increased risk of accumulating health outcomes. Therefore, our goal is to describe the coexistence of frailty and sarcopenia in a sample of HF outpatients. As pharmacologic therapies remain the foundation of HF intervention and left-ventricular ejection fraction (LVEF) is an important defining criterion of HF and its outcomes [8], we also aim to describe the association between these clinical variables and the coexistence of frailty and sarcopenia.

Methods

The data that supports this cross-sectional study were collected between September 2017 and July 2018 in an HF outpatients' clinic of a northern Portuguese university hospital. Patients aged 18 years and older, and with a clinically validated HF diagnostic according to the European Society of Cardiology [8], were randomly selected from the physicians' appointments lists. Participants with severe visual impairment or within New York Heart Association (NYHA) functional class IV were excluded, as their limitations would hinder the application of the study protocol.

Clinical data were collected during appointments with cardiologists. Medical records were also reviewed. The type of the disease was classified as heart failure with reduced ejection

fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), whenever patients presented LVEF <40%, 40-50% or ≥50 %, respectively [8]. Gathered data also included NYHA functional classes, incidental stroke, atrial fibrillation, diabetes, smoking habits and medicines. Polypharmacy was defined as the daily use of five or more medicines [9].

Anthropometrical measurements were carried out by a registered nutritionist as described previously [10] and include standing height, weight, triceps skinfold thickness, mid-upper arm circumference, calf circumference and mid-upper arm muscle circumference.

Frailty phenotype was evaluated according to Fried et al. [2] as the occurrence of three or more of the following criteria: low strength, slow gait, exhaustion, low physical activity and unintentional weight loss. Methods for assessing each criterion for this study can be found in a previous work [10].

Sarcopenia was diagnosed according to the revised consensus of the European Working Group on Sarcopenia in Older People (EWGSOP2) [3]. Grip strength was measured according to the instructions of the American Society of Hand Therapists [11], using a Jamar Plus+ digital hand dynamometer (Sammons Preston, USA). The average of three maximum compressions of the non-dominant hand was used. Low strength was defined as < 27 Kgf for men and < 16 Kgf for women [12]. Low muscle quantity was defined as mid-upper arm muscle circumference < 21.1 cm for men and < 19.2 cm for women [13], or as calf circumference < 31 cm [14].

Statistics

The sample was described according to the presence of frailty and sarcopenia and to the coexistence of frailty and sarcopenia, and categorised as: “none of the conditions”; “one of the conditions”; “both conditions”. Continuous variables were tested for normality using the Shapiro-Wilk test and were compared using parametric tests for variables with normal distribution and non-parametric tests for variables with skewed distribution. Values were respectively indicated in mean (M) and standard deviation (SD) and in median (Md) and interquartile range (IQR). Categorical variables were compared using the Qui-square or the Fisher exact tests, as adequate. Results were presented in number of individuals (n) and percentage (%).

An ordinal logistic regression was carried out to assess associations between the independent variables and the co-occurrence of frailty and sarcopenia as a dependent variable increasingly ordered regarding the number of conditions, from “none of the conditions” to “one of the conditions” to “both conditions”. The proportional odds model included the following predictors: age (continuous); sex; asymptomatic patients within NYHA Class I vs. Classes II and III; patients with HFpEF vs. HFrEF and HFmrEF and the use of medication (angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, statins, furosemide,

sacubitril + valsartan, ivabradine, thiazide diuretics, acetylsalicylic acid, nitrates, antidepressants, anxiolytics, digoxin, antiarrhythmic medicines, anticoagulants). Missing values for NYHA (n = 2), LVEF (n = 3) and medication (n = 1) were included in the reference categories. Cumulative odds ratios (OR) and respective 95% confidence intervals (95% CI) were calculated. The test of parallel lines was used to evaluate the proportional odds assumption of the model. All tests were performed for a level of significance of $p = 0.050$. SPSS ver. 27 (IBM, USA) was used to execute all statistical analyses.

Ethic disclosures

This study was implemented according to the principles of the Declaration of Helsinki. The Ethics Committee of the hospital in which this study took place approved the protocol (reference 57/17 of the Ethics Committee of the *Centro Hospitalar Universitário de São João*). All participants granted their informed consent for the use of data for research purposes.

Results

A total of 136 HF outpatients (33.8% women, aged 24-81 years, median age 59 years) integrated this study. **Table 1** depicts the characteristics of the sample regarding the presence of sarcopenia or frailty: 21 (15.4%) participants were frail and 25 (18.4%) were sarcopenic. The number of patients with concomitant frailty and sarcopenia was 11 (8.1%). Within sarcopenic participants, 44% were frail; 52% of frail participants were sarcopenic. Being a woman and having a higher usage of furosemide were the only common significant associations in frail and sarcopenic individuals. Frail patients were more likely to have fewer school years, to be at higher NYHA classes and to have a higher frequency of prescription of antiarrhythmic medicines, anticoagulants and antidepressants than non-frail ones. Sarcopenic patients were more likely to be older than non-sarcopenic ones, to have lower usage of statins and to be non-smokers.

A description of the sample stratified by the number of concomitant conditions can be found in **Table 2**. Roughly three-quarters of the sample were not frail nor sarcopenic and 17.6% had only one condition. Being a woman, being older than 65 years, having lower educational level, being at a higher NYHA class, being a non-smoker, not being prescribed aldosterone antagonists and statins and using furosemide were all factors related to being concomitantly frail and sarcopenic.

Results from the ordinal logistic regression are presented in **Table 3**. For every year increase in age, the cumulative odds of having more conditions increased by 12% (OR = 1.12; 95% CI = 1.05, 1.18). Women were much more likely to be allocated in higher categories of coexistence of frailty and sarcopenia than men (OR = 60.53; 95% CI = 13.11, 279.56). Patients

with HFpEF were more likely to have an accumulation of conditions than those with reduced or mid-range LVEF (OR = 6.34; 95% CI = 1.45, 27.69). Regarding medication, the participants who used statins were less likely to be allocated in higher categories of co-occurrence of frailty and sarcopenia than those who were not statin users (OR = 0.07; 95% CI = 0.02, 0.33), while patients who were prescribed anticoagulants and antidepressants were more likely to accumulate conditions (OR = 6.80; 95% CI = 1.90, 24.31 and OR = 10.73; 95% CI = 2.56, 44.94, respectively). No associations were found for the remaining 12 medicines nor for NYHA functional classification.

Table 1. Characterisation of the sample regarding frailty and sarcopenia

	Conditions					
	Frailty			Sarcopenia		
	Normal + pre-frail (n = 115)	Frail (n = 21)	*p*-values	Normal (n = 111)	Sarcopenic (n = 25)	*p*-values
Age, Md (IQR)	58.0 (49.0, 67.0)	64.0 (49.5, 71.5)	0.117	58.0 (49.0, 67.0)	67.0 (52.0, 70.5)	0.038
Age intervals, n (%)			0.146			0.009
< 65 years	79 (68.7)	11 (52.4)		79 (71.2)	11 (44.0)	
≥ 65 years	36 (31.3)	10 (47.6)		32 (28.8)	14 (56.0)	
Sex, n (%)			0.003			< 0.001
Women	33 (28.7)	13 (61.9)		24 (21.6)	22 (88.0)	
Men	82 (71.3)	8 (38.1)		87 (78.4)	3 (12.0)	
School years, Md (IQR)	9.0 (4.0, 12.0)	4.0 (4.0, 9.0)	0.023	9.0 (4.0, 12.0)	4.0 (4.0, 12.0)	0.399
NYAH classes, n (%)			0.003			0.189
Class I	45 (38.8)	2 (9.5)		42 (38.5)	5 (20.0)	
Class II	54 (47.8)	11 (52.4)		49 (45.0)	16 (64.0)	
Class III	14 (12.4)	8 (38.1)		18 (16.5)	4 (16.0)	
LVEF categories, n (%)			0.165			0.203
HFrEF	58 (51.3)	8 (40.0)		56 (51.9)	10 (40.0)	
HFmrEF	33 (29.2)	4 (20.0)		31 (28.7)	6 (24.0)	
HFpEF	22 (19.5)	8 (40.0)		21 (19.4)	9 (36.0)	
Polypharmacy, n (%)			0.593			0.127
< 5 medicines/day	30 (26.1)	4 (19.0)		31 (27.9)	3 (12.0)	
≥ 5 medicines/day	85 (73.9)	17 (81.0)		80 (72.1)	22 (88.0)	
Medicines, n (%)						
ACE inhibitors	90 (78.3)	16 (76.2)	0.781	87 (79.1)	19 (76.0)	0.734
Beta blockers	109 (94.8)	20 (95.2)	0.931	106 (96.4)	23 (92.0)	0.339
Aldosterone antagonists	81 (70.4)	10 (47.6)	0.041	77 (70.0)	14 (56.0)	0.178
Statins	78 (67.8)	11 (52.4)	0.171	77 (69.4)	12 (48.0)	0.042
Furosemide	38 (33.0)	13 (61.9)	0.012	37 (33.6)	14 (56.0)	0.037
Sacubitril/valsartan	16 (13.9)	0 (0.0)	0.132	13 (11.7)	3 (12.0)	1.000
Ivabradine	20 (17.4)	2 (9.5)	0.526	18 (16.2)	4 (16.0)	1.000
Thiazide diuretics	7 (6.1)	1 (4.8)	1.000	7 (6.3)	1 (4.0)	1.000
Calcium channel blockers	4 (3.5)	0 (0.0)	1.000	4 (3.6)	0 (0.0)	1.000
Acetylsalicylic acid	29 (25.2)	6 (28.6)	0.746	30 (27.0)	5 (20.0)	0.615
Nitrates	13 (11.3)	2 (9.5)	1.000	11 (9.9)	4 (16.0)	0.477
Digoxin	9 (7.8)	3 (14.3)	0.397	11 (9.9)	1 (4.0)	0.695
Antiarrhythmic drugs	10 (8.7)	6 (28.6)	0.009	12 (10.8)	4 (16.0)	0.495
Anticoagulants	35 (30.4)	12 (57.1)	0.018	38 (34.2)	9 (36.0)	0.867
Antidepressants	18 (15.7)	9 (42.9)	0.004	22 (19.8)	5 (20.0)	0.984
Anxiolytics	31 (27.8)	5 (23.8)	0.764	30 (27.0)	6 (24.0)	0.757
Diabetes, n (%)	34 (29.8)	5 (23.8)	0.794	33 (30.0)	6 (24.0)	0.550
Smoking habits, n (%)	45 (40.5)	4 (19.0)	0.084	46 (43.0)	3 (12.0)	0.005
Incidental stroke, n (%)	29 (25.7)	3 (15.0)	0.402	28 (25.7)	4 (16.7)	0.436
Atrial fibrillation, n (%)	13 (11.8)	6 (28.6)	0.083	16 (15.1)	3 (12.0)	1.000
BMI, $Kg.m^{-2}$, M (SD)	29.2 (4.4)	29.5 (4.2)	0.930	29.5 (4.2)	28.0 (4.7)	0.532
BMI categories, n (%)			0.952			0.118
Underweight + normal	21 (18.3)	4 (19.0)		17 (15.3)	8 (32.0)	
Overweight	48 (41.7)	8 (38.1)		46 (41.4)	10 (40.0)	
Obese	46 (40.0)	9 (42.9)		48 (43.2)	7 (28.0)	
Coexistence						
Frailty	-	-	-	10 (9.0)	11 (44.0)	< 0.001
Sarcopenia	14 (12.2)	11 (52.4)	< 0.001	-	-	-

Results presented in number (n) and percentage (%), in mean (M) and standard deviation (SD), or in median (Md) and inter-quartile range (IQR). NYHA: New York Heart Association. LVEF: Left-ventricular ejection fraction. HFrEF: Heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. ACE: angiotensin-converting enzyme. BMI: body mass index. MNA-SF®: Mini Nutritional Assessment – Short Form®. Missing values: LVEF = 3; NYHA = 2; medicines = 1; smoking habits = 4; incidental stroke = 3; atrial fibrillation = 5.

Table 2. Characterisation of the sample regarding the co-occurrence of frailty and sarcopenia

	Number of Conditions, n (%)			
	0 conditions	1 condition	2 conditions	*p*-value
	101 (74.3)	24 (17.6)	11 (8.1)	
Age, Md (IQR)	58.0 (48.5, 67.0)	59.5 (50.3, 67.8)	70.0 (50.0, 73.0)	0.065
Age categories, n (%)				0.021
< 65 years	71 (70.3)	16 (66.7)	3 (27.3)	
≥ 65 years	30 (29.7)	8 (33.3)	8 (72.7)	
Sex, n (%)				< 0.001
Women	21 (20.8)	15 (62.5)	10 (90.9)	
Men	80 (79.2)	9 (37.5)	1 (9.1)	
School years, Md (IQR)	9.0 (4.0, 12.0)	9.0 (4.0, 12.0)	4.0 (4.0, 4.0)	0.009
NYAH functional classes, n (%)				0.021
Class I	41 (41.4)	5 (20.8)	1 (9.1)	
Class II	46 (46.5)	11 (45.8)	8 (72.7)	
Class III	12 (12.1)	8 (33.3)	2 (18.2)	
LVEF categories, n (%)				0.194
HFrEF	51 (51.5)	12 (52.2)	3 (27.3)	
HFmrEF	29 (29.3)	6 (26.1)	2 (18.2)	
HFpEF	19 (19.2)	5 (21.7)	6 (54.5)	
Polypharmacy, n (%)				0.384
< 5 medicines/day	28 (27.2)	5 (20.8)	1 (9.1)	
≥ 5 medicines/day	73 (72.3)	19 (79.2)	10 (90.9)	
Medicines, n (%)				
ACE inhibitors	80 (80.0)	17 (70.8)	9 (81.8)	0.592
Beta blockers	97 (97.0)	21 (87.5)	11 (100)	0.143
Aldosterone antagonists	70 (70.0)	18 (75.0)	3 (27.3)	0.015
Statins	72 (72.0)	11 (45.8)	6 (54.5)	0.046
Furosemide	32 (32.0)	11 (45.8)	8 (72.7)	0.022
Sacubitril/valsartan	13 (13.0)	3 (12.5)	0 (0.0)	0.596
Ivabradine	17 (17.0)	4 (16.7)	1 (9.1)	0.927
Thiazide diuretics	6 (6.0)	2 (8.3)	0 (0.0)	0.827
Calcium channel blockers	4 (4.0)	0 (0.0)	0 (0.0)	1.000
Acetylsalicylic acid	27 (27.0)	5 (20.8)	3 (27.3)	0.844
Nitrates	11 (11.0)	2 (8.3)	2 (18.2)	0.794
Digoxin	9 (9.0)	2 (8.3)	1 (9.1)	0.999
Antiarrhythmic drugs	9 (9.0)	4 (16.7)	3 (27.3)	0.119
Anticoagulants	30 (30.0)	13 (54.2)	4 (36.4)	0.077
Antidepressants	16 (16.0)	8 (33.3)	3 (27.3)	0.124
Anxiolytics	28 (28.0)	5 (20.8)	3 (27.3)	0.799
Diabetes, n (%)	32 (32.0)	3 (12.5)	4 (36.4)	0.114
Smoking habits, n (%)	42 (43.3)	7 (29.2)	0 (0.0)	0.007
Incidental stroke, n (%)	26 (26.0)	5 (22.7)	1 (9.1)	0.573
Atrial fibrillation, n (%)	12 (12.5)	5 (20.8)	2 (18.2)	0.529
BMI, $Kg.m^{-2}$, M (SD)	29.6 (4.3)	27.4 (3.7)	30.1 (5.0)	0.068
BMI categories, n (%)				0.332
Underweight + normal	16 (15.8)	6 (25.0)	3 (27.3)	
Overweight	41 (40.6)	12 (50.0)	3 (27.3)	
Obese	44 (43.6)	6 (25.0)	5 (45.5)	

Results presented in number (n) and percentage (%), in mean (M) and standard deviation (SD), or in median (Md) and inter-quartile range (IQR). NYHA: New York Heart Association. LVEF: Left-ventricular ejection fraction. HFrEF: Heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. ACE: angiotensin-converting enzyme. BMI: body mass index. Missing values: LVEF = 3; NYHA = 2; medicines = 1; smoking habits = 4; incidental stroke = 3; atrial fibrillation = 5.

Table 3: Results from the ordinal logistic regression analysis (proportional odds model) regarding the ordinal cumulative number of conditions from none to one condition (frailty or sarcopenia), to two coexisting conditions (frailty and sarcopenia).

	OR (95% CI)	***p*-value**
Age	1.12 (1.05, 1.18)	< 0.001
Sex		
Men	1	
Women	60.53 (13.11, 279.56)	< 0.001
LVEF		
HFrEF + HFmrEF	1	
HFpEF	6.34 (1.45, 27.69)	0.014
NYHA Classification		
Classes II + III	1	
Class I	0.87 (0.18, 4.29)	0.864
Medicines		
ACE inhibitors	0.85 (0.11, 6.58)	0.878
Beta blockers	0.69 (0.06, 8.42)	0.772
Aldosterone antagonists	1.04 (0.26, 4.13)	0.950
Statins	0.07 (0.02, 0.33)	0.001
Furosemide	3.29 (0.94, 11.52)	0.063
Sacubitril/valsartan	0.54 (0.04, 7.70)	0.650
Ivabradine	1.22 (0.23, 6.48)	0.819
Thiazide diuretics	0.20 (0.01, 2.76)	0.227
Acetylsalicylic acid	4.23 (0.96, 18.68)	0.057
Nitrates	0.24 (0.04, 1,55)	0.135
Digoxin	0.18 (0.02, 1.59)	0.123
Antiarrhythmic drugs	2.09 (0.35, 12.50)	0.418
Anticoagulants	6.80 (1.90, 24.31)	0.003
Antidepressants	10.73 (2.56, 44.94)	0.001
Anxiolytics	0.28 (0.07, 1.18)	0.082

Results presented in cumulative odds ratio (OR) and 95% confidence intervals (95% CI). NYHA: New York Heart Association. LVEF: Left-ventricular ejection fraction. HFrEF: Heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. ACE: angiotensin-converting enzyme. The reference category for medicines (OR = 1) is "not using the medicine". Chi-square of final model fitness = 88.4, $p < 0.001$. Nagelkerke R-square = 62.4%. Test of parallel lines: $p = 0.944$.

Discussion

Studies on the overlap of frailty and sarcopenia are unknown in HF patients and are scarce in other populations. Sousa-Santos et al. found a frequency of 2.2% of coexistence of these conditions in a sample of community-dwelling Portuguese older adults (n = 1454, aged ≥ 65 years) [15]. Rasheedy & EL-Kawaly reported an overlap of 25.3% of frailty and sarcopenia in a sample of 206 hospitalized Egyptian patients with ages ≥ 60 years and with multiple comorbidities and diseases, including 21.4% of HF patients who were not stratified for the co-occurrence [16]. Both these studies used the same assessment methods (Fried et al. and EWGSOP2) for classifying frailty and sarcopenia as the present work. Ibrahim et al., using the Fried et al. and the previous EWGSOP criteria [17], found a frequency of 14% of overlapping between frailty and sarcopenia in a sample of older British patients hospitalised for acute disease (n = 233, aged ≥ 70 years) [18]. The same defining methods were used by Gingrich et al. in a sample of 100 German inpatients older than 70 years, with a reported frequency of 19% of co-occurrence of frailty and sarcopenia [19]. The present study's overlapping frequency of 8.1% seems to be placed between the reported percentage for community-dwelling older adults and data from hospitalised geriatric patients. The relatively low frequency of coexistence of frailty and sarcopenia signifies that each of these two conditions still deserves individual attention from health professionals in their clinical practice.

The association of depression with frailty is well established, with each condition being associated with increased prevalence and incidence of the other [20]. One of the criteria for assessing frailty according to Fried et al. is the presence of exhaustion [2], which is evaluated using two questions taken from the Center for Epidemiologic Studies of Depression scale [21] and in a previous work of this research group, we found that exhaustion was the most frequent criterion for defining frailty in this sample [10]. Sarcopenia also seems to be related to depressive symptoms [22–24]. For these reasons, it is no surprise that the prescription of antidepressants is associated with the cumulative existence of frailty and sarcopenia. The assessment of depressive symptoms and their relation with frailty and sarcopenia in this sample is to be further studied, but we believe that these patients could benefit from mental health interventions to improve their quality of life.

In this study, the use of anticoagulants was a predictor of co-occurrence of frailty and sarcopenia. Frail patients with atrial fibrillation have higher risks of incidental stroke, mortality and duration of hospitalisation than non-frail ones [25] and anticoagulants can improve the prognosis of frail individuals. Despite this, the prescription of anticoagulants is usually limited in frail patients due to the risk of falls and bleeding complications [26]. A meta-analysis by Oqab et al. comprising three studies on the prescription of anticoagulants in older adults with atrial fibrillation concluded that frail patients were less likely to receive this medication when

compared with non-frail ones [27]. In our bivariable analysis, both anticoagulant use and atrial fibrillation were not related to the categories of coexistence of frailty and sarcopenia, but frail patients were more likely to use anticoagulants. It is worth mentioning that the patients in this sample were not previously diagnosed for frailty nor sarcopenia, thus these conditions could not have been a factor for selective prescription of anticoagulants while having atrial fibrillation was: 95% of the patients in this condition were prescribed anticoagulants (data not shown). This result deserves further study. By contrast to anticoagulants and antidepressants, statins were associated with a reduced likelihood of accumulating frailty and sarcopenia. This finding is to be studied in another occasion.

Having HFpEF was associated with a very increased likelihood of having coexistence of frailty and sarcopenia. It is known that frail HF patients are more likely to have HFpEF, and sarcopenia may share a common pathophysiology with HFpEF and frailty [28,29], which seems to confirm our results. HFrEF and HFpEF have different epidemiological and aetiological profiles: patients with preserved LVEF are typically older, more often women and have a higher propensity for having a history of atrial fibrillation and hypertension than patients with HFrEF, whereas deaths and hospitalisations for HFrEF are more likely to be related to cardiovascular events such as myocardial infarction [30,31]. Treating patients with HFpEF remains a challenge in cardiology. While pharmacological treatment for HFrEF is mainly centred in the cardiac function, with demonstrated success for medicines such as ACE inhibitors and beta-blockers, no treatment has yet been shown effective in reducing mortality and hospitalisation in HFpEF patients [8,32]. However, a very recent double-blind trail comprising almost 6000 patients with LVEF > 40%, conducted by Anker et al., concluded that empagliflozin reduced the risk of cardiovascular death or hospitalisation for HF, irrespective of the presence of absence of diabetes [33]. Until further developments, guidelines and recommendations for treating HFpEF patients are limited to the management of symptoms and comorbidities and the improvement of their quality of life [8,32]. Similarly, drug treatments for sarcopenic patients with HF are in the embryonic stage and still to be proven safe and effective [34] and no exclusive medicine therapy is known for addressing frailty in HF. Sarcopenia is also associated with reduced quality of life in patients with HFpEF [35]. For these reasons, interventions centred on nutrition and exercise training can potentially improve the quality of life of HFpEF patients with associated frailty and sarcopenia [28,36,37].

Some study limitations can be accredited. First of all, causal associations cannot be inferred due to the cross-sectional nature of this study. Furthermore, the relatively small size of the sample might limit the interpretation of the results. Finally, muscle quantity was classified using anthropometric measurements, while EWGSOP2 recommends the use of other methods which were not available at the clinical setting this study was conducted in, such as dual-energy x-ray absorptiometry (DEXA) or bioelectrical impedance. In these circumstances, the

EWGSOP2 recommends the use of calf circumference [3], which is supported by a recent publication from Sousa-Santos et al., that showed a very high specificity of calf circumference and mid-upper arm muscle circumference to classify sarcopenia in comparison with appendicular skeletal muscle mass measured using DEXA [38]. We additionally estimated muscle mass from mid-upper arm muscle circumference as this body part is usually free from oedema in HF patients, as discussed elsewhere [10].

Regardless of the aforementioned limitations, this is, to our knowledge, the first work that describes the coexistence of sarcopenia and frailty in HF patients and associates the co-occurrence of these conditions to clinical variables such as LVEF and medicine use. However, the burden of the coexistence of frailty and sarcopenia remains unknown. It would be significant to investigate the outcomes resulting from the cumulative effects of both these conditions in HF patients, namely in mortality and hospitalisation. Additional studies should focus on the intervention on frail and/or sarcopenic patients with HFpEF. On a finishing note, our results also reinforce the need to assess sarcopenia and frailty in HF patients in daily clinical practice and to start planned and personalised nutrition and exercise intervention.

Conclusion

In resume, being a woman, being older, having HFpEF, using anticoagulants and anti-depressants and not using statins were associated with having concomitant frailty and sarcopenia. A relatively low frequency of coexistence of frailty and sarcopenia means that these conditions still deserve individual attention. Nevertheless, studying this coexistence allowed for isolating the patients who were at higher risk of developing HF complications and, more importantly, pinpointed the relevance of looking more thoroughly at the patients with HFpEF. Pharmacological therapies aimed at this triad of often coexisting conditions of sarcopenia, frailty and HFpEF are still to be proven effective. For this reason, patients can potentially benefit from interventions that impact their quality of life such as nutritional and mental health interventions and exercise training.

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Competing Interests

The authors have nothing to disclose.

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Chapter 4 – Hand Grip Strength

Hand grip strength cross-sectional association with clinical, nutritional, and physical activity variables in heart failure outpatients

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Title

Hand grip strength cross-sectional association with clinical, nutritional, and physical activity variables in heart failure outpatients

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Acronyms

HF: Heart failure
HGS: Hand grip strength
NYHA: New York Heart Association
LVEF: Left-ventricular ejection fraction
DeM: Deus ex Machina project
HFpEF: Heart failure with preserved ejection fraction
HFmrEF: Heart failure with mildly reduced ejection fraction
HFrEF: Heart failure with reduced ejection fraction
MUAC: Mid-upper arm circumference
MAMC: Mid-upper arm muscle circumference
TST: Triceps skinfold thickness

Abstract

Background and aim: Low hand grip strength (HGS) is associated with worse heart failure (HF) outcomes such as death and hospitalisation. Little is known regarding the associations between clinical, nutritional and physical activity statuses and HGS in HF patients, especially in Portugal, where HGS values remain undocumented. This work aims at describing these associations.

Methods and results: In this cross-sectional study, we recruited 136 ambulatory HF patients aged 24-81 years, 33.8% women, from whom HGS was measured using a Jamar dynamometer. Low HGS was defined as <16Kgf in women and <27Kgf in men. Clinical status (HF functional classes, ejection fraction, polypharmacy), nutritional status (anthropometrically estimated muscle mass, body mass index) and physical activity were evaluated. Median HGS was 28.9Kgf (men=34.6Kgf; women=21.3Kgf). Low HGS accounted for 41.9% of the sample. Logistic regression results showed that men had lower odds of presenting low HGS than women (OR=0.11, 95%CI=0.02, 0.49). Being active and having more muscle mass were associated with higher HGS (OR=0.21, 95%CI=0.06, 0.71 and OR=0.63, 95%CI=0.45, 0.88, respectively), whereas higher body mass index predicted low HGS (OR=1.28, 95%CI=1.05, 1.57). Age, polypharmacy, functional classes and ejection fraction were not associated with HGS.

Conclusions: In this sample, weight status, muscle mass and physical activity were associated with HGS but age and clinical indicators of HF were not. These associations between nutritional status and physical activity and muscle strength confirm the relevance of HGS as a marker of general muscle health and reinforce the importance of nutritional and exercise interventions in HF patients, which remain an unmet need.

Keywords

Handgrip strength; Heart failure; Left-ventricular ejection fraction; Polypharmacy; NYHA classification; Physical activity; Muscle mass

Introduction

Heart failure (HF) is characterised by lower cardiac output which reduces tissue perfusion and affects oxygenation to the skeletal muscle. HF is also associated with reduced physical activity, low-grade inflammation and metabolic changes such as insulin resistance. All of these factors cause a plethora of skeletal muscle abnormalities, which include alterations in fibre type and contractibility, reduction in the number of mitochondria, lowered oxidative metabolism and increased levels of cytokines, among others, leading to a reduction in skeletal muscle strength, bulk and function (1,2).

Hand grip strength (HGS) is a measure of global skeletal muscle strength, often used to classify sarcopenia and frailty phenotype (3,4). Evidence regarding the use of HGS as a biomarker for ageing has been growing (5), as well as its use as a marker of nutritional status (6) and as an end-point for therapies oriented for patients with cardiovascular disease (7). A recent meta-analysis by Pavasini et al., including 23480 patients from 7 studies, concluded that low HGS predicted cardiac death, all-cause death and hospital admission in HF patients (8). Moreover, HGS is inversely associated with the risk of developing HF (9,10).

Although HGS is gaining relevance as an important predictor of HF and its outcomes, evidence regarding its associations with clinical variables such as the severity of HF and the cardiac function are scarce, contradictive and is even inexistent regarding the intake of medicines. Similarly, associations between HGS and indicators of nutritional status and physical activity in HF patients have not been widely explored yet, let alone in the Portuguese HF population, where HGS values remain undocumented. The purpose of this study is, therefore, to describe associations between clinical, nutritional and physical activity variables and HGS in a sample of Portuguese HF outpatients.

Methods

Collection of data for this cross-sectional study was undertaken at an HF outpatients' clinic of a university hospital in northern Portugal, from September 2017 to July 2018, and was developed as a part of the Deus ex Machina (DeM) project, further studied within the AdHeart project. Participants were randomly selected from the patients' lists. Inclusion and exclusion criteria were applied at recruitment: participants were included if they were 18 years or older and had a clinically-validated diagnosis of HF (11); patients with severe visual impairment were excluded, as well as those within the NYHA class IV, for their difficulty in complying with the research protocol.

Clinical information was collected during appointments with cardiologists and medical records were consulted for completion. Data comprises the presence of atrial fibrillation, incidental stroke, medication, NYHA functional classification and phenotype of HF, classified

as heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF), whenever their left-ventricular ejection fraction (LVEF) was <40%, 40-50% or ≥ 50%, respectively. Polypharmacy was defined as the concomitant use of 5 or more different medicines per day (12).

Anthropometric measurements were carried on as described elsewhere (13) and include standing height, weight, mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST). Mid-upper arm muscle circumference (MAMC) was used to estimate muscle mass and was calculated using the Jelliffe equation (14): MAMC = MUAC - (3.14 x TST). Body mass index (BMI) was calculated using the standard formula: BMI ($Kg.m^{-2}$) = weight (Kg) / $height^2$ (m).

Physical activity was assessed by self-report, using the International Physical Activity Questionnaire – Short Form, validated for the Portuguese population. Individuals were categorised as "inactive", "minimally active" and "active" (15).

HGS was measured according to the instructions of the American Society of Hand Therapists (16), using a Jamar Plus+ digital hand dynamometer (Sammons Preston Inc., Bolingbrook, Illinois, USA), with a resolution of 0.1 Kgf. Measurements were undertaken with the patient seated in an upright position with the arm adducted at the side, the elbow flexed at 90 degrees and the wrist at 15-30 degrees of dorsiflexion. The average value of three repeated maximum contractions of the non-dominant hand was used for this study. A total of nine patients had their HGS measured using the dominant hand: four reported pain on the non-dominant hand; three had injuries; one underwent a recent hand surgery and one was amputated. Sex-specific cut-offs were used to define low HGS: < 27 Kgf for men and < 16 Kgf for women (17).

Statistical analyses

The sample was described according to HGS categories (normal vs. low). Shapiro-Wilk test was used to classify the normality of the distributions. Categorical data were analysed using Pearson's chi-square test or Fisher's exact test, as appropriate; parametric variables were analysed by Student's unpaired t-test and non-parametric variables by the Mann–Whitney U test. Categorical values are presented as number (n) and percentage (%). Continuous values with normal distribution are presented as means (M) and standard deviations (SD), whereas values with skewed distribution are depicted as medians (Md) and inter-quartile ranges (IQR). Bonferroni correction was used to assess significant differences between subsets of categorical data in comparisons with more than two categories.

The associations between independent variables and HGS were evaluated by logistic regression analysis. The following predictors were included in the model: NYHA functional classes I, II and III (categorical); HF LVEF classification, categorized as "HFpEF" and "HFrEF + HFmrEF"; polypharmacy as the daily use of 5 or more medicines (categorical); age

(continuous); sex (categorical); MAMC (continuous); BMI (continuous); physical activity categorized as “inactive” and “minimally active + active”. Missing values (LVEF, n = 3; NYHA, n = 2) were included in the reference categories. NYHA class II and class III were included as dummy-encoded variables in regard to NYHA class I. Linearity between continuous variables was assessed. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A value of $p < 0.050$ was considered to indicate statistical significance in all analyses. Software Package for Social Sciences (SPSS) for Windows (version 27.0; SPSS, Inc., Chicago, IL) was used to conduct all calculations.

Ethics

All participants provided a fully informed written consent to take part in this study. The project was conducted in compliance with the principles of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the *Centro Hospitalar Universitário São João* (process reference number 57/17).

Results

Of the 139 patients enrolled into DeM, 136 patients completed the entirety of the protocol and were included in the present study. Overall, median age of participants was 59.0 years (IQR = 49.0, 68.0 years) and 33.8% were women. Median HGS of the total sample was 28.9 Kgf (IQR = 23.2, 37.3 Kgf), being higher in men (Md = 34.6 Kgf; IQR = 28.7, 40.9 Kgf) than in women (Md = 21.3 Kgf; IQR = 17.4, 24.6 Kgf).

The sample’s characteristics, stratified by normal vs. low HGS, are shown in **Table 1**. A total of 57 (41.9 %) participants had low HGS. Patients with low HGS were more frequently women, were significantly shorter and lighter and had lower estimated muscle mass than those with normal HGS ($p < 0.001$ for all associations). Participants in NYHA class I were more likely to have normal HGS whereas low HGS was more frequent in patients within NYHA class III ($p = 0.002$). Participants with low HGS were also more likely to be physically inactive and less likely to be minimally active and active than those with normal HGS ($p = 0.001$).

The multivariable model was able to correctly classify 84.4% of the cases and to explain 64.9% of the variance (Nagelkerke R-square) in HGS. The logistic regression results are presented in **Table 2**: men had much lower odds of presenting low HGS than women (OR = 0.11, 95% CI = 0.02, 0.49). Being physically active and having higher estimated muscle mass were inversely associated with low hand grip strength (OR = 0.21, 95% CI = 0.06, 0.71 and OR = 0.63, 95% CI = 0.45, 0.88, respectively). Contrariwise, higher BMI was a predictor of lower HGS (OR = 1.28, 95% CI = 1.05, 1.57). Age, polypharmacy, functional classes and ejection fraction were not associated with categories of HGS in this sample.

Table 1. Characteristics of the sample according to hang grip strength categories

	Normal HGS (n = 79)	Low HGS (n = 57)	*p*-value
Age, years, Md (IQR)	58.0 (49.0, 65.0)	64.0 (49.5, 70.0)	0.069
Sex, n (%)			< 0.001
Women	6 (7.6)	40 (70.2)	
Men	73 (92.4)	17 (29.8)	
School years, Md (IQR)	9.0 (6.0, 12.0)	6.0 (4.0, 12.0)	0.053
NYHA Classes, n (%)			0.002
NYHA Class I*	36 (46.8)	11 (19.3)	
NYHA Class II	33 (42.9)	32 (56.1)	
NYHA Class III*	8 (10.4)	14 (24.6)	
LVEF categories, n (%)			0.312
HFrEF (< 40%)	39 (50.6)	27 (48.2)	
HFmrEF (40-50%)	24 (31.2)	13 (23.2)	
HFpEF (≥ 50%)	14 (18.2)	16 (28.6)	
Incidental stroke, n (%)	19 (24.4)	13 (23.6)	0.924
Atrial fibrillation, n (%)	9 (12.2)	10 (17.5)	0.386
Nr. of medicines/day, n (%)			0.178
<5 medicines/day	23 (29.5)	11 (19.3)	
≥5 medicines/day	55 (70.5)	46 (80.7)	
Physical Activity, n (%)			0.001
Inactive*	34 (43.0)	42 (73.7)	
Minimally active*	33 (41.8)	13 (22.8)	
Active*	12 (15.2)	2 (3.5)	
Weigth, Kg, Md (IQR)	81.8 (74.2, 91.8)	73.0 (64.6, 80.2)	< 0.001
Heigth, cm, M (SD)	169.6 (7.1)	157.5 (9.2)	< 0.001
BMI, $Kg.m^{-2}$, M (SD)	29.0 (3.9)	29.6 (4.9)	0.393
BMI classes, n (%)			0.678
Underweight + normal	14 (17.7)	11 (19.3)	
Overweight	35 (44.3)	21 (36.8)	
Obese	30 (38.0)	25 (43.9)	
MAMC, cm, M (SD)	26.7 (2.8)	23.3 (3.1)	< 0.001

Results presented in mean (M) and standard deviation (SD) or in median (Md) and inter-quartile range (IQR) or in number (n) and percentage (%). HGS: hand grip strength. NYHA: New York Heart Association. LVEF: Left-ventricular ejection fraction. HFrEF: Heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. BMI: body mass index. MAMC: mid-upper arm muscle circumference. Missing values: LVEF = 3; NYHA = 2; incidental stroke = 3; atrial fibrillation = 5. * denotes categorical subsets with significant differences as per Bonferroni adjusted *p*-values.

Table 2. Bivariable and multivariable results from the logistic regression regarding low hand grip strength

		Unadjusted			Adjusted	
		OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
NYHA functional classes						
Class I		1			1	
Class II		3.17 (1.38, 7.29)	0.007		1.29 (0.36, 4.64)	0.697
Class III		4.58 (1.59, 13.17)	0.005		2.33 (0.44, 8.95)	0.375
Ejection Fraction						
HFrEF + HFmrEF		1			1	
HFpEF		1.46 (0.68, 3.12)	0.332		1.71 (0.48, 6.14)	0.408
Polypharmacy						
< 5 medicines/day		1			1	
≥ 5 medicines/day		1.75 (0.77, 3.94)	0.181		2.15 (0.46, 10.07)	0.331
Age, years		1.02 (0.99, 1.05)	0.142		1.02 (0.98, 1.08)	0.343
Sex						
Women		1			1	
Men		0.04 (0.01, 0.10)	< 0.001		0.11 (0.02, 0.49)	0.004
BMI, $Kg.m^{-2}$		1.04 (0.96, 1.12)	0.391		1.28 (1.05, 1.57)	0.017
MAMC, cm		0.66 (0.52, 0.77)	<0.001		0.63 (0.45, 0.88)	0.006
Physical Activity						
Inactive		1			1	
Minimally active + active		0.27 (0.13, 0.57)	< 0.001		0.21 (0.06, 0.71)	0.012

Results presented in odds ratio (OR) and 95% confidence intervals (95% CI). NYHA: New York Heart Association. LVEF: left-ventricular ejection fraction. HFrEF: heart failure with reduced ejection fraction. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. BMI: body mass index. MAMC: mid-upper arm muscle circumference. Omnibus test $p < 0.001$; Nagelkerke R-square = 0.649; Hosmer and Lemeshow $p = 0.938$. Model accuracy = 84.4%. Model sensitivity = 78.9%. Model specificity = 88.5%.

Discussion

This study did not find associations between important characteristics of clinical status of patients with HF and HGS, namely with severity of symptoms and capacity for physical exercise classified according to the NYHA classes, with the type of HF classified according to LVEF and with polypharmacy.

The age of participants with low HGS was insignificantly higher than that of those with normal HGS; multivariable analysis confirmed the lack of association between age and HGS in this sample. In a previous work investigating frailty phenotype and conducted on the same dataset, we also did not find a relation between age and frailty, except for the oldest (≥ 70 years) participants, who were more likely to be frail. It is worth mentioning that low HGS was a criterion for defining frailty in roughly 75% of the participants (13). Therefore, age does not seem to be a defining condition for frailty nor for HGS in this population.

The relation between HGS and NYHA functional classes has not been comprehensively studied yet but the few works addressing it seem to support an inverse relation between grip strength and NYHA classes. Duarte et al. found an association between continuous HGS and the decrease in the risk of being at NYHA classes III/IV in a cross-sectional study comprising 500 older congestive HF patients (18). Other works report bivariate analysis, portraying a certain tendency of decrease of HGS with increase in functional classification (19–21). In our bivariate analysis, an increase in NYHA classification was associated with low HGS, with an increase in crude OR from class II to class III, but after adjusting for covariates this association lost significance. However, it is important to mention that our study did not include patients within NYHA class IV, which can limit the interpretation of our results.

Studies exploring the association between HGS and LVEF are even scarcer. Izawa et al. did not find significant differences in HGS between male elderly HF patients with HFpEF vs. HFrEF (23). Zhu et al. found a positive association between HGS and LVEF in men, but not in women, in a population-based study involving 908 participants. This study, however, did not specify the participants according to their diagnosed conditions, nor classified LVEF as a categorical variable (24). The present results add to the possibility that HGS is not associated with ejection fraction in HF patients.

We are not aware of any previous studies which have tested for associations between polypharmacy and HGS in the HF population. However, this relation seems to be inverse in other populations (25–27). The lack of association found in the present study can be potentially explained by the fact that there were also no differences between HGS categories and the severity or the phenotype of HF, hence patients with similar clinical statuses were more likely to be similarly medicated, irrespectively of their age and nutritional or functional conditions.

The loss of muscle strength can be perceived within the larger framework of sarcopenia, a disease that also involves the loss of muscle mass and, in severe forms, the impairment in muscle functionality (4). While sarcopenia in this sample is to be deservedly addressed in another work, the association of low estimated muscle mass with low HGS that we found in the present study confirms the need to look closely at this disease, which is very prevalent in HF patients (28) and foretells worst outcomes (29). Similarly, the inverse association that we found between BMI and HGS might also be a signal of sarcopenic obesity, which is associated with cardiovascular outcomes, comorbidities, hospitalisation and mortality in patients with HFpEF (30). As previously discussed, LVEF was not associated with HGS in this sample, but the frequency of HFpEF patients with low HGS is higher than those with normal HGS (28.6 % vs. 18.2 %), albeit without statistical significance. This tendency may indicate that there could be a cluster of patients with HFpEF that are at risk of complications related to metabolic impairment of the skeletal muscle combined with adiposity, and this idea seems to be supported by the association we found between physical inactivity and low HGS. This result is expectable, as exercise capacity is known to be associated with higher HGS in HF patients (31). It is also recognised that sarcopenia is one of the leading causes of poor physical performance and impaired cardiorespiratory fitness in HF patients (32). Furthermore, sarcopenic obesity is associated with exercise intolerance, which is the most frequent symptom in HFpEF patients (30), an idea that is supported by a study comprising 733 healthy participants, conducted by Jung et al., who reported that individuals with sarcopenic obesity had significantly lower exercise capacity than those who were only obese or sarcopenic (33). These relations between adiposity and muscle strength and mass warrant further investigation, namely within HFpEF patients.

Regarding sex, men were much less likely to have low HGS than women. This might be attributable to the sex-specific cut-offs used to define low HGS, which were calculated from T-scores of -2.5 of normative HGS values for the British population (17). These cut-offs were adopted by the European Working Group on Sarcopenia in Older People in their latest consensus regarding the definition and diagnosis of sarcopenia (4), and have been universally used. However, they do not take in consideration the influence of height, age or body mass on HGS, and they might not reflect the phenotypical variability between different populations from various geographical origins. In Portugal, reference HGS values are only available for older adults (34). Normative HGS values for the entire Portuguese population, stratified by age and height, would probably allow for a better definition of specific cut-offs, but these values are yet to be produced.

We recognise limitations of our study, such as the already discussed use of cut-offs for defining low HGS. Other limitations are related to the cross-sectional design, which cannot provide causal associations, and the small sample size, which might limit the interpretation of

the results. Moreover, patients within NYHA class IV were excluded from this study; as aforementioned, not including these patients can also limit the interpretation of our results, as this functional class comprises the patients that are the most symptomatic and less tolerant to exercise capacity. Finally, the use of MAMC for estimating muscle mass can also be regarded as a limitation; advantages and constraints concerning the use of this anthropometrical estimator were extensively explained in a previous work (13).

Regardless of the aforesaid limitations, this work is, to our knowledge, the first to study associations between nutritional, clinical and functional characteristics of patients with HF, and HGS values. Carrying out nutritional strategies aimed at HF patients remains an unmet need, either in research or within the HF guidelines (11). We believe that HGS can be used both as a marker for those at risk of adverse HF outcomes and as an end-point for longitudinal studies regarding nutrition and exercise training interventions in HF patients.

Conclusions

In this sample, weight status, estimated muscle mass and physical activity were associated with HGS but clinical indicators of HF, namely LVEF, NYHA classes and concomitant use of medication, were not. These associations of indicators of nutritional status and physical activity with muscle strength confirm the relevance of HGS as a marker of general muscle health and reinforce the importance of nutritional and exercise interventions in HF patients.

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Competing interests

The authors declare that they have no competing interests.

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General Discussion

General Discussion

There are several aspects within the present work that request a thorough discussion, either regarding the results presented in each paper or concerning the crosstalk between the results conveyed by the included papers.

The present study encompassed a sample of HF outpatients whose ages ranged from 24 to 81 years, with a median age of 59.0 years. Apart from some rare exceptions concerning end-stage HF patients, other studies that focused on frailty and sarcopenia in HF populations were generally developed around much older samples, an aspect that must be contemplated when establishing comparisons between this work and others.

Results from Paper 1 showed that frailty was frequent in HF Portuguese outpatients, at 15.4%, with pre-frailty being present in 57.4% of the participants. These values were higher than those for the general population, such as the pooled prevalence reported by O'Caoimh et al., of 12% and 46% for frailty and pre-frailty, respectively[55], but lower than the physical frailty prevalence in HF populations, as estimated by Denfeld et al. at 42.9%[96]. If only patients 70 years or older were selected, the frequency of frailty raised to 33.3%, which was a much more comparable value, as most works report frailty prevalence of older samples. This is the case with Pulignano et al., that accounts for 26.6% of frail individuals in a community-dwelling sample of ≥ 70 years Italian HF patients with reduced or normal LVEF[202], Newman et al., with 23.2% of frailty in US community-dwelling HF patients with ≥ 65 years[203], or Dominguez-Rodriguez et al., with 28.0% of

frail individuals within a sample of Spanish HF patients with 70 years or older with HFrEF[204].

Associations in Paper 1 were studied using ordinal logistic regression, hence the measures of association portrayed the transitions from normal status to pre-frail and from pre-frail to frail. Muscle mass, estimated by MAMC, was a consistent predictor for being pre-frail and/or frail: each unit (cm) increment in MAMC was associated with a 23% decrease in the likelihood of being classified from normal to frail. This association was expected, as the loss of muscle mass is one of the defining criteria of sarcopenia, which is a main contributor to physical frailty[65], while also being in line with the mechanisms that lead to wasting in HF, namely the catabolic imbalance fuelled by mitochondrial dysfunction and inflammation[180].

Obesity (BMI ≥ 30 Kg/m^2) was strongly associated with a higher likelihood of being pre-frail and/or frail, but only in men. The proportion of obese individuals in this sample was very high, at 40.4%, and was present in 42.9% of frail participants. If the obesity paradox was to be taken into consideration in the context of this association, it would conflict with the fact that frailty is associated with worse HF outcomes. The finding and confirmation of the obesity paradox were mainly based on BMI assessment[205]. Oroeopoulos et al., however, found that BMI lead to a frequent misclassification of fat mass in HF patients when compared with DEXA-measured fat and lean body masses, and that increased body fat was associated with unfavourable changes in HF prognostic factors while increasing lean mass was associated with favourable changes in other aspects. This means that BMI may not be a good surrogate measure to evaluate

fat mass in HF patients and that lean mass can have a preponderant role in the obesity paradox[206]. Interestingly, obese individuals with preserved muscle mass seem to have a better prognosis than patients with sarcopenic obesity[207], good cardiorespiratory fitness seems to mitigate the obesity paradox[208], and a reduction in lean mass impairs cardiorespiratory fitness, independent of cardiac function[209]. In the present sample, as aforementioned, muscle mass was inversely associated with the probability of being pre-frail and/or frail, which suggests that, if obesity was also present in the individuals with poorer frailty status and lower quantity of muscle mass, they would be at higher risk of worst outcomes.

The role of BMI in establishing the obesity paradox, as well as the heterogeneity of the studies and the many confounders and biases that can underlie the association of obesity with outcomes are still subject to criticism[210]. However, studies using other methods of body composition estimation, such as waist circumference, waist-hip ratio, skinfold estimates, and bioelectrical impedance analysis seem to also confirm the obesity paradox in HF[207]. It would be interesting to study if the obesity paradox would be observed in HF patients even in the presence of frailty, a study that would only be possible to carry on in a longitudinal fashion and with methods that would estimate lean and fat masses with better precision.

Age ≥ 70 years was associated with a very increased likelihood of being pre-frail and/or frail in women, but not in men. It is known that women live longer than men but at the same time they accumulate a higher number of comorbidities, a phenomenon that is known as the male-female health-survival paradox. Frailty

seems to be one of those age-related complications affecting more frequently older women and confirming the health-survival paradox, independently of the measurement of frailty that is used[211,212].

Men within NYHA class I were less likely to be categorised from normal to pre-frail and to frail when compared with men in NYHA classes II and III. In the overall sample, this effect was significant for patients in class I and class II. This is conflicting with the meta-analysis by Denfeld et al., which did not find associations between NYHA functional classification and frailty[96]. It is likely, however, that the inclusion of pre-frailty in the associative model might partially explain this finding, as this category, which comprises the majority of participants (n = 78), allows for a different predictive meaning of the NYHA classification; therefore, NYHA classes, in the present work, had a predictive function towards the transition from normal to pre-frail and/or to frail, not to the classification of an individual in the category of frail or non-frail.

It was highlighted in Paper 1 that more than half of the frail individuals were younger than 65 years. This finding aroused the need to investigate for literature on the phenomena of frailty in HF younger patients, which did exist but was related to critically ill individuals with advanced HF, such as elective patients for transplantation and/or undergoing the placement of a LVAD[105–108]. Therefore, frail and pre-frail younger ambulatory patients were not properly accounted for or described in the literature, which paved the road to Paper 2.

The analysis that was undertaken in Paper 2 was based on a heterodox approach of using age (< 65 years, ≥ 65 years) as a result variable. The objective was to quantify the variables that predicted the classification of frail and pre-frail

HF patients as younger or older using logistic regression. Significant differences asserted by the bivariable analysis were scarce and contributed to the foreseeable idea that frailty and pre-frailty affected both younger and older patients in similar ways. Moreover, this limited the number of independent variables to be included in the multivariable analysis. Nevertheless, HGS, GS and diabetes were able to predict the allocation of the individuals of the overall sample in age classes. When the sample was segregated by sex, only women's HGS predicted a lower likelihood of being 65 years or older by 31% for every Kgf increase.

Diabetes was a predictor of older age in the overall sample, but not in women or men alone. It is known that diabetes, which was present in 28.7% of the sample and in 34.3% of the pre-frail and frail individuals, shares pathophysiology mechanisms with both frailty and HF[38,213]. In this sample, ageing, frailty, diabetes and HF may have been interplaying towards worse outcomes, and it is important to attend to this observation in order to improve therapeutic approaches. While obesity was not associated with age, it was nevertheless very frequent in these individuals, which may anticipate a worse scenario regarding the risk factors associated with insulin resistance. It is possible that better weight management and more thorough attention to glycaemic control in younger pre-frail and frail patients may contribute to preventing or modifying diabetes at older ages.

In Paper 1, it was discussed that slowness was not an important defining criterion in this population, as it was only present in less than 40% of the frail participants. This was attributed to the rather young and active sample. In Paper

2, gait speed, which was readjusted to the standing height of individuals due to very evident differences in stature between participants in the < 65 and ≥ 65 years' categories, was a predictor of older age in the overall sample (but not in women or men alone), which confirmed the growing importance of this frailty criterion with age. In fact, in older patients, slow gait is associated with worse HF prognosis, including HF mortality, all-cause mortality and hospitalization[202], and short-term increments in gait speed are associated with lower risks of death and readmission[214]. Malnutrition seems to be a determinant of slow gait in older (> 80 years) HF patients[215].

Despite the associations of HGS, diabetes and GS with age, the general scarcity of differences between younger and older frail and pre-frail HF patients that were illustrated in Paper 2, stresses the need of assessing physical frailty in every HF patient, irrespective of age or HF severity. This recommendation was already conveyed in 2019 by Vitale and Uchmanowicz[216], two main contributors to the research of frailty in HF, and the present study further enhances the evidence underlying this imperative necessity.

Papers 1 and 2 acknowledged the need of studying sarcopenia in this sample, by identifying the presence of concomitant low HGS and low estimated muscle mass. Moreover, the high frequency of obesity among those who had low HGS raised suspicion regarding the presence of sarcopenic obesity. Paper 3, therefore, pursued the study of sarcopenia.

Regarding the reported frequency of sarcopenia of 18.4%, it seemed to be within the overall prevalence from other studies including HF patients, being smaller than the pooled prevalence of 26% in outpatients described in a meta-

analysis by Zhang et al.[179]. The papers included in the meta-analysis regarding ambulatory patients are referent, in general, to older samples, with the exception of the works by da Fonseca et al., reporting a prevalence of sarcopenia of 28% and 39.3% on two samples of Brazilian male patients, both of them with a median age of 58 years and including only patients with LVEF < 40%[217,218]. Older (65.6±13.0 to 67.3±10.1 years) outpatient studies included in the meta-analysis report sarcopenia frequencies between 10.3% and 21.5%[179], which are much similar to the frequency described in Paper 3.

Interestingly, Zhang et al. included in their meta-analysis[179] a study by Hajahmadi et al., who did not report sarcopenia but muscle wasting instead, estimated by DEXA-measured ASM, with a frequency of 47.3% in a sample of 55 Iranian HF patients with a mean age of 37.3±10.1 years[219]. This shows that the inconsistency in classifying sarcopenia goes beyond the different standards and methods used for individual studies, as a work that does not address sarcopenia according to international standards is included in a meta-analysis regarding the prevalence of sarcopenia. This very elevated frequency of appendicular muscle wasting might have contributed to a higher pooled prevalence of sarcopenia in ambulatory patients and the overall population.

Nevertheless, it is possible that the anthropometric methods that were used to estimate muscle mass may have induced some bias in the frequency of sarcopenia that was found in this work: MAMC and/or CC may underestimate muscle mass when compared with BIA and/or DEXA[122,162]. The ability to classify sarcopenia according to different methods may depend, however, on the cut-off points that are used to classify low muscle mass using BIA or DEXA and if the

muscle mass estimated by these methods is adjusted to standing height or not. Sousa-Santos et al. demonstrated that the plethora of measurement methods and different cut-offs could induce critical dissimilarities in the frequencies of individuals classified as sarcopenic, with differences in classification that ranged from 1.3% using DEXA and ASM/height^2, to 18.9% using BIA and skeletal muscle mass index. In the same study, CC was shown to have a very high specificity in classifying sarcopenia when compared with reference criteria of ASM measurements using DEXA, namely a specificity of 100% contrasted with ASM and of 94% contrasted with ASM/height^2. MAMC was not far behind CC, with respective values of sensitivity of 96% and 85%. This shows that anthropometry can be a valid indicator to rule in the presence of sarcopenia when no other method is present[162].

Statins were included in the prospective analysis that led to the production of Paper 3, as these drugs, which were prescribed to 65.4% of the sample, are deemed as a probable risk for developing sarcopenia[220] and are generally associated with muscle complications[221]. It was soon noted, however, that patients from this sample who used statins were remarkably less likely to be sarcopenic. This was confirmed in multivariable analysis, with the use of statins being associated with a very reduced likelihood of having sarcopenia (OR = 0.06; 95% CI = 0.01, 0.40), irrespective of age, sex, fat intake, polypharmacy, physical activity, BMI and HF aetiology.

The study of the use of statins as a specific therapy for treating HF is not a recent trend. In 2006, an observational study by Anker et al., using data from

various European cohorts, concluded that statins were associated with increased survival of HF patients[222].

In 2007, the CORONA study published its results of an RCT encompassing 5,011 systolic HF patients that were given rosuvastatin vs. placebo. The statin group presented decreased levels of low-density lipoprotein cholesterol and C-reactive protein, but statin use was not associated with primary outcomes of cardiovascular events or death. However, there were significantly fewer hospitalisations in the statin group, and no adverse events, including muscular effects, were reported in the statin group[223]. Despite the large sample, there are some aspects of the CORONA study that could have limited the associations between statins and primary outcomes: patients with LVEF ≥ 40% were not included, whereas many studies report beneficial effects, including reduced mortality, in patients with HFmrEF and HFpEF[224]; patients were of advanced age (73±7.1 years), therefore more likely to have a more advanced stage of HF, while rosuvastatin was associated with lower mortality and cardiovascular incidents in patients with lower amino-terminal pro-brain natriuretic peptide, which is a marker of cardiac dysfunction and worse HF prognosis[225]; and only rosuvastatin, a hydrophilic statin, was used, whereas the most beneficial effects may be exerted by lipophilic statins[224].

A similar and contemporary RCT, the GISSI-HF, also used rosuvastatin at the same doses as the CORONA but enrolled slightly younger and less symptomatic participants. Also, while the CORONA study was centred on ischaemic disease patients, the GISSI-HF had fewer participants with ischaemic conditions. The study population (n = 4,574) was mainly comprised of patients

with HFrEF (89.9%). The results were similar to the CORONA's, but non-significant for hospitalisation. Rosuvastatin was also deemed safe for HF patients[226].

A lipophilic statin, pitavastatin, was used in the PEARL study. This RCT, conducted by Takano et al., included 574 Japanese patients with LVEF ≤ 45%. Pitavastatin was not associated with the primary outcome of combined HF hospitalisation and death in the exposed arm but had a protective effect on a sub-group of patients with LVEF ≥ 30%[227].

A meta-analysis of 24 trials, conducted by Al-Gobari in 2017, also did not find relevant associations between statin use and sudden cardiac death and all-cause mortality in HF patients. Hospitalisation was, however, slightly reduced[228]. This meta-analysis included 11,463 patients, with roughly 70% of them being from the CORONA, GISSI-HF and PEARL studies.

The ESC guidelines from 2016 and 2021 reflect the aforesaid evidence – or lack of – and do not recommend initiating statin therapy in HF patients. As statins are safe for HF patients, those who are already using them as indicated for coronary artery disease and/or hyperlipidaemia do not need to discontinue the therapy[2,45].

There is no evidence that clearly associates the use of statins to the instalment or worsening of sarcopenia. A case-control study by Herghelegiu et al., that included 368 Romanian elderly community-dwelling older adults, concluded that atorvastatin and simvastatin, but not rosuvastatin, were associated with "high risk" of sarcopenia[229]. This risk was, however, defined as

lower gait speed. Therefore, the work of Herghelegiu et al. only used a single dimension of sarcopenia and not the full definition. Moreover, gait speed was relegated by the 2018 EWGSOP2 consensus as a classifier of severe sarcopenia and not as a defining criterion of sarcopenia or of the risk of sarcopenia[110]. Contrariwise, Lin et al. found a protective effect of statins against newly onset sarcopenia in a Chinese cohort of 75,637 chronic kidney patients[230]. In postoperative patients with abdominal aortic aneurysms, Lindström et al. found that statin users had lower mortality and a lower reduction in the psoas muscle area when compared with non-statin users[231].

The presumptive relation between statins and sarcopenia was built upon the associations between this medicine use and reported symptoms of side-effects, such as myalgia and rhabdomyolysis, and that statins do have a certain effect on muscle homeostasis, through mechanisms of inflammation, apoptosis, myostatin, mitochondrial dysfunction, insulin-like growth factor 1 and ubiquitin-proteasome system[232,233]. Yet, statin-induced myalgia does not seem to be associated with poorer muscle function, as demonstrated by a study conducted by Mallinson et al.: compared to a group of non-statin users, age-matched older men who had statin-induced myalgia did not show reductions in muscle strength and mass, dysregulations in protein turnover or increased inflammatory markers. The authors found, however, an increased expression of mRNA markers of mitochondrial dysfunction and apoptosis in statin users[234].

In an extensive systematic review, Bielecka-Dabrowa et al. hypothesised that the potential prosarcopenic effects of statins may limit their effectiveness in HF patients[232]. This very informative and elegantly constructed work was,

however, based on the premise that the promising beneficial effects of statins on HF patients were not confirmed in large randomised studies, such as the CORONA or GISSI-HF trials, and in the suggestion that statins could have a prosarcopenic effect.

More recently, Bielecka-Dabrowa and colls. went to search for further evidence towards the effects of statins in HF, particularly in the association of statin use and HF outcomes in every HF phenotype, as data in HFpEF and HFmrEF were lacking. The authors systematically rounded up a total of 17 studies, including 15 prospective cohorts and two RCT (CORONA and GISSI-HF). This allowed for a meta-analysis that included a total of 88,100 patients (mean age 67±7.2 years), with a mean follow-up time of 36 months, and the study of the effects of different statin types (lipophilic, hydrophilic) in patients within every range of LVEF. General conclusions were that statins were associated with a reduction of all-cause mortality, cardiovascular mortality and hospitalisation in HF patients, irrespectively of the LVEF or the HF aetiology, and that lipophilic statins had larger and more significant effects on all outcomes than hydrophilic ones[224].

Statins are competitive inhibitors to the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an early stage hepatic convertor of a cholesterol precursor[235]. This class of medicines arose from the work of Akira Endo, who committed himself to find a mechanism for inhibiting one of the 30 enzymatic reactions of cholesterol synthesis. It was observed by Endo that, as antibiotics inhibited many enzymatic reactions, it was possible that metabolites produced by fungi could inhibit the HMG-CoA reductase. In 1973, Endo was able

to isolate a metabolite from a *Penicillium* mould that had a potent inhibitory effect on HMG-CoA reductase, both *in vitro* and *in vivo*. Further research contributed to isolating, modifying and testing other substances. It was only in 1987 that the first commercial statin, lovastatin, went on sale[236].

It was soon noted that the lipid-lowering effect of statins was not enough to explain the improvements in cardiovascular outcomes of patients undergoing statin treatment and that statins could exert other beneficial effects that went beyond their primary target[237]. This pleiotropy can result in vascular and myocardial benefits[232,238].

Many of the pleiotropic effects of statins are exerted on the vascular endothelium through several mechanisms that contribute to an anti-atherogenic state. This includes, among others, reduction in the expression of adhesion molecules, decrease in plasminogen activity, decrease in the synthesis of endothelin-1, reduction of oxidative stress, inhibition in the proliferation of c-reactive protein and cytokines, increase in the number and in the differentiation of circulating endothelial cells, reduction in apoptosis and increase in the nitric oxide synthesis and bioavailability[237,239,240]. Statins also seem to reduce myocardial oxidative stress, suppress arrhythmogenesis and slow down cardiac remodelling[224].

A recent systematic review by Amarasekera et al. showed that endothelial dysfunction may be an early marker of physical frailty and sarcopenia and that endothelial dysfunction shares pathophysiologic factors between these conditions and cardiovascular diseases[134].

Dos Santos et al. studied the arm and leg blood flow, measured using venous occlusion plethysmography, in 228 HF patients and 32 controls, taken from a subsample of the SICA-HF study. The authors concluded that HF patients with sarcopenia had impaired endothelial function and that the lower vasodilation in sarcopenic patients negatively impacted exercise capacity[241].

A probable mechanism for the association of endothelial dysfunction and sarcopenia was suggested by Alcalde-Estévez et al., who used murine myoblasts incubated with a peptide, endothelin-1, which has elevated expression in dysfunctional vascular endothelium. The incubated myoblasts presented senescence and fibrosis[242]. Sahebkar et al. showed a significant effect of statins, particularly of the lipophilic type, in the reduction of plasmatic endothelin-1 in a meta-analysis comprising 15 RCT[243].

In resume, statins can improve endothelial and cardiac functions, contributing to improved muscle perfusion. Statins can also reduce substances that have deleterious effects on muscle cells, such as endothelin-1, cytokines, and c-reactive protein. Attending to the abovementioned mechanisms and to the observation that statin use was inversely associated with sarcopenia in the present work, it is possible to hypothesise that the pleiotropic effects of statins may contribute to better neuromuscular fitness and thus may mitigate or delay the onset of sarcopenia on HF patients.

In Paper 3, polypharmacy was associated with a higher likelihood of being sarcopenic, which is in line with the results of a cross-sectional study from König et al.[244]. Polypharmacy was also associated with sarcopenia, disability and mortality in a cohort of community-dwelling Japanese older adults[245]. However,

polypharmacy is universal in HF patients, and in many cases, strictly necessary towards the management of HF and its associated comorbidities. This, therefore, limits the strategies intending to reduce polypharmacy.

Hopper et al. conducted a pilot RCT to investigate if the withdrawal of statins or aspirin to patients with HFrEF would have any consequence. They concluded that, except for a rise in LDL-cholesterol values, removing statin medication did not have an effect in HF clinical status[246], which was evaluated using surrogate endpoints. The study had a duration of six months with the cross-over at three months; therefore, the exposure time was rather short. The study did not include outcomes such as HF incidents or other cardiovascular incidents, hospitalisation, cardiovascular death, or all-cause death. Consequently, it cannot be concluded if the withdrawal of statins had a beneficial effect just for the sake of reducing polypharmacy.

More evidence is needed regarding the effects of statins in HF patients and in sarcopenia before it can be asserted if they should be withdrawn or withheld in the logic of, respectively, reducing polypharmacy or treating HF and/or sarcopenia.

In the present study, physical inactivity, which was very frequent in this sample (55.9%), was associated with sarcopenia, as expected, as both HF and sarcopenia concur to limit exercise capacity. Statins do not seem to have a negative impact on exercise capacity[247] and may even increase the response to exercise training[248]. In HF patients, statins are also not associated with changes in exercise capacity and in the quality of life[249].

Patients who had an aetiological diagnosis of hypertrophic cardiomyopathy (HCM) were more likely to be sarcopenic. This association is undocumented. However, it can be reasoned that the inherited muscular disorders that comprise most of the causes of HCM can also possibly be responsible for phenotypical alterations in the skeletal muscle[250,251].

The lack of evidence regarding the overlapping between frailty and sarcopenia in HF patients was mitigated by the results of Paper 4, which reported a frequency of 8.1% of coexistence of these two conditions, with 44% of the sarcopenic participants being frail and 53% of the frail participants being sarcopenic, which confirms the observation by Mijnarends et al., that not all frail persons are sarcopenic and a smaller percentage of sarcopenic individuals are frail[252]. This relatively low frequency of coexistence of physical frailty and sarcopenia in HF patients was higher than that of community-dwelling older adults and lower than those of geriatric hospitalised patients and nursing home residents, ranging from 2.2% to 25.3% in the few works that addressed the overlap between these conditions[253–257].

It is interesting that sarcopenia and frailty universally present such low coexisting rates while having such clear overlaps between definitions[53,110,112,258], causes[52,110,190,259] and treatments[258,260,261]. This low frequency of coexistence was confirmed, per the present results, in HF patients. Considering that HF is a contributor to the instalment and worsening of both frailty and sarcopenia[43,98,177,180], this meagre overlap seems even more bewildering. However, sarcopenia is presently considered an established muscle disease and physical frailty, as defined by Fried et al.[53], is a syndrome with demarcated

phenotypical characteristics. The clear distinction between these conditions might have been amplified by the efforts of Cruz-Jentoft et al. in updating the definition and diagnosis of sarcopenia[112], and by the recent contributions of Fried et al. in establishing a more profound rationale for the crystallisation of the physical frailty phenotypical criteria as a sensible set of measurements for asserting changes in homeostasis[77]. In resume, physical frailty and sarcopenia are two unquestionably distinct conditions, and the low coexistence between them confirms this, even in the presence of HF. This strongly implies that, in clinical practice, one cannot be used as a surrogate to the other, hence frailty and sarcopenia must have individualised attention and therapeutic procedures.

In Paper 4, variables were associated using an ordinal regression towards the result variable categorised as a presentation of three degrees of the presence of frailty and sarcopenia. Measures of association would, therefore, quantify the transitions from not having any condition, to presenting one of the conditions (frailty or sarcopenia) and to having both conditions coexisting.

Older patients were more likely to be concomitantly frail and sarcopenic: for every year increase in age, the cumulative odds of transitioning towards coexistence increased by 12%. In Papers 1 and 2, age was not found to be an important variable in defining frailty in this sample, except for the oldest (≥ 70 years) participants. When this model of coexistence was used, it became clear that age was associated with having concomitant frailty and sarcopenia, which was an expected result.

As already discussed regarding the results of Paper 3, polypharmacy was associated with a higher likelihood of being sarcopenic, which is in line with the

literature[244]. It is also known that polypharmacy is associated with poor outcomes in frail individuals[262]. However, polypharmacy is a somewhat abstract construct that only accounts for the effect of the usage of five or more of any given medicine. For this reason, it was decided to include the most usually prescribed medicines in the analysis of Paper 4, in order to study possible associations between the use of individual medications and the increasing accretion of physical frailty and sarcopenia. The multivariable results showed direct associations between the use of antidepressants and oral anticoagulants and the likelihood of accumulating frailty and sarcopenia, and an inverse association with the use of statins.

Depression is common in HF[263], in frailty[264] and in sarcopenia[265]. For that reason, it is expectable that the use of antidepressants was associated with a growing degree of accumulation of conditions. It should be noted that depression is a very complex disease that is associated with worse HF outcomes, such as hospitalisation, cardiovascular death and all-cause death[266]. Therefore, this subject should merit further research.

Anticoagulants are usually prescribed to HF patients presenting atrial fibrillation, as they help to prevent thrombotic events[2]. Accordingly, 95% of patients with atrial fibrillation in this sample were prescribed anticoagulants. Frail patients with concomitant atrial fibrillation have a higher risk of incidental stroke, mortality and hospitalisation than non-frail ones[267]. The use of anticoagulants can improve the prognosis of frail individuals, but the prescription of these medicines to frail patients is to be made with caution, as frail patients have a higher risk of falls, which can result in haemorrhagic complications[268]. The risk

of falls can be further increased by polypharmacy in older patients[269]. Moreover, sarcopenic patients, and some of the frail, present reduced muscle mass, which reduces the concentration of hydrophilic anticoagulants in the muscle and raises them in the plasma, contributing to a supra-therapeutic activity of anticoagulants, with associated increase in the risk of bleeding complications[270]. Therefore, it is advisable that the risk of falls, thrombosis, bleeding events and other outcomes is assessed before initiating anticoagulant therapy[268]. This explains why frail patients are usually less likely to be medicated with anticoagulants than the non-frail, despite the advantages of anticoagulant therapy[271]. In contrast, the frail individuals in the present sample were more likely to be medicated with anticoagulants than non-frail ones (57.1% vs. 30.4%), which may be explained by the fact that the frailty status of these patients was unknown to the cardiologists prior to the collection of the data the present work was based upon. No differences were found between sarcopenic and non-sarcopenic participants in regard to anticoagulant use.

The results of Paper 4 seemed to reinforce the association of statin use with lower odds of being sarcopenic but applied to a model where sarcopenia and frailty were studied concomitantly. In fact, statin users had a reduced likelihood of being classified towards having coexistence of frailty and sarcopenia. As associations between physical frailty and statin use were not pursued in this work, this may warrant further study.

A result that may be considered impactful in Paper 4 was the association between the phenotype of HFpEF and the very high likelihood of increasing coexistence of frailty and sarcopenia. Patients with HFpEF are frequently frail[91]

and sarcopenia in these patients is associated with a reduced exercise capacity and quality of life[272]. In particular, sarcopenic obesity is notably associated with HFpEF and with comorbidities, worse cardiovascular health, exercise intolerance, quality of life, hospitalisations, and mortality in this HF phenotype[273].

Kinugasa and Yamamoto postulate that metabolic and endocrine abnormalities in sarcopenia, and to a greater extent, sarcopenic obesity, seem to be associated with the development of HFpEF. Patients with this HF phenotype are usually older, more frequently female and obese, and HFpEF is common in frail patients. The authors suggest that the interplay between the pathophysiologic mechanisms of sarcopenia and obesity contribute to the onset of cardiovascular remodelling or diastolic dysfunction that leads to HFpEF[274].

Treating patients with HFpEF remains an unmet need. This HF phenotype differs aetiologically and epidemiologically from HFrEF, and the pharmacological interventions that are standard to the treatment of HFrEF have consistently failed to demonstrate results in patients with preserved LVEF. Therefore, treating patients with HFpEF is usually limited to the improvement of their quality of life and the management of their comorbidities[2,275].

Notwithstanding this, future pharmacological therapies may possibly be considered towards treating HFpEF. A very recent double-blinded randomized controlled trial concluded that empagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced the combined risk of cardiovascular death and hospitalisation in HFpEF patients, regardless of the presence of diabetes[276]. Statins may also improve outcomes in HFpEF. In a study by Alehagen et al., including 9,140 Swedish patients with LVEF ≥ 50%, statins were associated with better survival,

reduced mortality and hospitalisation[277]. In two meta-analyses including patients with HFpEF, statins were associated with lower mortality risk[278,279]. As a matter of fact, statins exert beneficial effects in many factors that contribute to the pathophysiology of HFpEF, such as inflammation, left-ventricular hypertrophy, arterial stiffness and interstitial fibrosis[232].

In general, Paper 4 was able to round up the characteristics of the patients that, by having a higher likelihood of being concomitantly frail and sarcopenic, were also at a high risk of worse outcomes of HF, namely older adults, women, patients with HFpEF, those that may have presented depression symptoms, i.e., the ones who were prescribed antidepressants, and those that may have had atrial fibrillation, which are roughly the same as those who were undergoing anticoagulant therapy. As there are no proven pharmacological treatments for HFpEF, frailty and sarcopenia, these patients could benefit from exercise training, nutrition and mental health interventions.

The aim of Paper 5 was to seek associations between HGS and variables of clinical, nutritional and physical activity status, and to report HGS values for the Portuguese HF patients.

There are not many studies describing HGS values from HF populations, and a high heterogeneity is found in the measurement processes, used dynamometer, used hand and number of repetitions. Moreover, the present work reports medians and interquartile ranges of HGS, as this variable had a skewed distribution, whereas most works report mean values and standard deviations. Also, sample ages, settings and phenotypes of HF widely vary. This makes it difficult to establish comparisons between this sample's HGS values and other

HF populations and substantiates the need to standardise the measurement procedures across studies.

Nevertheless, the assumed, albeit incorrectly, HGS mean and standard deviation in this sample was 30.9±10.8 Kgf (women: 21.0±4.9 Kgf; men: 36.0±9.5 Kgf), which is higher than that of a sub-sample of Brazilian HF hospitalised patients without cachexia, at 26.6±10.5 Kgf, using the same methods as this study[280], and lower than a sub-sample of Spanish HF hospitalised patients without frailty, at 32.5±16 Kgf, using a slightly different methodology[281].

In Paper 5, associations were tested using multivariate logistic regression with the result variable being low HGS. There were no significant associations for participants' age nor any variable depicting HF clinical status, including NYHA classes, LVEF and polypharmacy.

Concerning NYHA classes, there are very few works to contrast with the present results but there seems to be a tendency for an inverse relation between HF severity and HGS. In a cross-sectional study from Duarte et al., continuous HGS inversely predicted the classification in NYHA classes III/IV in a sample of Brazilian congestive HF patients[282]. Other three studies report bivariate relations: Izawa found a significant difference in HGS values from NYHA class I in comparison with class II and III, but not between classes II and III in Japanese HF patients[283]; Cadena-Sanabria and Velandia-Carrillo found a gradual decrease in HGS according to NYHA class in Colombian geriatric HF patients[284]; Castillo-Martínez reported a significantly lower HGS in the NYHA class III/IV group when compared with the NYHA I/II in a sample of Mexican HF patients[285].

In regard to the HF phenotypes, the existing literature is even more diffuse. Izawa et al., again in a bivariable fashion, was not able to find significant differences in HGS between HFpEF and HFrEF in Japanese hospitalised HF patients[286]. Zhu et al. reported an association between continuous HGS and LVEF in men but not in women, in a population-based Chinese study where participants were not defined regarding their diagnosed condition[287]. The lack of association between HGS and LVEF the present study portrays seems to confirm that these dimensions are not associated.

As for polypharmacy, it is known to have an inverse association with HGS in populations of non-HF patients[288–290]. In the present study, it was not, however, associated with HGS. It is possible that the lack of association between HGS and NYHA functional classes or LVEF may indicate that the patients were similarly medicated, therefore the patterns of drug use were not different between categories of HGS.

Muscle mass estimated by MAMC and physical activity were inversely associated with low HGS, whereas BMI was directly associated. This interplay between low HGS, low muscle mass, low activity and obesity is suggestive of sarcopenic obesity, which was reported in Paper 3, with a frequency of 5.1%, and discussed in the context of the results of Paper 4, concerning patients with HFpEF.

General results regarding age revealed some inconsistencies. Continuous age was not related with frailty or pre-frailty, nor with HGS, but was associated with sarcopenia and with the coexistence of frailty and sarcopenia. Categorical age ≥ 70 years was associated with frailty in women but not in men, and age ≥

65 years was associated with sarcopenia. Moreover, patients with 65 or more years were also more likely to have concomitant sarcopenia and frailty, but not frailty. Only frail and pre-frail patients in the ≥ 65 years' category were more likely to have lower HGS.

Speculatively, it is possible that the decline of muscle strength with age in HF patients starts at younger ages than in general populations but at somewhat lower rates of decay, which could explain part of these inconsistencies, while the muscle mass might be preserved for a longer time and has a steeper decline at more advanced ages. This seems consistent with the observation that the loss of muscle strength precedes that of muscle mass[124], and in HF patients, this difference may be amplified at the onset of the pathophysiologic mechanisms that contribute to a pro-inflammatory state that leads to HF, namely through the effect of mitochondrial dysfunction and oxidative stress on the myocytes. This is also supported by the observation that HF patients that become frail present a different muscle fibre profile, with more preserved type II fibres - which are related to muscle strength - than frail patients without HF or those who develop HF while already frail[104]. Angiotensin-converting enzyme inhibitors, which are standardly prescribed to HF patients, especially those with HFrEF, may play a part in the speculated differences in the loss of muscle strength, as they may contribute to preserving muscle function and strength[291,292], albeit not in elderly patients[293]. Moreover, HGS was only the third more frequent criterion for classifying frailty in this sample, behind exhaustion and low physical activity, while in general populations HGS is usually the most frequent frailty criterion[58,190]. This might mean that, while HGS was low enough to present itself as a criterion of frailty, it may have a less steep decline with age than in general populations. However, as

per the results of Paper 2, HGS was the most frequent criterion among older pre-frail and frail subjects (≥ 65 years), which may be inconsistent with this argument.

In this logic, the early but conservative loss of muscle strength would contribute to fewer differences between age in frail and pre-frail HF patients, while the muscle mass would have a less gradual loss, thus would be more sensitive towards the classification of sarcopenia as patients' age increases. Therefore, it may be possible to hypothesise that HF patients – and especially those that develop HF at younger ages - have different rates of change in weakness and muscle loss than non-HF individuals, including those that also develop sarcopenia and/or physical frailty. These speculative differences between patterns of muscle dysfunction deserve further study, preferably in a longitudinal fashion.

The research that was developed within this work, despite its obvious limitations, marks the beginning of the much-needed investigation of frailty and sarcopenia and their associated factors in Portuguese HF patients. Throughout this discussion, it has become clear that the presented results contributed to identifying needs for further research. Also, many findings can have an impact on clinical practice. These subjects will be addressed over the next sections.

Clinical Applicability

Clinical Applicability

One of the main concerns regarding the management of HF in Portugal is the lack of integrated multidisciplinary programmes, as identified by Fonseca et al.[21]. Some of the findings from the set of papers this dissertation is based on can have direct clinical applicability and contribute to enriching the rationale underlying the design and implementation of the necessary multidisciplinary programmes to manage HF.

Assessing frailty and diagnosing sarcopenia in HF populations is an urgent need in clinical practice in Portugal. Both these conditions are modifiable and are associated with poor outcomes in HF, but it is still not usual to evaluate their presence in standard practice.

Frailty and sarcopenia secondary to HF can and do affect younger (< 65 years old) patients, including ambulatory ones. This fact demands a shift from the perspective of these conditions as exclusive to the geriatric domain. Geriatricians and other professionals who are experienced in dealing with frailty and sarcopenia should participate in the assessment of these conditions in younger HF patients and contribute to training other professionals in diagnosing and managing these conditions. The notion that all HF patients, irrespective of their age, must be assessed for frailty and sarcopenia, must gain traction in clinical settings.

Special attention should be given to patients with HFpEF regarding their frailty and sarcopenia status and their weight management. These patients tend to be older, more frequently frail and to have sarcopenic obesity. Moreover, as there is no pharmacologic therapy specifically aimed at HFpEF patients, their

symptoms are usually harder to control. Therefore, interventions centred on ameliorating their quality of life and their functional capacity are needed.

Assessing frailty and sarcopenia in patients undergoing anticoagulant therapy can contribute to informing the practitioners on the risks of bleeding complications and adjusting therapeutic interventions accordingly.

Hand grip strength is an adequate starting point to enhance the capacity of identifying patients at risk of frailty or sarcopenia in clinical practice. Dynamometry should be implemented in HF clinical settings to rule out the risk of sarcopenia or frailty and to monitor the progression of these conditions, as well as to support the prediction of HF outcomes. Measuring HGS is fast, easy and inexpensive. The Jamar dynamometer is recommended for use in both clinical and research settings, as its reliability and validity has been consistently proven through several studies[294]. The American Society of Hand Therapists laid down an extensively documented set of procedures for assessing HGS[295] which can be followed to standardise measurements across settings and to train health professionals. Cut-offs for assessing the frailty criterion of weakness and diagnosing probable sarcopenia by low HGS are readily available, although they are not based in Portuguese populations yet. Therefore, it would not be cumbersome to implement such a useful clinical assessment tool.

Programmes aimed at promoting physical activity, in the form of monitored exercise training, remain an unmet need in most Portuguese clinical settings and in the community. Exercise is at the forefront of the recommended therapies for both frailty and sarcopenia[260,261], a recommendation that is shared with the guidelines for managing HF[2].

Future Perspectives

Future Perspectives

This dissertation was developed around a limited sample which was studied in a cross-sectional fashion. For this reason, it was not the goal of these set of studies to assert causality or even external validity of the presented results and conclusions. However, the outputs of the five papers that integrated this work pave the road to further investigation in the HF populations. Some reflections towards the need for additional research are presented below.

The associations that were found between overlapping frailty and sarcopenia and the use of antidepressants are indicative of a well-documented relation between those conditions and depression. The multidisciplinary protocol this study was based upon includes measures of cognitive status, depression and anxiety, which were not fully analysed yet by the other participating researchers. Preliminary findings from the DeM sample, however, showed that 27% of the patients had moderate to severe depression symptoms[296] and that 47% had cognitive impairment, which coexisted with frailty and pre-frailty in 39% of the patients[297]. Collaborative work is warranted towards research on the associations between frailty, sarcopenia, HGS, and the aforementioned dimensions of mental health.

This study was developed on ambulatory patients. The status of hospitalised patients for HF and of those who live in residential care, regarding frailty and sarcopenia, remains undocumented in Portugal.

The association of statin use with a lower likelihood of having sarcopenia is one of the most curious results of this work, as statins are usually associated with muscle dysfunctions. Paper 3 raises the interesting hypothesis that the

pleiotropic effects of statins in vascular function may contribute to the preservation of muscle mass and function in HF patients, thus delaying the onset of sarcopenia. This hypothesis is sustained in enough biological plausibility to justify its further exploration in the form of experimental studies. These future studies should contemplate different HF phenotypes as well as diverse dosages and types of statins, as the effects of statins may vary according to the aforementioned variables.

Sarcopenic obesity and severe sarcopenia were, for the first time, accounted for in Portuguese HF patients. However, these conditions were not studied in the depth they deserve to. Larger samples would allow for a more concise perspective on these disorders.

The present sample was assessed for the presence of undernutrition and undernutrition risk, using the Mini Nutritional Assessment – Short Form®[298,299]. A total of 31.6% of the participants were at risk of undernutrition, and none was undernourished. As the bivariable analysis was not significant for frailty, sarcopenia or HGS status, this variable was not included in this work. It is possible that the generally younger average age and the ambulatory nature of this sample may be related to the lack of significant results. However, undernutrition is associated with HF, frailty and sarcopenia. Therefore, further studies comprising a larger number of participants and that include hospitalised and older patients should encompass the evaluation of undernutrition.

The coexistence of sarcopenia and physical frailty was identified and characterised in the present work, but its burden remains unknown in HF patients. Studies investigating the outcomes resulting from the cumulative effects of frailty and sarcopenia in HF are, therefore, warranted.

One of the main limitations of this set of studies, which was thoroughly reported in most papers, was the use of anthropometry to estimate muscle mass. However, there are no studies that compare the use of anthropometric estimators with other methods of body composition assessment such as BIA or DEXA, in HF populations. HF patients present a set of characteristics that may be of interest in further exploring the use of anthropometric measurements: they are usually well accepted by individuals with functional deficit, which is the case with many HF patients, and MAMC is performed in the upper arm, where oedema is very rare. Moreover, there are some limitations to the use of other methods of evaluation of muscle mass in HF patients: abnormal fluid distribution may induce errors in BIA; implantable devices may limit magnetic methods and safety concerns cannot be fully disregarded; non-anthropometric methods are costlier, non-portable and frequently unavailable, and exposure to radiation should be avoidable whenever possible. Sousa et al. found a quite dramatic underestimation of sarcopenia classified with the use of MAMC when compared to BIA in a sample of hospitalised patients[122], but in Paper 3, sarcopenia was classified using MAMC and CC as estimators for muscle quantity and the frequency of sarcopenic patients was in line with the global prevalence of sarcopenia in HF ambulatory patients[179]. Comparisons of different methods for evaluating muscle mass, including anthropometric measurements, should be therefore warranted in HF populations.

Another limitation of this study was that patients within the NYHA functional class IV were excluded during the recruitment process. This exclusion was made to avoid subjecting patients in such limiting conditions to the discomfort of going through a rather long and demanding multidisciplinary study protocol. Moreover,

the projects this study was nested in were aimed at testing a novel non-invasive telemonitoring integrated system, and the sample that served as a basis to this study was a baseline sample from which sets of individuals would be selected to test various iterations of the telemonitoring system in a following study phase. Having patients at NYHA IV participating in the tests was considered to be too cumbersome both to the patients and to the medical and research staff. However, it would be extremely useful to investigate frailty, sarcopenia and HGS in NYHA IV patients in future works, as this functional class is comprised of individuals that are the most symptomatic and have very severe limitations in physical activity.

This investigation identified the need of producing normative HGS values for the Portuguese population, stratified by age, sex and standing height, among other possible variables. These normative values, when available, will be used to compare individuals and samples and, more importantly, to define more specific cut-offs that allow for researchers and clinicians to base their evaluations on. Therefore, population-based studies aimed at collecting HGS values from healthy Portuguese individuals of all age strata should be carried on.

In parallel, it would be interesting to study the evolution of muscle strength and mass with age in HF patients or in individuals at risk of developing HF, as these parameters may have a slightly different pattern of evolution than in the general population.

Treatments to modify frailty and/or sarcopenia that are sustained on evidence are limited to multicomponent physical activity for frailty and resistance-based training for sarcopenia. Protein supplementation and combined exercise and protein intake can be conditionally recommended on the basis of low certainty of evidence. Vitamin D, hormonal and pharmacological therapies are

not recommended, as there is insufficient evidence for their effects[260,261]. In HF patients, the treatment of frailty should be aimed at the multifactorial nature of this syndrome, and can include physical exercise, protein supplementation and the treatment of comorbidities[97,300]. Resistance training can have benefits on sarcopenia in HF patients[301]. However, most of the evidence regarding interventions on frail and sarcopenic HF patients is related to older adults. In Papers 2 and 3, high proportions of individuals with frailty, pre-frailty and sarcopenia that were younger than 65 years were reported. It would be interesting to study how younger HF patients would respond to interventions aimed at preventing or modifying frailty and sarcopenia.

Telemonitoring interventions on HF patients have been shown to reduce the risk of mortality, and higher frequencies of monitoring can increase the effectiveness of the telemonitoring systems[302]. Systems using medicine support and mobile health were associated with improvements in mortality and hospital outcomes[303]. In fact, telemedicine has been emerging as an improvement in the management of HF patients. The COVID-19 pandemic has contributed to accelerating the implementation of various telemedicine solutions, which will most likely be reinforced in the upcoming years. Further advancements may come in the form of artificial intelligence, which can optimise the management of HF patients using telemedicine[304]. One of the monitoring solutions that can be easily implemented in a telemedicine system is the measurement of HGS. Dynamometers that can be connected to electronic devices such as smartphones are being developed for various applications[305–308]. The BodyGrip prototype seems to be particularly promising, as it was developed for detecting sarcopenia and physical frailty and can measure other parameters that regular

dynamometers cannot, such as real-time force applied at every moment of the exertion[308]. The inclusion of a wireless hand dynamometer in a non-invasive telemedicine system for HF patients could provide useful information on the evolution of muscle strength in these patients, such as assessing the risk of adverse HF outcomes, the risk of the onset of sarcopenia or frailty or monitoring for evolutions following integrated interventions aimed at treating HF, frailty and sarcopenia.

Conclusions

Conclusions

Frailty and pre-frailty were frequent in this sample of HF outpatients, inclusively in a large percentage of younger individuals. Low muscle mass was a consistent predictor of having pre-frailty and/or frailty and should be considered in interventions aimed at modifying frailty.

In frail and pre-frail outpatients, differences between the younger and the older individuals were very scarce, which confirms that all HF patients should be screened for frailty, irrespective of chronologic age. Lower HGS was associated with older age. Therefore, this measure could be potentially used to differentiate younger individuals with accelerated myopathy.

Sarcopenia was frequent among the studied patients. Severe sarcopenia and sarcopenic obesity were also diagnosed. Contrarily to what was expected, statin use was associated with a lower likelihood of being sarcopenic, irrespectively of age, sex, polypharmacy, physical activity and HF aetiology. It can be hypothesised that the pleiotropic effects of statins may exert benefits in endothelial function, thus contributing to better neuromuscular fitness.

The frequency of the coexistence of frailty and sarcopenia was low, which justifies the need for individualised attention to these conditions. However, studying their co-occurrence allowed for isolating the individuals who may be at a higher risk of poor outcomes, such as the older, the women, those who are prescribed antidepressants and/or anticoagulants, and patients with HFpEF. The latter share the inexistence of pharmacological therapies with frailty and sarcopenia, thus may benefit from exercise training, nutrition and mental health interventions.

Low HGS was particularly associated with a poorer nutritional status, namely with low muscle mass and high BMI, and with low physical activity, but was not predicted by HF clinical status variables, such as LVEF, NYHA classes or polypharmacy. This confirms the relevance of HGS as a marker of general muscle health and reinforces the importance of nutrition and exercise interventions in HF patients.

The present work's results contribute to increasing the evidence regarding these conditions and to reinforce the necessity of assessing physical frailty and sarcopenia in HF patients, which remains an unmet need in Portuguese clinical practice, as well as the importance of looking at these conditions and their clinical, functional and nutritional factors in regard to establishing intervention plans that can contribute to better HF outcomes.

This work unveiled aspects that were previously unknown and that warrant further research. Among those, some deserve to be highlighted: the high frequency of physical frailty in younger patients that were not critically ill; the unexpected protective effect of statins on sarcopenia and the hypothesis that statins may contribute to better muscle health through pleiotropic effects on endothelial function, and the coexistence of frailty and sarcopenia as possible indicators of clusters of individuals that have a potential increased risk of worst outcomes.

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