U.PORTO

DOUTORAMENTO

CIÊNCIAS MÉDICAS

Quality of life in heart failure: what matters?

Irene Marques

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Maria Irene Marques Moreira

Instituto de Ciências Biomédicas Abel Salazar

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Tese de Candidatura ao grau de Doutor em Ciências Médicas

Programa Doutoral da Universidade do Porto

(Instituto de Ciências Biomédicas Abel Salazar)

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Para o Paulo,

por tudo

Vê lá o que fazes, há tanto a fazer

Fazes que fazes, ou pões sementes a crescer?

Precisas de água, terra também

Ventos cruzados e o sol, a chuva que os detém

Vivida a planta, refeita a casa

É espaço em branco, o tempo de escrever e abrir asa

…

Vê lá o que fazes, há tanto a fazer

Fazes que fazes, ou pões sementes a crescer?

Sérgio Godinho

Grão da mesma mó

in Nação Valente, 2018

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FOREWORD

One of the most important insights I gained about life and medicine was realizing that people only truly understood a subject matter after learning its history, how it originated, and how it has evolved over the years. This is true for medicine, scientific knowledge, and people themselves. This is why I will share with you a small part of the history that brings us to the present and to this thesis.

I have not always wanted to be a physician. I wanted to be a psychologist; someone who understands and helps people live better lives. Back then, just before my university application, a teacher convinced me that I would lead a better life as a psychiatrist than as a possibly unemployed psychologist. At medical school, at the Instituto de Ciências Biomédicas Abel Salazar (ICBAS), I discovered patients and internal medicine. It was love at first sight.

As a physician, I have been caring for patients with heart failure (HF) for 25 years. As an internist at Hospital Santo António (HSA), I realized that HF was one of the most frequent causes of admission to the Emergency and Internal Medicine Departments. Nevertheless, there was no plan to reduce those admissions. HF was not an area of interest for most of my colleagues. In 2009, two other physicians and I decided to take action to improve the quality of care for HF patients. Eventually, only I pursued that goal. In 2010, the aim of creating a multidisciplinary HF clinic was embraced by my department. The team was assembled later that year, consisting of me, a cardiologist, a physiatrist with cardiac rehabilitation expertise, a nephrologist, a psychiatrist, a nutritionist, a social worker, and several nurses. Finally, in 2013, the GEstIC HF clinic began to offer optimized care to patients admitted for acute HF. We initiated interventions during hospitalization and ensured a smooth transition of care to our outpatient clinic, where a structured management program is in place.[1] This was our “gesture” (GEstIC meaning) to improve the HF scenario.

In the first years of dedicated care for HF patients, who are often aged 80 years or more, several questions have arisen in my mind: How bad is the prognosis? What can we do to make it better? How can we identify those at higher risk of death or rehospitalization? I often asked myself whether our work and effort at GEstIC were truly making a difference, in patients' lives and in the hospital quality indicators. I felt the need to investigate and measure what we were doing. This led me to fall in love with clinical research. Along this path, quality of life (QoL) was the most crucial question to answer. Back then, in 2016, I was asking: What matters most to my patients, especially those with predicted short survival and for whom are there no drugs that improve the prognosis?

ABBREVIATIONS AND ACRONYMS

USA	United States of America
6MWD	Six-minute walking distance
6MWT	Six-minute walking test
ACC	American College of Cardiology
ACEi	Angiotensin converting enzyme inhibitor
ADHERE	Acute Decompensated Heart Failure National Registry
AF	Atrial fibrillation
AHA	American Heart Association
ARNi	Angiotensin receptor and neprilysin inhibitor
BB	Beta-blockers
CHUdSA	Centro Hospitalar Universitário de Santo António
CKD	Chonic kidney disease
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy-defibrillator
CRT-P	Cardiac resynchronization therapy-pacemaker
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
EPICA	EPidemiologia da Insuficiência Cardiaca e Aprendizagem
ESC	European Society of Cardiology
FA	Fibrilhação auricular
FDA	Food and Drug Administration
FEVE	Fração de ejeção do ventrículo esquerdo
HADS	Hospital Anxiety and Depression Scale
HF	Heart failure
HFH	Hearf failure Hospitalization
HFimpEF	HF with improved LVEF
HFmrEF	HF with mildly reduced LVEF
HFpEF	HF with preserved LVEF
HFrEF	HF with reduced LVEF
HSA	Hospital Santo António
IC	Insuficiência cardíaca
ICBAS	Instituto de Ciências Biomédicas Abel Salazar
ICD	Implantable cardioverter-defibrillator
ICFEp	IC com fração de ejeção preservada
IECA	Inibidores de enzima de conversão da angiotensina
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid receptor antagonists
NAT:PD-HF	Needs Assessment Tool: Progressive Disease - Heart Failure
NP	Natriuretic peptides
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NutrIC	Nutrição e Funcionalidade na Insuficiência Cardíaca
NYHA	New York Heart Association
OCDE	Organization for Economic Co-operation and Development
PASP	Pulmonary artery systolic pressure
PDW	Platelet cell distribution width
PORTHOS	Portuguese Heart Failure Prevalence Observational Study

PRECIC	Pré Clínica de Insuficiência Cardíaca
PROM	Patient-reported outcome measures
PSAP	Pressão sistólica da artéria pulmonar
QdV	Qualidade de vida
QoL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin-angiotensin-aldosterone system inhibitors
RDW	Red cell distribution width
SGLT2i	Sodium–glucose cotransporter 2 inhibitor
T6MM	Teste de 6 Minutos de Marcha
TFGe	Taxa de filtração glomerular estimada
V-HeFT	Vasodilator-Heart Failure Trial
WHO	World Health Organization

1. ABSTRACT

Heart failure (HF) is a systemic syndrome affecting mostly older people. One in four Portuguese is aged 65 years or older. One in three Portuguese individuals aged 70 years or older has HF. HF is the most frequent cause of hospitalization among individuals > 65 years. HF has a higher 5-year mortality rate than some common cancers. Patients with advanced HF have a greater burden of symptoms and worse quality of life (QoL) than advanced cancer patients do. QoL is an independent endpoint in HF trials and QoL assessment should be integrated into the routine clinical care of HF patients.

The work reported in this thesis aimed to characterize and establish the prognosis of hospitalized HF patients, in terms of in-hospital mortality, the role of natriuretic peptides in guiding therapy during hospitalization and predicting events after hospital discharge, and the identification of independent predictors of rehospitalization and one-year mortality. Additionally, this work aimed to promote improved care for HF patients in Portugal, through the implementation and reporting of the outcomes of HF patients managed in an HF clinic, increasing awareness of the impact of optimized treatment on HF events and the need for more integrated care for HF patients. Finally, the aim was to validate a pragmatic instrument for QoL assessment in everyday clinical practice and to identify the factors with a significant impact on QoL. This work includes 14 articles that address those aims.

The article "*Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study*" reported a retrospective study with three sub-analyses that revealed that our real-world HF patients were very elderly. Additionally, 62.5% were female and 70.5% had a left ventricular ejection fraction (LVEF) ≥40%. These patients had an average of three comorbidities, among which hypertension and atrial fibrillation (AF) were the most common. We found a high burden of non-cardiovascular comorbidities, such as diabetes *mellitus*, dementia and sleep apnoea. The in-hospital mortality rate was 7.9%, and one-third of patients died or had experienced at least one rehospitalization for HF in the year following discharge. Cardiovascular (CV) deaths were as common as non-CV deaths.

In the PRECIC study sub-analysis concerning in-hospital mortality, reported in the article "*In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk vs Observed Mortality*", after patients in the PRECIC study were assigned to the Acute Decompensated Heart Failure National Registry (ADHERE) risk tree groups, the comparison between the predicted mortality and the observed mortality showed that the overall observed in-hospital mortality was two to three times higher than the predicted mortality. We found that our HF

patients were older, more frequently female, had hypertension and atrial fibrillation, and had a substantially greater LVEF than did the ADHERE sample.

The second PRECIC study sub-analysis, reported in the article "*One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)*", studied predictors for one-year mortality and revealed that the admission independent predictors of higher one-year mortality risk were age ≥80 years, active cancer, dementia, high urea levels, high red cell distribution width (RDW)(>16.3%), and low platelet cell distribution width (PDW). Among these variables, RDW was the strongest predictor of one-year mortality.

The third PRECIC study sub-analysis, reported in the article "*One-year rehospitalization and mortality after acute heart failure hospitalization: a competing risk analysis*", looked for predictors of one-year re-hospitalization for HF, by competing risk analysis. Atrial fibrillation, renal dysfunction, and beta-blocker (BB) prescription at discharge were identified as independent risk factors for one-year re-hospitalization for HF. After adjusting for sex, age, and LVEF, the risk of death without re-hospitalization was greater in men, patients aged ≥80 years, those with dementia, and those with RDW >16.3% at admission. Notably, taking a BB at discharge was associated with a greater risk of rehospitalization and a lower risk of death without rehospitalization. Additionally, renal dysfunction at the index HF admission was identified as a risk factor for overall mortality and rehospitalization, but not for death without rehospitalization. On the other hand, dementia was identified as a risk factor for overall mortality and death without rehospitalization, but not for rehospitalization.

The "*Multidisciplinary Heart Failure Clinic: How to Implement*" article reviewed the scientific evidence regarding multidisciplinary HF teams and clinics, along with testimonials of implementing such an organization. Additionally, we reported that the one-year mortality rate of patients admitted to the GEstIC between 2013 and 2015 was 10.4%, compared to the 16.1% mortality rate of the patients in the PRECIC study that had similar characteristics. The one-year rehospitalization rates for HF were 25.9% and 30.5% for GEstIC and PRECIC patients, respectively.

In the article "*NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)- Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized Controlled Trial*", we reported that patients with decompensated chronic HF who achieved an N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction of more than 30% without NT-proBNP-guided therapy, from admission to discharge, had a better prognosis. Compared to patients receiving standard-of-care therapy, patients treated to target a reduction of more than 30% in NT-proBNP levels showed no benefit in terms of event rates for all-cause mortality and

readmissions for HF within 180 days after randomization. This occurred despite a greater proportion of patients in the NT-proBNP guided therapy arm achieving the target of >30% reduction in NT-proBNP levels. A *post hoc* analysis revealed that non-guided patients had a significantly greater reduction in NT-proBNP levels than both successfully and unsuccessfully guided patients did. Finally, we found that it was not possible to lower NT-proBNP levels in 20% of patients.

Using patients from the PRIMA II trial, we proceeded with the external validation of the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score, reported in the article "*External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure*", which confirmed the predictive proportional value of the risk score and demonstrated that 6-month mortality increases with increasing score. This made it possible to predict 6-month all-cause mortality in patients hospitalized for acute decompensated HF, using NT-proBNP values in addition to easily obtained clinical and laboratory characteristics, namely: 1) absolute NT-proBNP levels at discharge; 2) the change in NT-proBNP of ≤30% from admission to discharge; 3) age, peripheral edema, systolic blood pressure and sodium levels at admission; and 4) the serum urea and New York Heart Association (NYHA) class at discharge. This reliable bedside score can be used in daily clinical practice for patients with both HFpEF and HFrEF, regardless of their NYHA class at discharge.

The "*Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study*" article reported the analysis of HF events and all-cause hospitalizations in the year following the first visit to our HF clinic, compared with the previous year. We studied 287 HF patients admitted to GEstIC between 2013 and 2019 with a minimum of 365 days of follow-up. Their characteristics were similar to those of the PRECIC study sample. We detected a decrease of 71.7% in HF hospitalizations (HFH), 53.7% in all-cause hospitalizations, and 39.1% in urgent HF visits at the end of the first year of follow-up, in comparison to the previous year. In addition to the reduction in the number of events, we found a significant reduction of 12.6 days of days passed in-hospital per patient. The 287 patients led to a total reduction of 3,624 days of hospitalization due to HF, which translates into the release of 9.9 hospital beds in the year following admission to the GEstIC. Considering only the reduction in HF events (hospitalizations and urgent visits) over the first year of follow-up in the GEstIC, we achieved an average savings of 5,439.77 euros per patient.

The "*conTemporary reflectiOns regarding heart failure management - How to ovERcome the PorTuguese barriers (TOGETHER-PT)*" article was the result of a

multidisciplinary initiative panel of twelve Portuguese HF experts, including cardiologists, internists, and general practitioners. This group designed a questionnaire to collect the opinions of a group of HF experts on how to improve HF management in Portugal. The questions focused on four areas of HF care: 1) HF awareness and literacy, 2) early HF diagnosis, 3) HF guideline-oriented treatment, and 4) HF organization of care. A group of 174 healthcare professionals with interest, expertise, and experience in HF care were invited to participate. This group included a balanced number of cardiologists, general practitioners, internists, and nurses working at primary healthcare facilities and regional or central hospitals all over Portugal. A total of 152 (87.4%) professionals answered the questionnaire. The participants identified HF literacy as an important unmet need among Portuguese HF patients and recognized the need to promote patient/caregiver education and empowerment. The study participants had a high level of agreement regarding the healthcare organization statements. Strategies to coordinate different healthcare levels and develop optimized care and effective prevention programs were identified as needed to decrease the economic and social impact of HF. This project aimed to promote changes in the HF landscape in Portugal to improve Portuguese HF patients' QoL.

The article "*Beyond clinical trials - The cost saving associated with dapagliflozin use in Portugal hospital clinical practice*" reported a multicentric study aimed at projecting the economic impact of dapagliflozin on HFH when initiated in patients who were hospitalized for HF. Dapagliflozin was one of the first drugs, alongside empagliflozin, to demonstrate a reduction in HF events and mortality in HF patients across the entire range of LVEF. The study gathered information from six Portuguese hospitals. GEstIC represented one of two hospitals that had an established HF clinic. Dapagliflozin was associated with projected HFH cost savings of 32,986.12 euros when applied to HF clinics in 2019, considering a conservative approach.

The publications that report a Portuguese expert panel position on the management of HFpEF, reported in the articles "*A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment*" and "*A Portuguese Expert Panel Position Paper on HFpEF Management - Part II: Unmet needs and Organization of Care in Portugal*", resulted from the collaborative work of cardiologists, internists and general practitioners that represent their medical societies and HF dedicated working groups, which includes me. The specific challenges in the diagnosis, treatment and management of patients with HFpEF are addressed step-by-step. The importance of multidisciplinary teams and their essential role addressing the multiple HF dimensions are reinforced, to reduce morbidity and mortality and improve patients' functional capacity and QoL. Part II focused on the unmet needs for

the organization of care for HF patients with HFpEF in Portugal. The ideal management of HFpEF patients was defined as a roadmap for screening, diagnosis, referral and treatment. Person-centred multidisciplinary care was promoted, through multidisciplinary integrated care teams involving cardiologists, internists, primary care physicians, nurses, and other health professionals, which were linked together in a seamless care system.

The validation of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) to Portuguese reported in the article "*Quality of Life Scores Association with other Patient Reported Outcomes: Validating Minnesota Living with Heart Failure Questionnaire to Portuguese*", revealed that the MLHFQ total score was associated with all the studied variables, namely: 1) the six-minute walking distance (6MWD), 2) the Borg fatigue score at the end of the six-minute walking test (6MWT), 3) the Hospital Anxiety and Depression Scale (HADS) depression score and 4) the HADS anxiety score. We reported the existence of three sub-scores: physical, emotional and social. Furthermore, we found associations between the physical score and both the Borg fatigue score and the 6MWD and between the emotional score and the anxiety and depression HADS scores.

In the study reported in the article "*Quality of life in heart failure patients: factors associated with clinically important changes. The QUALIFIER prospective cohort study*" we found that having an implanted cardiac resynchronization therapy-pacemaker (CRT-P) was the only factor associated with clinically important improvement in QoL. Additionally, other factors were associated with improved QoL: past smokers, patients with a sleep-related breathing disorder, those with higher systolic blood pressure (SBP) and those taking an angiotensin converting enzyme inhibitor (ACEi). With respect to QoL deterioration, NYHA class II-IV, an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 and recent HFH were associated with clinically important QoL changes. A comprehensive group of demographic and clinical factors were analysed using a nested model approach with adjustments for sociodemographic factors, comorbidities, self-care adherence and HF severity factors. The QoL of HF patients in the QUALIFIER study was relatively good at 3 months of follow-up in the GEstIC (25 points). The QoL improved rapidly in the first months and then more slowly, until a nadir at 10 months of follow-up. The nested models used revealed that some factors that were previously reported to negatively or positively affect the QoL of HF patients did not influence QoL after adjusting for markers of HF severity. This is the case for age, male sex, depression, poor self-care, cardiac rehabilitation, recent urgent HF visits, HFpEF and greater pulmonary artery systolic pressure (PASP).

In conclusion, we found that real-world HF patients are elderly, have a high burden of symptoms and comorbidities, and are at a high risk of death and HFH. We found that it is

possible to predict the individual risk of events using data collected in routine clinical practice. A multidisciplinary HF clinic can reduce HF events, days passed in the hospital, and costs. The MLHFQ enables QoL assessment in routine clinical practice and helps with person-centred care. Importantly, we found that what matters most to the QoL of our HF patients is living without HF symptoms and events and implanting a CRT-P when eligible. This knowledge should be applied to each clinical encounter.

Keywords: Heart failure, Quality of life, Risk stratification, Person-centred care, Heart failure clinic, GEstIC

2. RESUMO

A insuficiência cardíaca (IC) é uma síndrome sistémica que afeta principalmente idosos. Um em cada quatro portugueses tem mais de 65 anos. Um em cada três portugueses com 70 ou mais anos tem IC. A IC é a causa mais frequente de hospitalização nos indivíduos com mais 65 anos. A IC apresenta uma mortalidade aos 5 anos mais elevada do que algumas das neoplasias malignas mais comuns. Os doentes com IC avançada têm uma maior carga de sintomas e pior qualidade de vida (QdV) do que os doentes com neoplasias avançadas. A QdV é um *endpoint* independente nos ensaios clínicos sobre IC e a avaliação da QdV deve ser integrada nos cuidados aos doentes com IC.

O trabalho relatado nesta tese teve como objetivo caracterizar e estabelecer o prognóstico de doentes hospitalizados por IC, em relação à mortalidade intra-hospitalar, ao papel dos peptídeos natriuréticos na orientação da terapêutica durante o internamento e na previsão de eventos após a alta hospitalar, e à identificação de preditores independentes de re-hospitalização e de mortalidade no primeiro ano após alta. Além disso, teve como objetivo promover um melhor cuidado aos doentes com IC em Portugal, através da implementação e comunicação dos resultados de uma clínica de IC, aumentando o conhecimento sobre o impacto do tratamento otimizado nos eventos relacionados com a IC e sobre a necessidade de cuidados integrados na gestão dos doentes com IC. Finalmente, outro dos objetivos foi validar um instrumento pragmático para a avaliação da QdV na prática clínica diária, assim como identificar os fatores com impacto significativo na QdV. Este trabalho inclui 14 artigos que abordaram esses objetivos.

O estudo reportado no artigo "*Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study*" foi um estudo retrospetivo com três sub-análises que revelou que os nossos doentes com IC eram muito idosos. Também verificamos que 62,5% eram do sexo feminino e 70,5% apresentavam uma fração de ejeção do ventrículo esquerdo (FEVE) ≥40%, tinham em média três comorbilidades, das quais a hipertensão e a fibrilhação auricular (FA) foram as mais comuns. Verificámos uma elevada carga de comorbilidades não-cardiovasculares, como diabetes *mellitus*, demência e apneia do sono. A mortalidade hospitalar foi de 7,9%, e um terço dos doentes morreu ou teve pelo menos uma re-hospitalização por IC no ano seguinte à alta. As mortes de causa cardiovascular (CV) foram tão frequentes como as mortes de causa não-CV.

Na sub-análise do estudo PRECIC referente à mortalidade intra-hospitalar, descrita no artigo "*In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk vs. Observed Mortality*", após a atribuição dos doentes do estudo PRECIC aos grupos de risco do *Acute*

Decompensated Heart Failure National Registry (ADHERE), a comparação entre a mortalidade prevista e a que foi observada mostrou que a mortalidade intra-hospitalar observada foi duas a três vezes superior à prevista. Verificámos que os nossos doentes com IC eram mais velhos, mais frequentemente do sexo feminino, tinham mais frequentemente hipertensão e FA, e uma FEVE substancialmente mais elevada em comparação com a amostra de doentes do registo ADHERE.

A segunda sub-análise do PRECIC, descrita no artigo "*One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)*", estudou os preditores de mortalidade no primeiro ano após alta e mostrou que, na admissão, os preditores independentes de maior risco de mortalidade no primeiro ano foram: idade ≥80 anos, neoplasia ativa, demência, níveis elevados de ureia, *Red cell Distribution Width* (RDW) >16,3% e valores baixos de *Platelet cell distribution Width* (PDW). Destes, o RDW foi o melhor preditor de mortalidade no primeiro ano após alta.

A terceira sub-análise do estudo PRECIC, descrita no artigo "*One-year rehospitalization and mortality after acute heart failure hospitalization: a competing risk analysis*", procurou preditores de re-hospitalização por IC no primeiro ano após alta hospitalar, através de uma análise de riscos competitivos. A FA, a disfunção renal e a prescrição de betabloqueadores (BB) à data de alta foram identificados como fatores de risco independentes para a re-hospitalização por IC no primeiro ano. Após ajuste para o sexo, a idade e a FEVE, o risco de morte sem re-hospitalização foi maior nos homens, em doentes com idade ≥80 anos, aqueles com demência ou com RDW >16,3% à admissão. Notavelmente, a toma de um BB à data de alta foi associada a um maior risco de re-hospitalização e a um menor risco de morte sem re-hospitalização. Além disso, a disfunção renal à admissão foi identificada como um fator de risco para a mortalidade global e para a re-hospitalização por IC, mas não para a morte sem re-hospitalização. Por outro lado, a demência foi identificada como um fator de risco para a mortalidade por todas as causas e para a morte sem re-hospitalização, mas não para a re-hospitalização por IC.

O artigo "*Multidisciplinary Heart Failure Clinic: How to Implement?*" reviu a evidência científica sobre equipas e clínicas multidisciplinares de IC, juntamente com testemunhos sobre a implementação de uma organização deste tipo. Adicionalmente, reportamos que a taxa de mortalidade no primeiro ano dos doentes admitidos no GEstIC entre 2013 e 2015 foi de 10,4%, em comparação com 16,1% dos doentes com características semelhantes incluídos no estudo PRECIC. A taxa de re-hospitalização por IC ao fim de um ano foi de 25,9% vs 30,5% para os doentes no GEstIC e no estudo PRECIC, respetivamente.

No estudo reportado no artigo "*NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide) - Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized Controlled Trial*", verificámos que os doentes com IC crónica descompensada que atingiram uma redução superior a 30% no pro-peptídeo natriurético tipo B N-terminal (NT-proBNP) sem terapêutica guiada por NT-proBNP, desde a admissão até à alta hospitalar, tiveram um melhor prognóstico. Os doentes tratados para atingir uma redução superior a 30% nos níveis de NT-proBNP não mostraram qualquer benefício em comparação com os doentes que receberam terapêutica habitual, em termos de taxas de mortalidade por todas as causas e readmissões por IC nos 180 dias após a randomização. Isto aconteceu apesar de uma maior proporção de doentes no braço da terapêutica guiada por NT-proBNP atingir o objetivo de redução de >30% dos níveis de NT-proBNP. Uma análise *post hoc* revelou que as diferenças nas taxas de eventos de IC refletiram as diferenças na redução da percentagem de NT-proBNP. Os doentes do braço da terapêutica habitual tiveram uma redução significativamente maior dos níveis de NT-proBNP, em comparação com os doentes guiados com e sem sucesso. Por fim, verificámos que não foi possível reduzir os níveis de NT-proBNP em 20% dos doentes.

Utilizando os doentes do estudo PRIMA II, procedemos à validação externa do *score* ELAN-HF (*European Collaboration on Acute Decompensated Heart Failure*), descrita no artigo "*External Validation of the ELAN-HF Score, Predicting 6-Mont All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failur*e", que confirmou o valor preditivo do *score* de risco e demonstrou que a mortalidade aos 6 meses aumenta com o aumento da pontuação. Isto permitiu prever a mortalidade por todas as causas aos 6 meses em doentes hospitalizados por IC aguda descompensada, utilizando valores de NT-proBNP, para além de características clínicas e laboratoriais facilmente obtidas, nomeadamente: 1) níveis absolutos de NT-proBNP à data de alta; 2) redução do NT-proBNP ≤30% entre os valores de admissão e da alta; 3) idade, edema periférico, pressão arterial sistólica e níveis de sódio à admissão; 4) e ureia sérica e classe NYHA à data de alta. Esta pontuação fiável e facilmente acessível pode ser utilizada na prática clínica diária na gestão de doentes com HFpEF and HFrEF, independentemente da classe NYHA no momento da alta.

O estudo reportado no artigo "*Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study*" reportou a análise de eventos relacionados com a IC e hospitalizações por todas as causas no ano seguinte à primeira consulta na nossa clínica de IC, em comparação com o ano anterior. Estudámos os 287 doentes com IC admitidos no GEstIC entre 2013 e 2019 com um mínimo de 365 dias de seguimento. As suas características foram semelhantes às da amostra do estudo

PRECIC. Mostramos uma redução de 71,7% das hospitalizações por IC, 53,7% das hospitalizações por todas as causas e 39,1% das visitas urgentes por IC no primeiro ano de seguimento, em comparação com o ano anterior. Para além da redução do número de eventos, verificamos uma redução significativa de 12,6 dias de internamento por doente. Os 287 doentes levaram a uma redução total de 3624 dias de hospitalização por IC, o que se traduziu na redução de ocupação de 9,9 camas hospitalares no ano seguinte à admissão no GEstIC. Considerando apenas a redução dos eventos relacionados com a IC (hospitalizações e visitas urgentes) ao longo do primeiro ano de seguimento no GEstIC, obtivemos uma poupança média de 5439,77 euros por doente tratado no GEstIC.

O artigo "*conTemporary reflectiOns regarding heart failure management - How to ovERcome the PorTuguese barriers (TOGETHER-PT)*" foi o resultado da iniciativa de um painel multidisciplinar constituído por 12 especialistas portugueses em IC, entre os quais cardiologistas, internistas e médicos de clínica geral. Este grupo elaborou um questionário para recolher a opinião de um grupo de peritos em IC sobre como melhorar a gestão da IC em Portugal. As questões focaram-se em quatro áreas de cuidados de IC: 1) sensibilização e literacia sobre a IC, 2) diagnóstico precoce da IC, 3) tratamento orientado pelas recomendações para a IC e 4) organização dos cuidados na IC. Foram convidados a participar 174 profissionais de saúde com interesse, conhecimento e experiência na área da IC. Este grupo incluiu um número equilibrado de cardiologistas, clínicos gerais, internistas e enfermeiros que trabalham em unidades de cuidados de saúde primários, hospitais regionais ou centrais em Portugal. Um total de 152 (87,4%) profissionais responderam ao questionário. Os participantes identificaram a literacia sobre a IC como uma importante lacuna nos doentes portugueses com IC e reconheceram a necessidade de promover a educação e o empoderamento dos doentes/cuidadores. Os participantes do estudo apresentaram um elevado nível de concordância em relação às declarações sobre a organização de cuidados. Foram identificadas estratégias para coordenar os diferentes níveis de cuidados de saúde, desenvolver cuidados otimizados e programas de prevenção eficazes, necessários para diminuir o impacto económico e social da IC. Este projeto teve como objetivo ser promotor de mudança no panorama da IC em Portugal para melhorar a QdV dos doentes portugueses com IC.

O artigo "*Beyond clinical trials - The cost saving associated with dapagliflozin use in Portugal hospital clinical practice*" reportou um estudo multicêntrico que teve como objetivo projetar o impacto económico da dapagliflozina nas hospitalizações por IC, quando iniciada em doentes hospitalizados por IC. A dapagliflozina foi um dos primeiros medicamentos, juntamente com a empagliflozina, a demonstrar a redução dos eventos relacionados com a IC e a mortalidade em doentes com IC em toda o especto da FEVE. O estudo reuniu

informação de seis hospitais portugueses e incluiu doentes internados por IC. O GEstIC representou um dos dois hospitais que tinham uma clínica de IC estabelecida. A dapagliflozina esteve associada a uma projeção de poupança de 32986,12 euros em hospitalizações por IC em doentes seguidos em clínicas de HF em 2019, considerando uma abordagem conservadora.

As publicações que relatam a posição de um painel de peritos portugueses sobre o tratamento da IC com FEVE preservada (ICFEp), nos artigos ""*A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment*" e "*A Portuguese Expert Panel Position Paper on HFpEF Management - Part II: Unmet needs and Organization of Care in Portugal*", resultaram da colaboração de cardiologistas, internistas e médicos de família que representam as suas sociedades médicas e grupos de trabalho dedicados à IC, nos quais me incluo. Os desafios específicos no diagnóstico, tratamento e gestão de doentes com ICFEp são abordados passo-a-passo. A importância das equipas multidisciplinares e o seu papel essencial no abordagem das múltiplas dimensões da IC são reforçados, para reduzir a morbilidade e a mortalidade e melhorar a capacidade funcional e a QdV dos doentes. A segunda publicação centra-se nas necessidades de organização dos cuidados aos doentes com ICFEp em Portugal. A gestão ideal dos doentes com ICFEp foi definida num roteiro para rastreio, diagnóstico, referenciação e tratamento. Foi promovido o cuidado multidisciplinar centrado na pessoa, através de equipas multidisciplinares de cuidados integrados envolvendo cardiologistas, internistas, médicos de medicina geral e familiar, enfermeiros e outros profissionais de saúde, interligados num sistema de cuidados integrado.

A validação do *Minnesota Living with Heart Failure Questionnaire* (MLHFQ) para português, descrita no artigo "*Quality of Life Scores Association with other Patient Reported Outcomes: Validating Minnesota Living with Heart Failure Questionnaire to Portuguese*" revelou que a pontuação total do MLHFQ estava associada a todas as variáveis estudadas, nomeadamente: 1) distância percorrida no Teste de 6 Minutos de Marcha (T6MM), 2) pontuação de fadiga na escala de Borg no final do T6MM, 3) pontuação de depressão segundo a *Hospital Anxiety and Depression Scale* (HADS) e 4) pontuação de ansiedade da HADS. Relatamos a existência de três sub-*scores*: físico, emocional e social. Adicionalmente, encontrámos associações entre o *score* físico e a pontuação de fadiga na escala de Borg e a distância percorrida no T6MM, assim como entre o *score* emocional e as pontuações de ansiedade e depressão da HADS.

No estudo prospetivo QUALIFIER, reportado no artigo "*Quality of life in heart failure patients: factors associated with important changes. The QUALIFIER prospective cohort study* ", verificámos que a implantação do dispositivo de ressincronização cardíaca com função de pacemaker (CRT-P) foi o único fator associado a uma melhoria clinicamente importante da QdV. Além disso, outros fatores foram associados a uma melhor QoV: ex-fumadores, doentes com distúrbios respiratórios do sono, aqueles com pressão arterial sistólica mais elevada e aqueles que tomavam inibidores de enzima de conversão da angiotensina (IECA). Relativamente à deterioração da QdV, as classes II-IV da NYHA, a taxa de filtração glomerular estimada (TFGe) < 30 mL/min/1,73 m2 e a hospitalização recente por IC estiveram associadas a alterações clinicamente importantes na qualidade de vida. Um grupo abrangente de fatores demográficos e clínicos foi analisado utilizando uma abordagem com modelos *nested* com ajustes para fatores sociodemográficos, comorbilidades, adesão aos autocuidados e marcadores de gravidade da IC. A QdV dos doentes com IC no estudo QUALIFIER foi relativamente boa aos 3 meses de seguimento no GEstIC, de 25 pontos na MLHFQ. A QdV melhorou rapidamente nos primeiros meses e depois mais lentamente, até atingir o máximo de melhoria aos 10 meses de seguimento. Os modelos utilizados permitiram observar que alguns fatores previamente reportados como afetando negativa ou positivamente a QdV dos doentes com IC não tiveram qualquer influência na QdV após o ajuste para os marcadores de gravidade da IC. É o caso da idade, sexo masculino, depressão, autocuidado deficiente, reabilitação cardíaca, visitas urgentes por IC, ICFEp e pressão sistólica da artéria pulmonar (PSAP) mais elevada.

Concluindo, verificámos que os doentes com IC do mundo real são idosos, com uma elevada carga de sintomas e comorbilidades, com elevado risco de morte e hospitalizações por IC. Verificámos que é possível prever o risco individual de eventos relacionados com a IC utilizando dados recolhidos na prática clínica diária. Uma clínica multidisciplinar de IC pode reduzir os eventos de IC, os dias de internamento hospitalar e os custos. O MLHFQ permite a avaliação da QdV na prática clínica diária e ajuda a pôr em prática os cuidados centrados na pessoa. Salienta-se que verificámos que o que mais importa para a qualidade de vida dos nossos doentes com IC é viver sem sintomas, sem eventos associados à IC e implantar um dispositivo CRT-P, quando indicado. Este conhecimento adquirido deve ser aplicado em cada encontro com o doente com IC.

Palavras-chave: Insuficiência cardíaca, Qualidade de Vida, Estratificação de risco, Cuidados centrados na pessoa, Clínica de insuficiência cardíaca, GEstIC

3. BACKGROUND

3.1. Heart failure

3.1.1. Definitions and classifications

There are several definitions of HF, some focusing on diagnostic approaches, whereas others view the definition as a characterization of the hemodynamic and physiological aspects. In 2021, American, European and Japanese heart failure scientific societies published a consensus statement with the first Universal definition and classification of HF. The document defines HF as a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by at least one of the following: 1) elevated natriuretic peptide (NP) levels; 2) objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities, such as imaging or hemodynamic measurement at rest or with provocation.[2]

In terms of HF classifications, a variety of classification frameworks are currently in use that attempt to define distinct subsets of HF. Some of these, such as the New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) categories, have been subsequently used as entry criteria for clinical trials, leading to their incorporation into product labelling and guideline recommendations regarding which patients should receive a given therapy. Others, such as classifying patients by HF etiology (ischemic, hypertensive, valvular, etc), may have important implications for prognosis or differential response to therapy.[2]

LVEF classification is a result of the historical success of early drug HF clinical trials that used LVEF <35 or 40% as a clinical trial inclusion criterion, and that for many years showed benefit only in this subgroup of HF patients. Consequently, patients are subcategorized according to LVEF when recommended treatments are defined in clinical practice guidelines since the early guidelines.[2] The cut-off points for LVEF classification subcategories have evolved over the years. Since 2021 and according to the aforementioned Universal Definition of and classification HF consensus document, patients have been categorized into the following subgroups: 1) LVEF≤40%, also called HF with reduced LVEF (HFrEF); 2) LVEF between 41-49%% or HF with mildly reduced LVEF (HFmrEF); 3) LVEF ≥50% or HF with preserved LVEF (HFpEF); and 4) HF with improved LVEF (HFimpEF) defined as HF with a baseline LVEF ≤40% with a ≥10 point LVEF increase from baseline and a second measurement of LVEF >40%.[2]

The NYHA classification was first described in 1921[3] as a simple way to categorize patients with heart disease based on symptoms and limitations in physical activity. It evolved

over time but preserved its original four categories: 1) Class I, no limitation of physical activity; 2) Class II, slight limitation of physical activity, i.e. patient is comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; 3) Class III, marked limitation of physical activity, i.e., less than ordinary activity results in the above symptoms; and 4) Class IV, unable to carry out any physical activity without discomfort, i.e., symptoms at rest can be present and if any physical activity is undertaken, discomfort is increased.[4] The NYHA classification has endured time owing to its simplicity and ease, as well as its overall prognostic value.[5] The NYHA class is recommended to be specified at baseline after the initial diagnosis and after treatment throughout the continuum of care for patients with HF. Worsening the NYHA class is associated with a worse prognosis, and any symptomatic HF patient (NYHA class II-IV) should undergo further optimization of therapy.[2]

3.1.2. Historical perspective

It is believed that the oldest identified case of decompensated HF is the remains of an Egyptian dignitary discovered in the Valley of Queens, dating back more than 3,500 years. Nevertheless, only in 1628 William Harvey clearly described circulation and provided the basis for understanding the haemodynamic abnormalities in HF patients. The next major scientific advance in this area occurred in the 1940s and 1960s with the introduction of cardiac catheterization and cardiac surgery. Before the 1980s, the only attempts to explain the changes occurring in HF were related to the backward/forward theories and treatment was based on bed rest, inactivity and fluid restriction. On the pharmacological side, only digitalis and diuretics were prescribed.[6] The "Pharmacologic Era" of HF began in the 1980s, with the first large randomized clinical trial, the Vasodilator-Heart Failure Trial (V-HeFT), conducted in 1986, showing that the addition of hydralazine and isosorbide dinitrate to digoxin and diuretics could improve LVEF and prolong survival.[7]

In the 1980s, scientific knowledge changed direction with the idea that nature provides humans with various mechanisms to counteract HF, allowing for the survival of the species. This is a stereotypical response that is very useful for overcoming short-term and acute stressful conditions. However, in HF, the neuroendocrine response is chronically activated, leading to deleterious consequences as the persistent increase in catecholamines of the renin-angiotensin-aldosterone system (RAAS) damages the function and structure of myocytes. Since then, HF has become a neuroendocrine disease rather than a heart disease. Therefore, angiotensin converting enzyme inhibitors (ACEis) and beta-blockers (BB) were successfully introduced as treatments for HF.[6] ACEis reduce the risk of death and hospitalization in all patients with HFrEF, regardless of the severity of the symptoms.[8]

Paradoxically, BB improve LVEF, eliminate symptoms and decrease the risk of mortality and hospitalization.[9] Another class of drugs subsequently joined the family of neuroendocrine blockers: mineralocorticoid receptor antagonists (MRA). The beneficial prognostic effect of MRAs has been demonstrated in addition to therapy with ACEis and BB.[10]

In the 1990s, HF was no longer a disease but a ‘syndrome’, a Greek word meaning ‘going together’. This signifies that the heart is merely the starting point of the disease, which then spreads to the periphery, where if affects the neuroendocrine and neurohormonal (cytokine) systems as well as the peripheral muscles, kidneys, and even the gut. However, while there has been a remarkable reduction in incidence and an improvement in prognosis in almost all heart diseases over the last few decades, this has not been the case for HF. The recognition of HFpEF has contributed to an increase in diagnoses and reinforces the notion that the periphery is significant in HF. In HFpEF the problem originates in the periphery (hypertension, metabolic syndrome etc.) and spreads to the heart. In HFrEF, the problem begins in the heart (infarction or infection) and subsequently spreads to the periphery. It has also been demonstrated that the relationship between the frequency (heart rate) and force (contraction) of the left ventricle is altered in HF.[6] Reducing the heart rate with BB or more selective drugs, such as ivabradine, decreases left ventricle remodelling and improves the LVEF.[11]

The "Device Era" of HF began with the recognition that ventricular arrhythmias are responsible for many sudden deaths in HF patients and led to the introduction of implantable cardioverter-defibrillators (ICDs) in the 1980s in the United States of America (USA). Later, approved in 2002, cardiac resynchronization therapy (CRT) was developed with devices that pace and resynchronize the contraction of the ventricles.[12] There are two types of CRT devices: one that just resynchronizes the ventricles, CRT-pacemaker (CRT-P), and another that functions also as defibrillator (CRT-D). For selected patients with advanced HFrEF with NYHA class IV symptoms, mechanical circulatory support (MCS) devices are available to prolong life and improve functional capacity. They can be used as short- or long-term therapies, the latter usually representing “destination therapy” for patients deemed ineligible for transplant.[4]

Heart transplantation, performed since 1967[13], has been the gold standard for the treatment of advanced HFrEF in the absence of contraindications, but it is a treatment option for only a few patients.[4]

Returning to the history of HF medical therapy, in 2010, ivabradine demonstrated a reduction in HF hospitalizations (HFH) and HF deaths in symptomatic patients with an LVEF ≤35%, in sinus rhythm after optimized therapy with ACEis and BB.[11] This is a less useful

drug because of the minority of HFrHF patients in whom it is indicated. Meanwhile, a new era of HF pharmacological therapy began in 2014, when, for nearly 30 years, a new drug, sacubitril/valsartan, with dual angiotensin receptor and neprilysin inhibition (ARNi), showed better results in HFrEF than a classical ACEi.[14] This was a turning point in HF drug therapy, as it was the first RAAS modulation therapy, not just an inhibitor such as the previous one. Since then, the last decade has offered a new world of medical therapy for HF. In 2019, dapagliflozin, a sodium–glucose cotransporter 2 inhibitor (SGLT2i) developed for the treatment of diabetes *mellitus*[15], proved to reduce mortality and HFH in HFrEF patients; empagliflozin demonstrated similar results in the following year.[16]

Other drugs with different mechanisms of action have also been developed for HFrEF. In 2020, vericiguat, a novel oral soluble guanylate cyclase stimulator, demonstrated a reduction in the incidence of death from cardiovascular causes or HFH in patients with an LVEF<45% and a recent worsening HF event.[17] Omecamtiv mecarbil, a cardiac myosin activator, proved to reduce a composite of a HF failure events or death from cardiovascular causes in a study published in 2021[18], but the drug was never commercialized because the USA Food and Drug Administration (FDA) found the overall evidence insufficient. A new trial is currently recruiting patients to explore the potential of omecamtiv mecarbil in a subgroup of HFrEF patients with severely reduced LVEF.[19]

In 2021, empagliflozin was a milestone in the history of HF. Empagliflozin was the first drug that, simultaneously, proved to reduce HFH and mortality in patients with HFpEF and to have this effect in patients with HF across the entire range of LVEF. Dapagliflozin accomplished the same in the following year.[20] Soon after, in 2024, finerenone, a nonsteroidal MRA, demonstrated a reduction in a composite of total worsening HF events and death from cardiovascular causes in patients with LVEF ≥40%.[21]

In the last 30 years, the diagnosis, management and treatment of HF have been guided by European, American and other national guidelines. The first European Society of Cardiology (ESC) HF guidelines were published in 1995 and were dedicated solely to diagnosis[22]; the most recent guidelines were issued in 2021 and were updated in 2023.[4]

3.1.3. Epidemiology

HF has been defined as a global pandemic.[23] The syndrome of HF has been compared to an iceberg. The visible section represents established HF cases in the community: the majority are managed in the primary care setting, with the top cases handled by

cardiologists. The larger invisible part “below the water level” represents cases of undetected HF.[24]

Currently, the incidence of HF in Europe is estimated to be approximately 5/1,000 person-years in adults. Several studies have reported that the incidence of HF significantly increases with age. A lower socio-economic status is associated with a greater risk of developing HF.[25]

The prevalence of HF ranges between 1% and 3% of adults in the general adult population in industrialized countries. It is projected to increase substantially due to the availability of better diagnostic tools, which ensure an appropriate diagnosis and life-saving medical treatments that prolong life after an HF diagnosis.[25,26] As studies usually include only patients diagnosed with HF, the true incidence and prevalence are likely to be greater. The prevalence increases with age and is estimated to be more than 10% in those aged 70 years or older.[24] It is generally believed that, of those with HF, approximately 50% have HFrEF and 50% have HFpEF/HFmrEF, primarily based on studies in hospitalized patients.[4,27] While it seems that the prevalence of HFrEF is most likely to remain stable or even decline, the prevalence of HFpEF is steadily increasing and may become the most common form of HF in the future.[25,28]

In Portugal, two epidemiological studies on HF have been conducted. The EPICA (EPidemiologia da Insuficiência Cardiaca e Aprendizagem) study reported that the overall prevalence of HF in mainland Portugal was 4.36% in 1998. In the group of patients over 80 years old, the HF prevalence was 16.14%. These numbers were slightly higher than those reported in other European studies.[27] The Portuguese Heart Failure Prevalence Observational Study (PORTHOS) was a large, population-based, cross-sectional study of people aged 50 years or older living in mainland Portugal.[29] In 2024, the results of the PORTHOS study were presented. The estimated overall HF prevalence was of 16.5%. The prevalence of HF in women was 21.0%, whereas it was 10.4% in men. The prevalence of HFrEF was 0.4% whereas that of HFpEF was 15.2%. In people aged ≥ 70 years, the overall HF prevalence increased to 30.7% and the prevalence of HFpEF increased to 74.2%. Supporting the “iceberg perspective”, 90.0% of the participants had not been diagnosed with HF prior to study inclusion. The number of undiagnosed cases was greater in women, those aged ≥ 70 years, and those in HFpEF group.[30]

The findings of the PORTHOS study give us reasons to doubt the much lower HF prevalence reported by other European countries. Notably, Portugal has one of the highest proportions of people over 65 years of age, reported at 24% in 2023, according to the World Bank Group.[31] Nevertheless, the life expectancy at birth has increased by more than ten

years across Organisation for Economic Co-operation and Development (OECD) countries since 1970. This has been accompanied by an increased number of people living with chronic conditions, such as HF.[32] Therefore, the prevalence of HF in European countries is likely much higher than what has been reported.

Ischemic heart disease represents the aetiology of HF in approximately about 40% of the HF population worldwide, although large geographical variations exist. Ischemic heart disease is a more common HF aetiology of HFrEF and HFmrEF than of HFpEF. Hypertension is the aetiology of HF in 15% of the HF population, with higher estimates in some parts of the world.[25] Valvular heart disease is the third most common cause of HF. Amyloid cardiomyopathy is an increasingly diagnosed cause of HF. Transthyretin amyloidosis should be suspected in HF patients older than 65 years with left ventricular hypertrophy.[4]

HF events are defined as HFH and urgent HF visits. An HFH is defined as an event in which the patient is admitted to the hospital for at least 24 h with a primary diagnosis of HF (new or worsening symptoms of HF on presentation and objective evidence of new or worsening HF by physical examination and/or laboratory criteria) and initiates or intensifies HF treatment. An urgent HF visit is defined as an emergency department visit with a primary diagnosis of HF and receiving intravenous diuretics, but not meeting the criteria for HFH.[33] Urgent HF visits have been considered equivalent to HFH as outcomes in recent clinical trials.[15,21] Indeed, even episodes of worsening HF leading to outpatient intensification of medical therapy have been associated with an increase in the risk of subsequent death, similar to that observed following hospitalization. In addition, a sub-analysis of a large HF trial revealed that two-thirds of the episodes of intensification of outpatient therapy and urgent HF visits were followed by HFH within 30 days.[34]

HF is the most frequent cause of hospitalization among individuals >65 years.[4] Additionally, both cardiac and non-cardiac comorbidities are common in patients with HF and are associated with worse outcomes. Patients with HF experience frequent hospitalizations, which have slightly improved over time. Both incident and recurrent HFH are associated with an increased risk of mortality.[25] The median survival decreases with each HF event. After three HFH, the median survival time is 12 months.[35]

The annual healthcare cost per HF patient is up to 25,000 euros in the Western world. Most of the costs are linked to direct costs (inpatient care and HFH) and non-cardiovascular comorbidities. Based on the overall increasing prevalence of HF, direct and indirect costs are expected to increase significantly, especially in older HF patients.[25] The impact of HFpEF on hospitalization costs may be greater. Thus, improving the care and treatment of

HFpEF patients is a priority, as it is expected to become the major player in the HF stage in the coming years.[25,36]

In recent decades, the prognosis of HF has slightly improved, but mortality remains high, with a one-year mortality risk ranging from 15 to 30% and a 5-year risk up to 75% in specific populations, without significant differences in risk between HFpEF and HFrEF. Although cardiovascular (CV) death is predominant in HF patients, increasing evidence has highlighted a gradual shift towards non-CV death over the last two decades, especially in patients with HFpEF.[25] Notably, despite advances in care, patients with a diagnosis of HF have worse survival than patients with one of several common cancers, namely, breast or colon cancer.[37] In recent years, the terminology traditionally used in oncology has been adopted for HF. Indeed, a consensus document on HF proposes terms such as “HF remission” for patients with resolution of symptoms and signs of HF along with resolution of previously present structural and functional heart disease, after a phase of symptomatic HF. “Persistent HF” should be used for those patients who remain symptomatic and lack improvement in markers of worse prognosis. “Recovered HF”, the equivalent for a cure in cancer, should be reserved for patients who have persistent resolution of HF syndrome, normalization of cardiac structure, function, and biomarker profile after resolution and treatment of a fully reversible cause. This is very rare.[2]

In Portugal, 5,226 HF patients died in 2018, with a mean age of 87 years. HF has a significant economic impact in Portugal, representing approximately 2.6% of total public health expenditures.[38] Direct costs associated with HF in 2014 were estimated at in 299 million euros, with 39% spent on HFH.[39] Over the last decade, a group of experts, consisting of cardiologists, internists and general practitioners has addressed the problem of HF in Portugal. Together, they proposed strategies for improving HF scenario at various levels. Their work has been published to increase awareness and improve the management of HF.[40]

3.1.4. State-of-the-art

The state-of-the art concerning the diagnosis, management, patient care, and treatment of HF are summarized in the latest international guidelines and consensus documents. These include the following: 1) Universal definition and classification of HF[2]; 2) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[4]; 3) 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[41]; 4) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology(ACC) /American Heart Association

(AHA) [28]; and,5) 2023 ACC Expert Consensus Decision Pathway on Management of HF with Preserved Ejection Fraction.[42]

3.1.4.1. Diagnosis

The diagnosis of HF requires the presence of symptoms and/or signs typical of HF and objective evidence of cardiac dysfunction. The diagnosis of HF is more likely in patients with a history of heart disease or CV risk factors. The following diagnostic tests are recommended for assessing patients with suspected chronic HF: 1) an electrocardiogram (ECG); 2) measurement of NP; 3) basic investigations such as serum urea and electrolytes, creatinine, full blood count, and liver and thyroid function tests; 4) an echocardiogram; and, 5) a chest X-ray. The diagnosis of HFpEF remains challenging in some patients.[4]

Low levels of NP in a patient with suspected HF rule out the diagnosis. NT-proBNP is the preferred NP because sacubitril/valsartan does not interfere with its levels. A NT-proBNP level < 125 pg/mL rules out chronic HF for most patients; to rule-out acute HF, the value should be < 300 pg/mL.

An echocardiogram is recommended as the key investigation for assessing cardiac function. In addition to determining the LVEF, echocardiography also provides information about the underlying heart disease.[4]

3.1.4.2. Management and patient's care

Multidisciplinary HF clinics with management programs reduce hospitalizations and mortality of HF patients. They enable patients to receive the correct investigations, an accurate diagnosis, appropriate evidence-based therapy, education, and suitable follow-up. The optimal implementation of HF clinics requires a multidisciplinary team that is active throughout the entire HF trajectory: from onset, through critical events, periods of apparent stability, and terminal stages.[43] A meta-analysis, including randomized trials, concluded that disease-management clinics reduce all-cause mortality compared with usual care, and that self-management interventions in HF patients improve outcomes, despite heterogeneity in the intensity, content, and the personnel who deliver interventions.[44,45]

Adequate patient self-care is essential in the effective management of HF. Self-care can be defined as a process of maintaining health through health promoting and preventive practices. Self-care is an overarching concept formed by three key concepts: 1) self-care maintenance, those behaviours used by persons with a chronic illness to maintain physical and emotional stability; 2) self-care monitoring, the process of observing oneself for changes in signs and symptoms; and 3) self-care management, the response to signs and symptoms when they occur.[46] An easy guidance to help patients with HF monitor

themselves is a chart such as the HF zones, where patients can be instructed to place themselves every day in one of 3 zones: green (safety zone), yellow (warning zone) and red (alert zone), and to act accordingly. A recent study revealed that one in five patients had persistently poor self-care behaviour despite self-care education and follow-up at an HF clinic.[47] Non-adherence to self-care predicts adverse outcomes in HF patients.[48] Depression is known to be a risk factor for poor self-care.[47,48]

HF patients who report more effective self-care have a better QoL, lower readmission rates, and reduced mortality.[4,45,48] Improving patients' knowledge of their condition is fundamental for the development of self-care skills. Education should be tailored to the individual patient.[4]

Exercise is recommended for all patients who can to improve their exercise capacity and QoL and reduce HFH. Supervised cardiac rehabilitation should be considered in HF patients who are frail and who have more severe disease or comorbidities.[4]

HF clinics should be person-centred and take a holistic approach to the patient rather than focus solely on HF. The management program should include the management of comorbidities and improve patient well-being and self-management. There is current evidence that HF clinics may improve mortality, hospitalization rates, self-care, and QoL in patients with HFpEF, who are older and have a greater burden of comorbidities.[49] The organization of a HF clinic should be adapted to the healthcare system, available resources, and administrative policies and tailored to the patient's needs.

Many patients with HF progress into a phase of advanced HF, characterized by persistent symptoms despite maximal therapy.[4] These patients would benefit from the early integration of a palliative and supportive approach within the care provided by all members of the HF multidisciplinary team. Palliative care should be considered for all patients with HF, regardless of the stage of their illness.[4,50,51]

Palliative care improves QoL. Palliative care is defined by the World Health Organization (WHO) as an approach that improves the QoL of patients and their families who are facing problems associated with life-threatening illness. Furthermore, the WHO reports that most adults in need of palliative care have chronic cardiovascular diseases (38.5%), followed by cancer patients (34%). Pain and difficulty breathing are two of the most common symptoms experienced by patients in need of palliative care.[52] In contrast to cancer, HF as a disease has an unpredictable trajectory. Patients can die suddenly, especially those who have a reduced LVEF, can die in the first HFH or can suffer from progressive worsening of symptoms for months to years, as advanced cancer patients usually do. As the HF trajectory of each patient is unique, and consequently unpredictable, palliative care should be

introduced early in the disease trajectory and should increase as the disease progresses, alongside optimal HF-specific management.[53] Communication about the disease trajectory and anticipatory planning should start when a patient is diagnosed with advanced HF.[4]

Randomized trials have investigated the impact of standard and multidisciplinary palliative care interventions combined with usual HF management on HF-related and overall QoL in patients with advanced HF. Significant clinical benefit was demonstrated both in hospitalized patients and outpatients with advanced HF.[54,55]

Symptom assessment should be performed on a regular basis, in addition to clinical assessment, with specific questionnaires such as the Integrated Palliative care Outcome Scale (IPOS). The need for palliative care in HF patients should also be assessed by specific questionnaires, as the Needs Assessment Tool: Progressive Disease - Heart Failure (NAT:PD-HF).[56] Compared to usual medical history, validated assessment tools increase the identification of symptoms 10-fold. Palliative care improves the QoL of many people living with HF, their families and loved ones. Responsive integrated cardiac and palliative care for all patients with HF when needed, regardless of prognosis, should be the landmark of modern comprehensive care.[53]

3.1.4.3. Treatment

Pharmacotherapy is the cornerstone of treatment for HFrEF and should be implemented before considering device therapy and alongside non-pharmacological interventions. There are three major goals of treatment for patients with HFrEF: 1) reducing mortality, 2) preventing recurrent HFH, and 3) improving their clinical status, functional capacity, and QoL.

Modulation of the RAAS and sympathetic nervous systems with an ACEi or an ARNi, BB, an MRA and an SGLT2i has been shown to improve survival, reduce the risk of HFH, and reduce symptoms in patients with HFrEF. They should be uptitrated to the doses used in the clinical trials, or to maximally tolerated doses if that is not possible. Other drugs, such as ivabradine, vericiguat, iron and diuretics, may be used for selected patients with HFrEF. Most recent drugs have been shown to improve QoL, sometimes defined as a secondary endpoint in clinical trials. This is the case for sacubitril/valsartan, dapagliflozin and empagliflozin. Even those drugs that do not have studies with QoL outcomes generally improve symptoms and reduce HFH, so presumably, they should improve QoL.

Cardiac devices, ICD and CRT, are indicated for symptomatic HFrEF patients, i.e., NYHA functional class II or III patients, who maintain LVEF ≤ 35% under optimized medical

therapy, provided that are expected to survive significantly longer than one year with good functional status. ICDs have been shown to reduce sudden cardiac death and all-cause mortality.[4] CRT is one of the most effective therapies for HFrEF resulting in improved QoL, beneficial reverse remodelling of the left ventricle and reductions in HFH rates and all-cause mortality.[57]

Finally, heart transplantation is the gold standard for the treatment of advanced HFrEF in the absence of contraindications and is associated with a median survival of 12.5 years. Unfortunately, for many patients this is not a treatment option because of their older age and organ donor shortages.[4]

No substantial prospective randomized controlled trials have been performed exclusively in patients with HFmrEF. International guidelines recommend considering the same medications used for HFrEF.[4]

Until recently, no drugs proved to improve the prognosis of HFpEF patients. Currently, dapagliflozin or empagliflozin, are recommended as they proved to reduce mortality and HF events. In 2024, finerenone showed also to be a disease-modifying drug in HFmrEF and HFpEF. However, this drug has not yet been approved for HF patients by regulatory agencies.

HFpEF differs from HFrEF and HFmrEF in that HFpEF patients are older and more often female. Atrial fibrillation (AF), chronic kidney disease (CKD), and non-CV comorbidities are more common in patients with HFpEF than in those with HFrEF.[58] A holistic and personalized approach is even more fundamental to the care of HFpEF patients, given the high burden of comorbidities usually present.[42]

3.2. Quality of life

3.2.1. Definition

The WHO defines QoL as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”.[59]

In a very recent ESC document, the definition of QoL includes three components: 1) the ability to carry out activities (physical and social), 2) the ability to maintain happiness, and 3) the ability to engage in fulfilling relationships with others.[60]

3.2.2. Historical perspective

In Ancient Greece, illness was initially regarded as a divine punishment and healing as, quite literally, a gift from the gods. Influenced by Egyptian ideas, Greeks initially sought remedies from the gods. However, as knowledge grew, they began to focus on the physical body, incorporating diet, exercise, and herbal remedies, alongside the theory of four humors, to explain illness. Medicine as a profession was born in Greece, 2500 years ago, not as one of the fields of knowledge about world interpretation (*sophia*) but as a technical practice (*technos*). Medicine, or *iatrikē*, was considered a *techne*, a skilled craft or art, rather than just a body of knowledge. As there were no professional qualifications for medical practitioners, anyone could set themselves up as a doctor and travel around looking for patients on whom to practise what was known as the *tekhnē* of medicine (or art, albeit a mysterious one).[61] This perspective emphasized practical application and the ability to produce a desired result (healing or relief) through specific techniques and expertise. In this vein, QoL improvement is the very first mission of medicine.

For the past 24 centuries, despite a striking shortage of knowledge about anatomy and physiology, medicine has built a complex number of theories and practices to achieve its everlasting aim: improving patients’ QoL. The characteristics of a ‘good life’ and its constitutive elements can be traced back to Aristotle, who thought the ‘blessings of life’ can be divided into three classes: those that come to us from without, those of the soul, and those of the body.[62] This “good life” is the conceptual ancestor of QoL. However, that aim of the ancient medicine seems to have taken a secondary role for a long period of time, as scientific knowledge has given physicians the power to prolong life. Public health frameworks in the first half of the XX century were developed and articulated to help cope with the complex patterns of “premature” mortality, and, to a lesser extent, the incidence

and prevalence of morbidity. In other words, medicine focused its attention on the quantity of life.

The term QoL was first reported in the medical literature by Elkinton in 1966, who defined QoL as “the harmony within a man, and between a man and his world” and stated the “need to continue to search for answers to these basic questions concerning the goals and values of human life daily”.[63] Since the early 1990s, there has been a paradigm shift in human development theory due to a slow but steady increase in the attention given to the concepts of QoL, wellbeing and happiness.[64]

3.2.3. Guidelines for assessment in heart failure patients

QoL was only recently identified as an important outcome and quality indicator for the management of patients with heart failure (HF).[65,66]

Until recently, new drugs for HF were approved by the regulatory agencies only if they could reduce mortality. In 2013, an ESC consensus document reported that QoL should be an independent endpoint in HF trials.[65]

In 2022, a working group of the ESC defined quality indicators for the care and outcomes of adults with HF, including a domain for the assessment of patients’ QoL and the recommendation for the use of a validated tool. The experts considered that QoL assessment by itself constitutes an accomplishment of that quality indicator, without setting any target score, given concerns about the feasibility of capturing QoL in clinical practice.[66] This position of the ESC highlights the unmet need for a very pragmatic instrument in the assessment of HF-specific QoL.

In March 2025, the ESC reported the consensus statement “Quality of life in heart failure. The heart of the matter” that aims to foster the systematic integration of the patient’s standpoint in HF care. The document discusses in detail the evidence about QoL in HF patients and sets the basis for QoL assessment and interpretation in clinical practice.[60] Clinically important changes in the QoL of HF patients have been proposed, to identify patients who experience improvement or deterioration. The study of within-patient changes in QoL was set as an aim for research.[60,67]

3.2.3.1. Questionnaires and patient-reported outcomes

There are several validated instruments to assess QoL in patients with HF. Among the disease-specific questionnaires, the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[68] and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[69] have been

qualified as Medical Device Development Tools by the FDA and are the most commonly used in clinical trials.[60] The use of these instruments, however, remains largely limited to clinical trials.[70] They are both time-intensive, and their current use in real-world care is very limited.[66,71] Other authors identified the MLHFQ as the most appropriate instrument for QoL assessment in HF patients after a search of relevant databases because it has a simple structure and is easy to administer.[72] Additionally, the acceptability and feasibility of implementing validated QoL instruments in HF clinics were studied, and it was reported that the MLHFQ had a higher completion rate than did the KCCQ, with all the questions answered by 85% and 49% of patients, respectively.[70] Both questionnaires cover many important HF symptoms, with some of them considered by only one of the tools, others covered by both tools, and others not considered by either tool.[60].

In HFpEF patients, the MLHFQ and KCCQ are both reliable and valid tools for assessing QoL, but the KCCQ is more strongly associated with baseline functional status, whereas the MLHFQ is more sensitive in detecting improvements in the six-minute walking distance (6MWD). In two large recent clinical trials testing sacubitril/valsartan in patients with HFpEF and HFrEF, HFpEF patients had lower QoL, as measured by KCCQ scores, in nearly all domains than did those with HFrEF. Patients with HFpEF tend to be older and have multiple comorbidities. HF symptoms along with frequent hospitalizations pervade all aspects of daily life, eventually impairing function and independence, two commonly important limitations in older adults. Consequently, improving QoL is a key therapeutic target for HFpEF patients, who value autonomy and activity.[60]

Disparities in socioeconomic status, cultural response to disease and disability, social support, and health care resources and delivery systems make the validation of questionnaires reporting QoL in every region important. This is the solution for the global variation in background QoL. One of the largest drug trials in HFpEF reported that QoL in Western European countries, where Portugal is included, had the worst QoL metrics at randomization, in comparison with the rest of the world.[73]

3.2.3.2. Clinically important changes

Using QoL questionnaires as patient-reported outcome measures (PROMs) to assess treatment efficacy is critical for defining clinically important thresholds of change. In this respect, the definition of minimal clinically important difference, i.e., the level that is meaningful to patients, is crucial. While population-level mean differences between the active and control groups can be compared in a research setting, understanding how these differences impact individual patient QoL is more complicated. Efforts to understand within-

patient changes have created estimates of 5, 10, and 15–20 points that indicate small to moderate (but clinically important), moderate to large, and large to very large clinical changes, respectively.[60,67] There seems to be an asymmetry of QoL changes between patients with HFrEF and those with HFpEF. A study reported an improvement of 9 points in the HFrEF patients and 7 points in HFpEF patients, as clinically important changes in KCCQ scores.[67] In most pharmacologic trials, including more recent trials on SGLT2i, the average treatment effect on KCCQ was <5 points.[60]

3.2.4. Current evidence in heart failure patients

Maintaining a high QoL for most patients with progressive, chronic illnesses is equally as important as ensuring their survival.[60] This should lead to personalized discussions of patients' preferences in treatment and care decisions and could guide the development of more person-centred care.[74] HF symptoms such as breathlessness, reduced exercise tolerance and fatigue result in a diminished QoL. HF events are frequent in the HF trajectory and represent not only worsening HF but also worsening QoL. QoL is impaired equally in HFpEF and HFrEF patients. [75]

Remarkably, a study reported that HF patients have a similar number of physical symptoms and depression scores as advanced cancer patients do but that patients with worse HF-specific QoL scores have significantly greater overall symptom burden, more depression symptoms and lower spiritual well-being than patients with advanced cancer do.[76]

Several studies have reported that worse QoL is associated with increased mortality and HFH in HF patients.[77,78] A study including more than 23,000 HF patients from 40 countries demonstrated that the associations between poor QoL and higher mortality and HFH are independent of NYHA class and LVEF. This finding points to the potential benefit of using QoL assessment as a simple, readily available, and inexpensive prognostic tool in routine clinical care.[79] The same authors reported that the severity of HF was the most important correlate with QoL, concluding that improving symptom control is likely to have a large effect on QoL.[80]

A scoping review of the available evidence on the impact of non-CV comorbidities on QoL in patients with chronic HF revealed that the impact was consistently negative and significant. The non-CV with a significant impact on QoL were anaemia, iron deficiency, diabetes mellitus, and mental and behavioural disorders.[81]

Knowledge of the determinants of QoL can contribute to clinical decision making for the treatment of HF patients. A literature review identified important predictors of HF specific QoL in chronic HF patients. Age, sex, depression, and diabetes were related to QoL. Older participants were more satisfied with their lives than their younger counterparts were. Being female was a significant predictor of a worse QoL. Furthermore, most variables traditionally defined as strong predictors of hard endpoints, such as renal function and blood pressure, were not found to be significant predictors of QoL and were often not in relation to QoL. One such variable was LVEF, which was not associated with QoL. Depression and a higher NYHA functional class were identified as the strongest predictors of a worse QoL.[82] Another study revealed that patients who were obese, had diabetes, were younger, and had lower NT-proBNP levels had the poorest QoL.[83]

There is evidence that some HF disease-modifying drugs, particularly sacubitril/valsartan, SGLT2i, and MRA, may improve patient-reported clinical outcomes (PROs), but further studies are needed. Overall, the magnitude was larger and more homogeneous for studies on cardiac devices.[60] A recent clinical trial reported that incorporating PROMs into routine care improved the accuracy of clinical assessments and improved patients' experiences with care.[84]

4. AIMS

The work reported in this thesis is the result of the search for answers raised during my clinical practice caring for HF patients over the last 12 years. The thesis theme centres around the question that I have been posing all that time - Quality of life in HF: what matters? Obviously, we suspect that when a patient is symptomatic, needs to visit the emergency department, or stays in the hospital for a week or more, the QoL is likely worsening. It is never good to tell patients that they need to stay in the hospital. Most patients see alternative solutions and accept hospitalization only after we explain that the severity of the disease justifies such a drastic change in their lives. To be unable to eat homemade food, share moments with loved ones and pets, sleep in one's own bed, and even see the landscape from that special window, are all things that patients miss when they are in the hospital. Therefore, we cannot separate the idea of hospitalization from poor QoL.

The initial research questions were directly related to the HF events we were witnessing, before having a dedicated organization or structured follow-up to address them. We aimed to establish the baseline prognosis of HF patients hospitalized in the Internal Medicine Department before GEstIC HF clinic implementation. This led to the Pré Clínica de Insuficiência Cardíaca (PRECIC) study and its three sub-analyses. We aimed: 1) to determine the characteristics of HF patients hospitalized in a Portuguese public hospital and establish their prognosis[85]; 2) to compare in-hospital mortality predicted by the Acute Decompensated Heart Failure National Registry (ADHERE) risk tree with the mortality we observed in our hospital[86]; 3) to identify predictive factors of one-year mortality of patients hospitalized for HF[87]; and 4) to identify independent predictors of rehospitalization and death after HFH, considering death without rehospitalization as a competing event of re-hospitalization.[88]

At the beginning of the GEstIC HF clinic, we also aimed to share our experience in establishing a multidisciplinary HF team in a Portuguese public hospital. The objective was to motivate other health professionals to create additional HF clinics in their hospitals. Therefore, we published a review article summarizing the scientific evidence concerning HF clinics and describing the implementation of the GEstIC.[1]

In 2014, we were invited to participate in a multicentric, prospective, randomized, controlled, investigator-initiated clinical trial – PRIMA II (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?).[89] The aim of this study was to investigate whether, compared with conventional therapy, NT-proBNP-guided therapy during hospitalization for acute decompensated HF could improve outcomes, by randomizing patients to one of two arms.

Later, we intended to perform an external validation of the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score using the PRIMA II cohort. This could allow us to accurately predict 6-month mortality in hospitalized HF patients.[90]

Over the years, we aimed to measure the impact of optimized care for HF on events in patients followed in the GEstIC. This was the rationale of the GEstIC study.[91]

The collaboration between national HF experts, including me, and other colleagues with interest in this area has been the source of multicentric studies, original articles and the publication of consensus documents, all with the aim of improving the diagnosis and care of HF patients in Portugal.[92–94]

The continuous search for answers concerning QoL led us to validate the MLHFQ in Portuguese. This is the HF-specific QoL patient-reported outcome (PRO) instrument that we have chosen to use in daily clinical practice at the GEstIC. It is a questionnaire with 21 questions, with answers rated on a Likert scale ranging from 0-5 points. The entire questionnaire fits on a single page, and the total score is immediately available by summing the points. We aimed to validate the MLHFQ and to look for sub-scores that could indicate how patients' health was in different domains: physical, emotional and social.[95]

Finally, after a substantial amount of data was collected from the first seven years of GEstIC practice we sought answers to the following QoL-specific questions: 1) which factors influence QoL? 2) In which direction (improving or deteriorating)? 3) and, how much is the magnitude of that effect?[96]

5. METHODS AND RESULTS (PUBLICATIONS)

Under this thesis theme, the following publications were published, accepted or submitted for publication as original and review articles:

5.1. Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study

Marques I, Abreu S, Bertão MV, Ferreira B, Ramos RL, Lopes J, Nunes S, Mendonça D, Teixeira L. Rev Port Cardiol. 2017;36:431-8. http://dx.doi.org/10.1016/j.repc.2016.10.011 (original article)

5.2. In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk vs. Observed Mortality

Marques I, Bertão MV, Mendonça D, Teixeira L. Int J Phys Med Rehabil. 2022;10: 1000645. https:// doi: 10.35248/2329-9096-22.10.645 (original article)

5.3. One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)

Marques I, Ramos RL, Mendonça D, Teixeira L. Rev Port Cardiol. 2023;42:505-13. https://doi.org/10.1016/j.repc.2022.07.017 (original article)

5.4. One-year rehospitalization and mortality after acute heart failure hospitalization: a competing risk analysis

Marques I, Mendonça D, Teixeira L. Open Heart. 2023;10:e002167. https://doi:10.1136/openhrt-2022-002167 (original article)

5.5. Multidisciplinary Heart Failure Clinic: How to Implement?

Marques I, Gomes C, Viamonte S, Ferreira G, Mendonça C. Medicina Interna. 2017;24:308–17. https://doi: 10.24950/rspmi/R58/17/2017 (review article)

5.6. NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)- Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz RAM, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayés-Genis A, Tijssen J, Pinto YM, Kok WE. Circulation. 2018;137:1671-83. https://doi: 10.1161/circulationaha.117.029882 (original article)

5.7. External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure

Salah K, Stienen S, Moons AHM, Bakx ALM, van Pol PE, Kortz RAM, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayes-Genis A, Pinto YM, Tijssen JG, Kok WE. J Am Heart Assoc. 2019;8:e010309. https://doi: 10.1161/jaha.118.010309 (original article)

5.8. Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study

Rego R, Pereira N, Pinto A, Pereira S, Marques I. Front Cardiovasc Med. 2023;10:1232291. https://doi: 10.3389/fcvm.2023.1232291 (original article)

5.9. conTemporary reflectiOns regarding heart failure management - How to ovERcome the PorTuguese barriers (TOGETHER-PT)

Silva-Cardoso J, Santos J, Araújo I, Andrade A, Sarmento PM, Santos P, Moura B, Marques I, Peres M, Ferreira JP, Agostinho J, Pimenta J. Rev Port Cardiol. 2024;43:225-35. https://doi.org/10.1016/j.repc.2023.05.012 (original article)

5.10. Beyond clinical trials - The cost saving associated with dapagliflozin use in Portugal hospital clinical practice

Brito D, Fonseca C, Franco F, Lopes V, Gonçalves S, Baptista R, Sequeira J, Marques I, Rego R, Pimenta J, Silva-Cardoso J, Lopes M, Almeida M. Rev Port Cardiol. 2024;43:685-694. https://doi.org/10.1016/j.repc.2024.04.012 (original article)

5.11. A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment

Silva-Cardoso J, Moreira E, Melo RT, Sarmento PM, Cardim N, Oliveira M, Gavina C, Moura B, Araújo I, Santos P, Peres M, Fonseca C, Ferreira JP, Marques I, Andrade A, Baptista R, Brito D, Cernadas R, Santos J, Leite-Moreira A, Gonçalves L, Ferreira J, Aguiar C, Fonseca M, Fontes-Carvalho R, Franco F, Lourenço C, Martins E, Pereira H, Santos M, Pimenta J. Rev Port Cardiol. 2025;44:233-43. https://doi.org/10.1016/j.repc.2024.11.011 (review article)

5.12. A Portuguese expert panel position paper on HFpEF management - Part II: Unmet needs and organization of care in Portugal

Silva-Cardoso J, Moreira E, Melo RT, Sarmento PM, Cardim N, Oliveira M, Gavina C, Moura B, Araújo I, Santos P, Peres M, Fonseca C, Ferreira JP, Marques I, Andrade A, Baptista R, Brito D, Cernadas R, Santos J, Leite-Moreira A, Gonçalves L, Ferreira J, Aguiar C, Fonseca M, Fontes-Carvalho R, Franco F, Lourenço C, Martins E, Pereira H, Santos M, Pimenta J. Rev Port Cardiol. 2025;44:291-302. https://doi.org/10.1016/j.repc.2024.11.011 (review article)

5.13. Quality of Life Scores Association with other Patient Reported Outcomes: Validating Minnesota Living with Heart Failure Questionnaire to Portuguese

Marques I, Viamonte S, Severo M, Pinto AG, Fonseca C, Carvalho HC. Rev Port Cardiol. 2025;44:607-18. https://doi.org/10.1016/j.repc.2025.03.005 (original article)

5.14. Factors Associated with Clinically Important Changes in Quality of Life of Heart Failure Patients: The QUALIFIER Prospective Cohort Study

Marques I, Severo M, Pinto AG, Fonseca C, Carvalho HC. J Clin Med. 2025;14:5079.

https://doi.org/10.3390/jcm14145079 (original article)

5.1. Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study

Marques I, Abreu S, Bertão MV, Ferreira B, Ramos RL, Lopes J, Nunes S, Mendonça D, Teixeira L. Rev Port Cardiol. 2017;36:431-8. http://dx.doi.org/10.1016/j.repc.2016.10.011 (original article)

My contributions to this work were as follows: I designed the study, collected data, wrote and edited the manuscript after all the authors reviewed and commented, prepared and submitted the manuscript, and served as the corresponding author. To the best of my knowledge this article has not been included in any other thesis. This is an open access publication, with no financial, legal or technical barriers to accessing it.

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ORIGINAL ARTICLE

Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study

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Abstract
Objective: This study aims to characterize patients hospitalized for acute heart failure (HF) in an internal medicine department and their one-year mortality and rate of rehospitalization for decompensated HF.
Methods: This retrospective observational study enrolled all patients discharged in 2012 after hospitalization for acute HF. Discharge summaries, clinical records and telephone interviews were analysed. The data reports to the year before implementation of a heart failure clinic.
Results: Four hundred and twenty-nine patients were enrolled, with a mean age of 79 years, 62.5% female. The most prevalent comorbidity and etiology was hypertension (86.7%) and the most frequent decompensation trigger was infection. HF with preserved ejection fraction (HFpEF) was present in 70.5%. In-hospital mortality was 7.9%. At discharge more than half of the patients were prescribed beta-blockers (52.8%) and angiotensin-converting enzyme inhibitors (52%). Women presented a significantly higher proportion of HFpEF than men (75.3% vs. 62.7%,

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p=0.01). Patients with diabetes and those with ischemic etiology had significantly higher proportions of HF with reduced ejection fraction (HFrEF) (34.8% vs. 24.3% in non-diabetic patients, p=0.027, and 56.2% vs. 15.6% for other etiologies, p<0.001). The HFrEF group were more frequently discharged under beta-blockers and spironolactone (75.2% vs. 46.4% in the HFpEF group, p<0.001 and 31.2% vs. 12.6% in the HFpEF group, p<0.001, respectively). Mortality was 34.3% and rehospitalization for HF was 30.5% in one-year follow-up.
Conclusions: The population characterized is an elderly one, mainly female and with HFpEF. Nearly a third of patients died and/or were rehospitalized in the year following discharge.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
Mortalidade;
Hospitalização;
Reinternamento;
Rehospitalização

Características e prognóstico da hospitalização por insuficiência cardíaca PRÉvios a uma Clínica de Insuficiência Cardíaca: estudo PRECIC

Resumo
Objetivo: Caracterizar os doentes hospitalizados por Insuficiência Cardíaca (IC) aguda num Serviço de Medicina Interna, a mortalidade e rehospitalização por IC no primeiro ano.
Métodos: Estudo retrospetivo observacional incluindo todos os doentes com alta em 2012 de hospitalização por IC aguda, com base em Notas de Alta, registos clínicos e entrevistas telefónicas. Reporta-se ao ano prévio à implementação de uma clínica de IC.
Resultados: Identificaram-se 429 doentes, com idade média de 79 anos; 62,5% eram mulheres. A comorbilidade e etiologia mais prevalente foi a hipertensão arterial (86,7%) e o fator precipitante mais frequente da descompensação foi a infeção. Verificou-se Fração de Ejeção Preservada (FEp) em 70,5% dos doentes. A mortalidade intra-hospitalar foi 7,9%. À alta, a maioria dos doentes tinha prescrição de betabloqueadores (BB) (52,8%) e inibidores de enzima de conversão da angiotensina (52%). As mulheres apresentaram mais frequentemente FEp do que os homens (75,3% *versus* 62,7%, p=0,01). Os doentes diabéticos e os com etiologia isquémica apresentaram mais frequentemente Fração de Ejeção Reduzida (FEr) (34,8% *versus* 24,3% em não diabéticos, p=0,027 e 56,2% *versus* 15,6% com outras etiologias, p<0,001, respetivamente). No grupo com FEr, os BB e a espironolactona foram mais prescritos à alta (75,2% *versus* 46,4% no grupo com FEp, p<0,001 e 31,2% *versus* 12,6% no grupo com FEp, p<0,001, respetivamente). No primeiro ano, a taxa de mortalidade foi 34,3% e de rehospitalização por IC 30,5%.
Conclusões: A população estudada é idosa, predominantemente feminina e apresenta IC com FEp. Um terço morreu e/ou foi reinternada no ano seguinte.
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List of abbreviations

ACE	angiotensin-converting enzyme
AF	atrial fibrillation
ARB	angiotensin receptor blocker
EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD-9	International Classification of Diseases, 9th Revision
NIV	non-invasive ventilation
NT-proBNP	N-terminal-pro-B type natriuretic peptide

Introduction

Heart failure (HF) is a major global burden in terms of patients' quality and duration of life and of health expenditure.[1–4] Approximately 1-2% of the adult population in developed countries has HF, the prevalence rising to ≥10% among those 70 years of age or older.[1,5,6] In Portugal, the overall prevalence of chronic HF was 4.36% in a community-based epidemiological survey carried out in 1998, rising sharply with age; this was slightly higher than that of other European countries.[7]

Across the globe, 17-45% of patients hospitalized with HF die within a year of hospitalization[3,4,8] and a quarter are rehospitalized within one month and up to two-thirds within a year.[1,8–10] HF is the most common reason for hospitalization

in people over 65 years of age in economically developed regions.[6,9,11–13]

According to national registries of the Portuguese Directorate-General of Health, in 2014 18 588 patients were hospitalized for HF and the in-hospital mortality rate was 12.5%.[14]

The increasing incidence of acute HF and associated morbidity and mortality mean there is an urgent need to better understand this patient population.[15] Despite the high prevalence of acute HF, few studies have been conducted specifically in the hospitalized HF population, and data on clinical characteristics and outcomes for these patients are lacking, especially in Portugal. Observational studies provide useful information about real-world patients and routine clinical practice.[2] Interest in this type of research has been growing in recent decades, for various reasons.[4]

According to the latest guidelines on heart failure, the standard-of-care for HF patients recently hospitalized for acute de novo or chronic decompensated HF should include enrollment in a multidisciplinary care management program,[5,16] also known as a heart failure clinic.[17]

The present study covers the year before the implementation of an HF clinic, using a multidisciplinary approach to HF patients, in a Portuguese tertiary university hospital. The study was designed to improve knowledge of the characteristics of patients hospitalized and treated for HF in an internal medicine department and to present one-year follow-up outcomes, reporting in-hospital and one-year mortality and rehospitalization for HF, which will help to evaluate the impact of our HF clinic on those outcomes.

Methods

Study design and clinical setting

This was a single-center retrospective observational study. All patients hospitalized in the internal medicine department of a tertiary university hospital and discharged between January 1 and December 31, 2012 were considered for enrollment. The study population was selected using the International Classification of Diseases, 9th Revision (ICD-9) codes, as listed in the discharge summary. All discharge summaries reporting one of the ICD-9 HF codes (428, 428.0, 428.1, 428.2, 428.3, 428.4, 428.9, 402.01, 402.11, 402.91 or 398.91) in the first three codes were reviewed. Based on review of the discharge summary, patients were selected if they had been hospitalized for acute, de novo or chronic decompensated HF as stated in their medical record, and were aged 18 years or older. HF was diagnosed according to European Society of Cardiology guidelines.[5] All patients without an echocardiogram had relevant cardiac disease documented in their clinical record and NT-proBNP values higher than 1000 pg/ml.

For the purposes of the study, the first hospitalization for acute HF in the study period was considered the index hospitalization.

Data collection

Data were collected based on discharge summaries, medical records and telephone interviews.

The following data were collected from the discharge summary: gender, age, risk factors for HF, comorbidities, functional status, HF etiology, decompensation trigger and treatment. HF comorbidities considered for analysis were hypertension, diabetes, cerebrovascular disease, peripheral arterial disease, atrial fibrillation (AF), active cancer, chronic lung disease, sleep apnea and/or hypoventilation syndrome, and dementia.

Other clinical records were reviewed for biometric, laboratory, echocardiographic, follow-up and rehospitalization data. The etiology of cardiac disease was established through clinical data and echocardiography. Only rehospitalizations at the study center were considered.

Mortality data were obtained through clinical records and telephone interviews.

Outcomes

The main outcomes were the characteristics of the study population, namely age, gender, comorbidities, HF risk factors and etiology, HF decompensation trigger, left ventricular ejection fraction (EF), in-hospital mortality, discharge treatments, rehospitalization for decompensated HF and death in the year following discharge from the index hospitalization.

Study oversight

The two lead authors prepared the manuscript, and all authors reviewed it. All the authors vouch for the accuracy and completeness of the data and analysis.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are presented as means and standard deviation (SD) plus median and interquartile range (IQR). Proportions were compared using the chi-square test for categorical variables. The statistical analysis was performed using SPSS for Windows, version 22.

Results

Patients and comorbidities

In the study period 429 patients were identified and analyzed, as depicted in Figure 1. The characteristics of the study group are reported in Table 1. Mean age was 79 years and the majority of patients were female (62.5%). The most prevalent comorbidity was hypertension, followed by AF and diabetes.

On average, each patient had three comorbidities. A third of patients had more than three comorbidities.

Regarding functional ability, 96 patients (22.4%) had severe disability, being completely dependent on a caregiver for their daily needs.

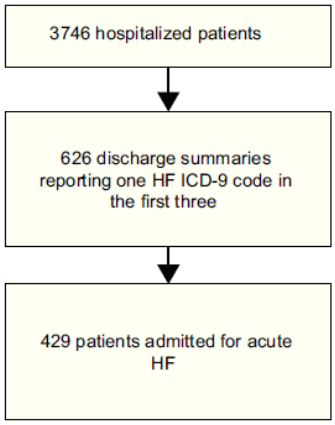


Figure 1 Flow diagram of patient enrollment. The data refer to admissions to the internal medicine department in the study period. HF: heart failure; ICD-9: International Classification of Diseases, 9th Revision.

Heart failure

Ischemic etiology of HF was recorded in 139 patients (34.6%) and valve disease in more than 74 (18.4%), of which severe aortic stenosis was the most common, found in 27 patients (6.7%) (data not shown). An echocardiogram was available in 400 patients, most of them with HF with preserved ejection fraction (HFpEF) (70.5%), defined as EF >40%, and only 36 patients (9%) had EF ≤25%.

The most frequent HF decompensation trigger was infection, followed by non-adherence to treatment and rhythm disturbances (Table 1). A trigger was not found in only two cases.

Non-invasive ventilation

During hospital stay, 80 patients (18.6%) were treated with non-invasive ventilation (NIV), 51% of whom were not diagnosed with sleep apnea/hypoventilation syndrome.

Discharge medication

At discharge, 394 patients were alive and prescribed appropriate cardiovascular medications, as reported in Table 2. About half of the patients discharged were prescribed a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Beta-blockers were prescribed significantly more frequently for patients with HF with reduced ejection fraction (HFrEF) but ACE inhibitors/ARBs were not.

Oral anticoagulants were prescribed for 118 (29.9%) patients, mainly to the 201 patients with a history of AF

Table 1 Characteristics of the study population.

		n
Age (years), mean ± SD; median (IQR)	79±10; 81 (11)	429
Female, %	62.5	429
Ischemic etiology, %	34.6	402
Admission SBP (mmHg), mean ± SD; median (IQR)	139.5±29.2; 136 (36)	420
Ejection fraction >40%, %	70.5	400
Hypertension, %	86.7	429
Diabetes, %	47.8	429
AF, %	51.7	429
Cerebrovascular disease, %	19.1	429
Peripheral arterial disease, %	11.7	429
Chronic pulmonary disease, %	28	429
Active cancer, %	6.8	429
Sleep apnea/hypoventilation syndrome, %	19.3	429
Dementia, %	24.7	429
>3 comorbidities, %	31.9	429
Physically active, %	77.6	429
HF decompensation trigger		429
Infection, %	39.4	
Non-adherence to treatment, %	17.5	
Rhythm disturbances, %	16.1	
Anemia, %	4.9	
Plasma creatinine >1.5 (mg/dl) %)	30.8	428
Admission plasma creatinine (mg/dl), mean ± SD; median (IQR)	1.3±0.6; 1.2 (0.78)	428
Admission sodium (mmol/l), mean ± SD; median (IQR)	136.4±5.7; 137 (6)	428
Hemoglobin (g/dl), mean ± SD; median (IQR)	12±2.1; 12 (2.8)	429
First NT-proBNP (pg/ml)	6698±10848; 2697 (6105)	366

AF: atrial fibrillation; IQR: interquartile range; NT-proBNP: N-terminal-pro-B type natriuretic peptide; SBP: systolic blood pressure; SD: standard deviation.

Table 2 Medications prescribed at discharge for the 394 patients discharged alive.

Patients *Drug*	All	HFrEF[a]	HFpEF[a]	p
Beta-blocker	52.8	75.2	46.4	<0.001
ACE inhibitor/ARB	52.0	58.7	51.3	0.237
Spironolactone	17.3	31.2	12.6	<0.001
Anticoagulant	29.9			

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.
Values refer to percentage of patients discharged in each group.
[a] Ejection fraction was available in 400 patients.

(83.1%), of whom 48.8% had anticoagulants prescribed at discharge, while only 10.4% of those without AF received anticoagulation (p<0.001). This represents 20 patients anticoagulated for reasons other than AF, mainly arterial peripheral disease, venous thromboembolism, previous ischemic stroke or mechanical prosthetic cardiac valves; only two had a history of intracardiac thrombus (data not shown). The small number of patients prevents further statistical analysis.

Relation between ejection fraction and other clinical characteristics

The relations between EF and characteristics including age, gender, HF etiology, comorbidities, plasma creatinine at admission and HF drug therapy prescribed at discharge are presented in Table 3. Women presented a significantly higher proportion of HFpEF than men.

Patients with diabetes and those with ischemic etiology had significantly higher proportions of HFrEF. The HFrEF group were more frequently prescribed beta-blockers and spironolactone at discharge (Table 2). Age, other comorbidities and plasma creatinine at admission were found to have no statistical relation with EF.

Follow-up outcomes

In-hospital mortality was 7.9%. Mortality in one-year follow-up was 34.3% (Figure 2A). One patient was lost to follow-up after discharge. The cause of death was established in 136 patients (92.5% of deaths) and a cardiovascular cause was found in 42.9% (data not shown).

Rehospitalization at least once for HF occurred in 30.5% of patients during the first year of follow-up, within a median of 86 days (IQR 176) after discharge (Figure 2B). The number of rehospitalizations per patient ranged between one and six (Table 4).

During the first year of follow-up after discharge, 62% of patients had an outpatient appointment with a cardiologist or an internist in our hospital. It was not determined which patients were followed previously by one of these specialties or whether the appointment was scheduled prior to the HF hospitalization. The median time between discharge and appointment was 63 days (IQR 64.5).

Table 3 Relation between ejection fraction and other characteristics.

	HFrEF	HFpEF	p
Age			0.439
<80 years	31.7	68.3	
≥80 years	27.6	72.4	
Gender			0.010
Female	24.7	75.3	
Male	37.3	62.7	
Ischemic etiology			<0.001
Yes	56.2	43.8	
No	15.6	84.4	
Hypertension			0.216
Yes	28.3	71.7	
No	38.3	61.7	
Diabetes			0.027
Yes	34.8	65.2	
No	24.3	75.7	
AF			0.704
Yes	30.6	69.4	
No	28.4	71.6	
Cerebrovascular disease			0.637
Yes	32.4	67.6	
No	28.8	71.2	
PAD			0.176
Yes	38.8	61.2	
No	28.2	71.8	
Chronic pulmonary disease			0.189
Yes	24.3	75.7	
No	31.6	68.4	
Active cancer			0.522
Yes	22.2	77.8	
No	30.0	70.0	
Sleep apnea/hypoventilation syndrome			0.095
Yes	21.3	78.8	
No	31.6	68.4	
Dementia			0.782
Yes	31.2	68.8	
No	29.0	71.0	
Plasma creatinine>1.5 mg/dl			1.000
Yes	29.6	70.4	
No	29.6	70.4	

AF: atrial fibrillation; PAD: peripheral arterial disease.
Data on 400 patients with ejection fraction estimated by echocardiography. Values refer to percentage of patients in each group.

Regarding potential admission to our HF clinic, 73% of patients were considered candidates. Referral to the clinic is considered for all patients hospitalized for acute HF. Exclusion criteria are total dependence on caregivers for basic daily needs and inability to communicate.

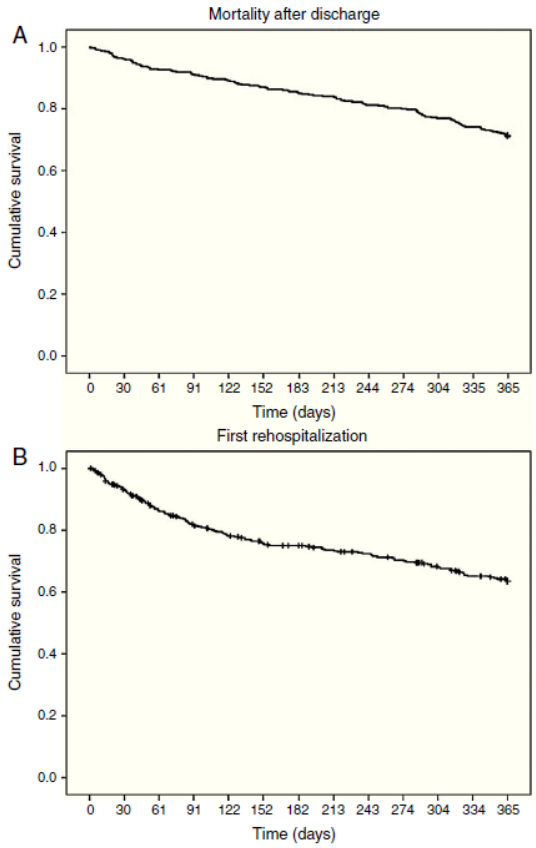


Figure 2 Kaplan-Meier curves for time to death (A) and rehospitalization for heart failure (B).

Table 4 Readmissions for acute or chronic decompensated heart failure during follow-up.

No. of readmissions	Patients (n)
1	77
2	38
3	9
4	3
5	3
6	1
Total	131

Data on 394 patients discharged alive.

Discussion

The main results of this study consist of the clinical findings of a large population hospitalized for HF in the internal medicine department of a tertiary university hospital. In Portuguese hospitals, many HF patients are treated by internists, even in hospitals where there is a cardiology department,[18,19] so this is a real-world survey, enrolling all patients discharged following hospitalization due to acute or chronic decompensated HF during a one-year period.

Our patients are older, more frequently female and more often with HFpEF than HF patients in other series, who tend to be mainly hospitalized in cardiology departments.[2,4] The mean age is similar to that reported in a recent French single-day survey in 170 hospitals of all patients hospitalized for acute HF,[13] but 10 years older than in a recent Portuguese study enrolling patients hospitalized for acute HF only in the cardiology department of the other tertiary university hospital in the city where our study took place. In that study 73.2% of patients had HFrEF, which reflects considerable differences between the two study populations and is evidence of how observational studies provide valuable information about acute HF managed in different clinical scenarios.[20,21] Our data on gender are in agreement with other reports showing that elderly patients hospitalized with HF are mainly women[22] and that patients with HFpEF are older and more often female than those with HFrEF.[1,5,6,8,13] HF patients managed by internists are more likely to have the characteristics of those managed by general practitioners. In the UK, the mean age of HF patients in general practice is 77 years, similar to that of our population. The HF patient seen in general practice is generally 15 years older, more often female, more likely to have a history of hypertension and less likely to have had myocardial infarction than the HF patient seen by a cardiologist.[1,6] It has been shown that in Portugal chronic HFpEF mainly affects older women[7] and that patients aged over 75 hospitalized for acute HF in an internal medicine department mainly have HFpEF.[19]

The average of three comorbidities per patient shows the complexity of this population and is in agreement with data on older people with HF in the USA.[16] Of note, the prevalences of the two commonest comorbidities, hypertension and diabetes, in our study were similar to that report; this is not the case for AF, which was twice as common in the present study.[16] Patients with more than three comorbidities have a higher risk of death and HF hospitalization, as shown by van Deursen et al.,[23] although in their study only non-cardiovascular comorbidities were analyzed. Another study, on incident HF, reported that patients with HFpEF were more likely to have both cardiac and non-cardiac comorbidities.[24]

AF and a history of hypertension were more prevalent in this study population than in others in which HFrEF was more prevalent than HFpEF and patients were enrolled in cardiology wards.[2,4] This is consistent with the literature on HFpEF populations and with data on Portuguese HF patients.[4,19,25]

Hypertension was the main etiology for HF, according to its prevalence in this population, but the retrospective nature of the study and the non-invasive diagnostic methods used for determining HF etiology prevent further analysis.

An ischemic etiology was less prevalent (34.6%) than reported by the above-cited European observational trials, which included mostly HFrEF patients (42%-50.7%), as expected.[1,3,4,13] It is known that patients with HFpEF are less likely to have coronary heart disease and more likely to have hypertension and AF than those with HFrEF.[5,6] We confirmed that ischemic HF patients more often had HFrEF.

The patient characteristics in this study were similar to those reported by a Spanish heart failure unit in a recent paper from the internal medicine department of a tertiary referral hospital, which describes an elderly population with a mean age of 80.3 years, of whom 54.8% were female, 72.2%

had HFpEF (≥50% according to the criteria of this study) and the main etiologies were ischemic and hypertensive in the HFpEF group and ischemic in the HFrEF group.[26]

Infection was the most frequent trigger of HF decompensation in our study, as has been found in other Portuguese and European surveys.[7,13,25]

In addition to the significant correlation between sleep apnea/hypoventilation syndrome and treatment by NIV during hospitalization, it is noteworthy that the numbers of patients undergoing NIV with and without one of these diagnoses were similar. This probably means that relieving acute pulmonary congestion and improving pulmonary gas exchange were the main treatment goals in a large number of those treated with NIV.

Our in-hospital mortality was double (7.9%) that reported in a large European observational survey (3.8%)[2] and in a US registry (4.0%)[27] but similar to that reported in other Portuguese studies and in Italian and French surveys (7.7%, 6.9% and 8.2%, respectively).[4,13,25]

Pharmacological treatment at discharge should be considered in the light of the prevalence of HFpEF in this population. Bearing in mind that no drug therapy has been proved to change prognosis in the HFpEF phenotype,[5,16] it is interesting to see that half of the patients were prescribed beta-blockers or ACE inhibitors. This proportion is similar to that reported in the OFICA study in the HFpEF subgroup, in which 44.2% and 47.3% of this group of patients were discharged under ACE inhibitors and beta-blockers, respectively.[13] This reflects the use of these drug classes in HFpEF patients with the aim of controlling blood pressure and ventricular rate in AF and decreasing hospitalizations. Ceia et al. found that therapy with ACE inhibitors in Portuguese chronic HF patients was also similar between patients with HFpEF and HFrEF.[28]

Our finding that beta-blockers and spironolactone were more often prescribed for HFrEF patients shows adherence to current guidelines and their incorporation into clinical practice. The rate of such prescription is similar to that in a European survey for beta-blockers (75.2% vs. 80%) but lower for aldosterone blockers (31.2% vs. 52%).[2]

The total one-year mortality was higher than that reported from the same European region (34.3% vs. 24.7%) by Maggioni et al. in the ESC-HF Pilot survey for the period 2009-2010 and in an Italian survey (24%).[2,4] Cardiovascular causes accounted for half of deaths, a smaller proportion than reported in other observational trials, probably because the type of HF patients hospitalized in cardiology departments are more liable to die of cardiovascular causes, while those hospitalized in internal medicine wards are equally likely to die of other causes. In this respect, it is noteworthy that the patients in our study were 10 years older and had a higher prevalence of comorbidities.[3,4] Comorbidity was found to be one of the prime determinants of prognosis in a study of patients hospitalized with HF[1] and HFpEF patients have a higher likelihood of non-cardiovascular death,[6] supporting our findings.

It should be noted that, although it is commonly accepted that the lower the EF the worse the survival,[5] in our predominantly HFpEF population neither mortality nor rehospitalization rates were lower. This is in agreement with other hospital-based studies of patients hospitalized with HF that reported similar one-year mortality rates in patients with HFpEF compared to those with HFrEF,[1,6] but not with the OFICA study, which reported higher mortality in the HFrEF population.[13]

The rehospitalization rate for HF in the first year of follow-up was similar in this study to that found for the same European region in the previously mentioned survey (30.5% vs. 33.9%, respectively). Of note, the highest rates of mortality and rehospitalization for HF were observed in this region, in comparison with three other European regions.[3,4] Bearing in mind the differences in prevalence of HFpEF, this is in agreement with studies reporting that HFpEF patients are as likely to be rehospitalized as HFrEF patients.[6]

The median time between discharge and first follow-up appointment was much longer than the recommended 7-14 days,[16] a situation that we expect to change drastically with the implementation of our heart failure clinic.

To our knowledge this is the largest Portuguese observational study of patients hospitalized for HF, and the most recent.

Our findings should be considered in the context of several limitations. This was a retrospective registry and did not include all patients hospitalized for HF, including those admitted to the cardiology department of our hospital. Unmeasured variables may have been present that could have influenced the findings. Chronic renal dysfunction was not included in the comorbidities because of the difficulty of ascertaining the chronicity of renal dysfunction in some patients with cardiorenal syndromes. Rehospitalizations were considered only at the study center, and thus may have been underestimated. We did not examine the use of cardiac devices, although there is unlikely to be a significant number of patients with such devices, given the low prevalence of reduced ejection fraction and the old age of this population.

Conclusions

This is one of the few published observational studies showing the situation in Portugal in terms of HF hospitalization and outcomes. We characterized a large group of patients admitted to an internal medicine department with acute HF: elderly, mostly female, with hypertension and HFpEF. Diabetic patients and those with ischemic heart disease were significantly more likely to have HFrEF. At discharge, more than half of patients were prescribed beta-blockers and ACE inhibitors/ARBs, and those with HFrEF were significantly more often prescribed beta-blockers and spironolactone. Nearly a third of patients died and/or were rehospitalized in the following year.

Multicenter observational studies in the Portuguese HF population are an unmet need. For the time being, the data presented here will be helpful to measure the impact of the heart failure clinic at our institution in important areas, particularly mortality and rehospitalization outcomes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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5.2. In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk vs. Observed Mortality

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My contributions to this work were as follows: I designed the study, collected data, wrote, edited and revised the manuscript, and served as the corresponding author. To the best of my knowledge this article has not been included in any other thesis. This is an open access publication, with no financial, legal or technical barriers to accessing it.

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Research Article

In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk *vs.* Observed Mortality

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ABSTRACT

Background: Acute heart failure in-hospital mortality varies between 3.8-28%. The Acute Decompensated Heart Failure National Registry (ADHERE) risk tree is a landmark risk prediction model for in-hospital mortality. This study compares in-hospital mortality predicted by the ADHERE risk tree with the observed mortality of patients from the Pre Heart Failure Clinic (PRECIC-Pré Clínica de Insuficiência Cardíaca) study.

Methods and findings: This is a retrospective, single-centre, observational sub-analysis of the previously reported PRECIC study. The ADHERE risk tree was applied. In-hospital predicted and observed mortality was compared in 419 patients with a mean age of 79.5 years. The majority were female and had left ventricle ejection fraction ≥ 40%. In-hospital mortality was 8.1% (n=34). After being classified in the ADHERE risk groups, the observed mortality rates between 3 groups were significantly different (p<0.001): Low, Intermediate 2, and Intermediate 1 (4.5% *vs.* 2.3%, p=0.0017; 12.5% vs. 5.6%, p=0.024; and 40% *vs.* 13.2%, p=0.003, respectively). The observed mortality was twice the predicted mortality in the Low and Intermediate two groups and threefold in the Intermediate 1 group. The small number of patients in the High group impairs solid conclusions to be drawn for this group.

Conclusion: The ADHERE risk tree cannot accurately predict the in-hospital mortality rates of patients with the characteristics of those included in the PRECIC study. This finding supports the need to locally validate risk trees to take into account different patient characteristics and healthcare settings.

Keywords: Heart failure; Risk groups; In-hospital mortality

Abbrevations: AHF: Acute Heart Failure; ADHERE: Acute Decompensated Heart Failure National Registry; HF: Heart Failure; SBP: Systolic Blood Pressure; BUN: Blood Urea Nitrogen; LVEF: Left Ventricle Ejection Fraction;

INTRODUCTION

Acute Heart Failure (AHF) is a leading cause of hospital admission in the elderly, being associated with increased hospital stay and higher risk of mortality [1], and represents a significant burden on overall healthcare costs [2]. A better understanding of this high-risk patient population is therefore needed [3].

In-hospital mortality due to AHF varies between 3.8-28% in developed countries [2,3]. Several mortality predictors have been identified for outpatients with chronic Heart Failure (HF), but few risk-prediction models have been developed specifically for the hospitalised AHF population [3]. The complex pathology, incomplete prospective data, and the different epidemiological characteristics among populations make it very difficult to identify good predictors of in-hospital mortality [2].

Clinical and therapeutic decisions should be tailored to the

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patient's risk for adverse outcomes. Although a clinical risk prediction model for in-hospital mortality cannot replace physician assessment, it is beneficial to guide the healthcare strategy based on the anticipated risk of death, optimising the use of healthcare resources and generating better clinical outcomes [2,4,5].

The Acute Decompensated Heart Failure National Registry (ADHERE) is a landmark study that addressed the need for prediction models of in-hospital death risk [5]. The main outcome of the ADHERE study is a risk tree, which provides clinicians with a practical bedside prediction tool for in-hospital mortality for patients hospitalised with AHF. It is based on Systolic Blood Pressure (SBP), serum Blood Urea Nitrogen (BUN), and serum creatinine parameters at the time of admission [5]. The ADHERE study was validated for the USA population, and it remains to be clarified whether its risk model can accurately predict in-hospital mortality in other populations [5].

This study aims to compare in-hospital mortality predicted by the ADHERE risk tree with the observed mortality in a cohort of Portuguese HF patients that have previously been enrolled in the PRECIC study [6].

METHODOLOGY

Study sample and design

This is a retrospective, single-centre, observational study based on a sub-analysis of the previously reported PRECIC study [6]. All patients hospitalised with AHF in the Internal Medicine Department of a large tertiary university hospital for one year were considered for enrolment. Clinical records and telephone interviews were used for data collection. The study was approved by the institutional Ethics Committee, and patient confidentiality was preserved because no direct patient identifiers were collected.

Data collection and in-hospital mortality risk groups

Clinical records were analysed for data collection as previously described [6]. The ADHERE risk tree was applied to all patients based on SBP value and levels of BUN and plasma creatinine at the time of hospital admission. Patients were classified according to the five risk groups of in-hospital mortality of the ADHERE risk tree: High Risk, Intermediate Risk 1, Intermediate Risk 2, Intermediate Risk 3, and Low Risk [5]. Ten patients were excluded from the analysis due to the absence of clinical data needed for model application. All comparisons were made between the PRECIC study population and the ADHERE validation cohort [5]. For this purpose, urea levels were converted into BUN using the following equation: BUN (mg/dL)=urea (mg/dL)/2.14.

Statistical analysis

Baseline characteristics of the PRECIC sample were previously reported [6]. Fisher's exact test and univariate logistic regression model were performed to compare mortality according to the ADHERE risk groups. Chi-square and Fisher's exact test were used to compare the in-hospital mortality rates of this study population with the ADHERE validation cohort [5] in terms of ADHERE risk groups. A level of α=0.05 was used as a boundary for statistical significance in all analyses. Statistical analyses were performed using the statistical software SPSS® IBM® 22.0.

RESULTS

During the PRECIC study period, 429 patients were hospitalised with AHF. Of these, all the required clinical data at admission for stratification according to the ADHERE risk tree was available for 419 patients. The 419 enrolled patients had a mean age of 79.5 years, the majority were female (63.2%), and 74.7% had Left Ventricle Ejection Fraction (LVEF) ≥ 40%. The demographic and clinical characteristics of this study sample are reported together with those from the ADHERE validation cohort (Table 1). Based on the ADHERE risk tree criteria, patients were assigned to the five in-hospital mortality risk groups shown in Figure 1. Two risk groups were underrepresented: the High-risk group, with only 4 patients, and the Intermediate 1 group, with 20 patients.

The observed in-hospital overall mortality was 8.1% (34 deaths). The leading cause of death was cardiovascular: 21 out of 34 deaths (61.8%). The assignment of patients to the ADHERE risk groups revealed significantly different ($p<0.001$) mortality rates between groups (Table 2) [5]. The mortality Odds Ratio (OR) of the Intermediate 1 and 2 risk groups compared to the Low-risk group were 14.0 and 3.0 (95% CI, 4.82-40.6, and 1.24-7.23), respectively. Due to the small number of patients assigned to the High-risk group (n=4), it was not possible to detect any significant difference between this and the Low-risk group (p=0.103).

The overall in-hospital mortality observed in this study (8.1%) was twice that reported in the ADHERE validation cohort (4.0%)

Table 1: Demographic and clinical characteristics of this study sample and the ADHERE validation cohort.

Baseline Characteristics	Study Sample	ADHERE Validation cohort
Demographic variables		
N	419	32 229
Mean age (SD), years	79.5 (10)	72.5 (14)
White (%)	100	72
Female (%)	63.2	51
Medical history		
Hypertension (%)	86.4	72
Diabetes mellitus (%)	47.3	44
Coronary artery disease (%)	32	56
Atrial fibrillation (%)	52.7	30
Peripheral vascular disease (%)	11.7	18
Active cancer (%)	8.8	NA
Dementia (%)	50	NA
Clinical status		
Systolic Blood Pressure(mean, SD, mmHg)	139.4 (29)	144.7(32.5)
Sodium(mean, SD, mmol/L)	136.4 (5.8)	138.3(4.8)
Serum creatinine(mean, SD, mg/dL)	1.3 (0.7)	1.8(1.7)
Blood Urea Nitrogen(mean, SD, mg/dL)	32.9 (19.2)†	31.5 (20.8)
Haemoglobin(mean, SD, g/dL)	12 (2.1)	12.4 (2.6)
LVEF ≥ 40% (%)	74.7	47

Note: †Blood Urea Nitrogen was converted from urea by the following equation: BUN (mg/dL)=Urea (mg/dL)/2.14;
Abbreviation: ADHERE: Acute Decompensated Heart Failure National Registry; LVEF: Left Ventricle Ejection Fraction; NA: Not Available; SD: Standard Deviation

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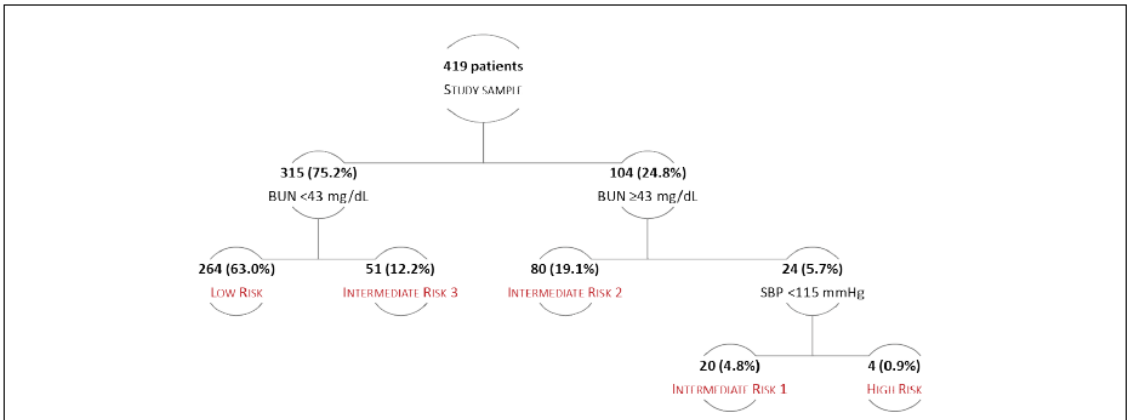


Figure 1: Distribution of the study patients according to the ADHERE risk tree. **Note:** ADHERE: Acute Decompensated Heart Failure National Registry; BUN: Blood Urea Nitrogen; SBP: Systolic Blood Pressure

Table 2: In-hospital mortality rates, according to ADHERE risk groups.

ADHERE risk group	Mortality (%)	OR	95% CI	p value
Low	4.5	1	-	
Intermediate 3	5.9	1.312	0.357-4.827	0.682
Intermediate 2	12.5	3	1.244-7.233	0.014
Intermediate 1	40	14	4.823-40.639	<0.001
High	25	7	0.677-72.385	0.103

Note: OR: Odds Ratio; CI: Confidence Interval

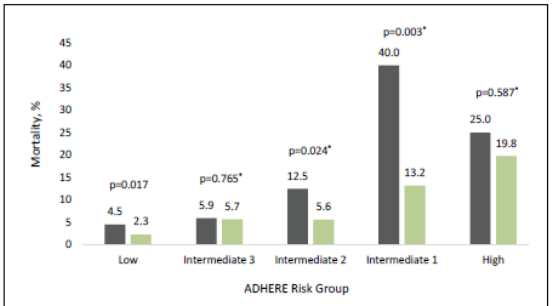


Figure 2: Observed mortality (%, vertical axis) in this PRECIC sub-study and ADHERE validation cohort mortality, according to ADHERE risk groups (horizontal axis). **Note:** *Fisher's Exact Test for every other group; PRECIC, ADHERE

[5]. The comparison between in-hospital mortality rates in this study and those reported in the ADHERE validation cohort for each ADHERE risk group also revealed statistically significant differences (Figure 2). Observed and predicted in-hospital mortality was statistically different in three risk groups: Low, Intermediate 2, and Intermediate 1. The mortality rate found in this study was twice that reported in the ADHERE for the Low and Intermediate 2 risk groups and threefold for the Intermediate 1 group.

DISCUSSION

This study found a higher overall in-hospital mortality rate than the one reported for the ADHERE validation cohort. After the assignment into the ADHERE risk groups, the observed mortality rates between groups differed significantly. Additionally, we found that the observed mortality was twice that of the one predicted by the ADHERE risk tree in the Low and Intermediate 2 risk groups and threefold in the Intermediate 1 risk group. Due to the small number of patients assigned to the High-risk group in our study population, it was not possible to draw consistent conclusions relative to this group.

The differences between the in-hospital mortality rates found in this study and those reported for the ADHERE cohort must be interpreted in light of the size and baseline characteristics of the two study populations. In fact, our study population (n=419) was much smaller than that of the ADHERE study (n=32,229). Looking at the baseline characteristics of the two study populations, patients had similar diabetes mellitus and peripheral vascular disease prevalence, SBP mean value, and BUN, sodium, and haemoglobin levels at the time of hospital admission. In contrast, the two populations differed in clinical characteristics such as coronary artery disease, atrial fibrillation, and LVEF. This study population presented a higher mean age, with more white and female patients, a more frequent history of hypertension and atrial fibrillation, less coronary artery disease, lower mean plasma creatinine levels at admission, and substantially higher LVEF. We did not analyse the direct individual impact of those factors on the in-hospital mortality rate. Still, of these factors, only age was found to be an independent predictor of mortality at one-year in the PRECIC study [7]. Other studies have also reported age as one of the strongest independent predictors of in-hospital mortality in AHF patients [4,5,8].

The in-hospital mortality rate reported in this study is similar to those reported in other studies from Portugal and other European countries [8-10], yet higher than those reported for USA large cohorts, such as ADHERE and OPTIMIZE-HF registry [3,5]. Interestingly, the mean ages of the ADHERE and OPTIMIZE-HF cohorts were 72.5 and 73 years, respectively, and the mean age of patients who died while hospitalised in the OPTIMIZE-HF, was 78.5 years, which is similar to the rate found in this study (79.5 years) [3].

In a large French HF registry–the OFICA study–the multivariate analysis identified age, low blood pressure and renal failure as the strongest independent predictors of in-hospital mortality for AHF

patients. The mean age and mortality rate of the OFICA study were similar to those reported in this study [8]. In the OPTIMIZE-HF registry, Abraham, *et al.* developed a predictive clinical model for in-hospital mortality among a large cohort of hospitalised HF patients in the USA, and also found that increasing age, low SBP, low sodium levels, increased heart rate, and increased creatinine at the time of admission were independent predictors of higher in-hospital mortality. However, the OPTIMIZE-HF cohort has some significant differences compared to this study population, mainly in respect to the lower mean LVEF and the fact that some patients were not primarily hospitalised due to AHF [3].

In the 2017 report from the European Society of Cardiology Heart Failure Long-Term Registry, among the hospitalised subgroup of patients, the highest in-hospital mortality rates were observed in cardiogenic shock patients and in those with SBP lower than 85 mmHg, at the time of admission. The latter was associated with less geographic variation, supporting its more general applicability in clinical practice [11].

The role of BUN as an independent predictor of mortality in HF patients was reinforced in the report of the BIOSTAT-CHF risk model [12]. In the preliminary observations of the ADHERE study, renal kidney dysfunction was considered a hallmark of that study population [13], suggesting that it is one of the best discriminators of mortality risk [5].The mean serum urea level (or BUN) found in this study was not very different from that of the ADHERE validation cohort. Nevertheless, our patients had higher in-hospital mortality rates.

Likewise, we did not find a lower mortality risk in female or in patients with higher LVEF, as reported elsewhere [1,8,14]. Our study population characteristics, with a high percentage of females and high LVEF values (in contrast to the ADHERE population), is in accordance with previous studies that have shown that these two characteristics are linked [14-16], and are associated with hypertension, atrial fibrillation, and non-ischemic HF aetiology [1,17]. The MAGGIC risk score, based on a meta-analysis of 31 cohort studies, found that, in HF patients with LVEF>50%, age was more predictive of mortality than SBP, but the data is mostly from stable rather than acute hospitalised HF patients [14,18]. The high prevalence of patients with LVEF ≥ 40% in our study population has already been discussed in the PRECIC study report [6] and is primarily explained by the fact that patients originated from an Internal Medicine department. Nevertheless, we do not believe this factor justifies the higher in-hospital mortality observed, as the vast majority of published studies demonstrate similar or even lower mortality rates in patients with LVEF ≥ 40% [1,8,14,17].

Although we did not find any report of mortality variation related to race among hospitalised patients with AHF, the higher percentage of White patients in our sample could be one of the factors contributing to the higher in-hospital mortality observed, as previously suggested by Lim et al. in their analysis of risk-adjusted models for in-hospital mortality, which considered key laboratory and race/ethnicity data [19].

It is essential to highlight that, in this study, 50% of patients who died while hospitalised had some degree of dementia, and that 8.8% had an active cancer. In the PRECIC population, dementia and active cancer were independent predictors of mortality in the year following hospitalisation [7]. We could not find any data for the prevalence of dementia in the ADHERE population. Nevertheless, since in our study only about two thirds of in-hospital deaths were attributed to cardiovascular causes, we believe that dementia and active cancer might have had a major impact on the mortality rates and cause of death. Besides the common association between cancer and death, it is well-known that patients with dementia are prone to die in the hospital from complications, such as infections [20].

The ADHERE risk tree could not predict the in-hospital mortality rates for patients of this study. In this study, patients were more prone to die, even those in the Low-risk group. In line with this observation, in a recent analysis investigating the performance of four predicting tools for the mortality of AHF patients, including the ADHERE, Scrutinio et al. concluded that risk assessment tools work well for stratifying patients in risk groups, but have limited clinical utility in estimating the risk of mortality for individuals [21].

Nevertheless, we believe that our data reflect real-world treatment patterns and in-hospital clinical outcomes of patients hospitalised with AHF, at our hospital. So, what differences could explain the higher overall in-hospital mortality in the Low, Intermediate 2, and Intermediate 1 ADHERE risk groups? Firstly, age differences between the two study populations might be a major factor, because of the high impact of age on mortality in AHF cohorts, as previously described [13]. Secondly, the higher prevalence of atrial fibrillation found in our study could have had a negative impact on mortality. In fact, patients with chronic HF and atrial fibrillation have a poorer prognosis than those with sinus rhythm, which is largely explained by more advanced age and HF severity [1]. Thirdly, we compared patients hospitalised with AHF at different time periods and different countries with very different healthcare systems (Europe *vs.* USA). For instance, in this study, patients were recruited from the Internal Medicine Department, where most AHF patients are treated in Portugal, whereas, in the ADHERE study, most of the patients were recruited from the Cardiology Department [22,23]. It is also worth noting that our in-hospital and one-year all-cause mortality rates are in accordance with those reported in the European registries [8, 24-27], and in Portuguese studies [10, 26].

Given the rise in prevalence of HF, there is an unmet clinical need for tools to accurately assess the prognosis of HF patients [28]. Undoubtedly, a quick and simple tool to predict in-hospital mortality would be very attractive for supporting clinical decision-making, through a better knowledge of the patients' prognosis. However, it is unlikely that any one model can be universal, as the specificities of each healthcare scenario are likely to affect the outcomes. Additionally, it has been shown that the real-world performance of prediction models is generally poorer in new patient populations when compared to the original development study population. Therefore, every mortality risk predictor model must be tested for the local population and healthcare setting before the model can be implement in routine clinical practice [29].

In short, this study addresses a relevant issue: risk prediction models must be validated in the population/healthcare setting where they will be applied in clinical practice. We should be cautious and not extrapolate the findings validated for different countries and healthcare settings to other countries and settings, such as applying the USA ADHERE risk tree to AHF patients admitted to a large tertiary university hospital in Portugal. The findings of this study also pave the way for a better understanding of the real-world practice and clinical outcomes and, therefore, of the design

of intervention strategies aimed at reducing short-term mortality of AHF patients.

CONCLUSION

After assigning the hospitalised AHF patients to the ADHERE risk groups, this study found that the in-hospital mortality rates among risk groups were significantly different. Overall, the observed mortality was higher than that predicted by the ADHERE risk tree. These findings contribute to a better awareness of AHF mortality and may pave the way to better patient management strategies and, as such, better clinical outcomes. Prediction models for the in-hospital mortality of AHF are important tools that need to be locally validated before they can be implemented in routine clinical practice.

STUDY LIMITATIONS

This study has four major limitations. Firstly, it is a retrospective study, which makes it challenging to analyse the causes and influencing factors of the mortality rates observed. Secondly, there is the possibility that other clinical factors relevant to in-hospital mortality were not considered in the analysis. Thirdly, patients hospitalised with AHF who died in the emergency room, and patients admitted to departments other than the Internal Medicine department, were not included in this study, which could contribute to an even higher mortality rate compared to the ADHERE study. Fourthly, our study population is much smaller than that of the ADHERE.

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COMPETING INTERESTS

None to declare.

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5.3. One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)

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My contributions to this work were as follows: I designed the study, collected data, wrote, edited and revised the manuscript, and served as the corresponding author. To the best of my knowledge this article has not been included in any other thesis. This is an open access publication, with no financial, legal or technical barriers to accessing it.

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ORIGINAL ARTICLE

One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)

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KEYWORDS
Heart failure;
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Abstract
Introduction and objectives: One-year mortality after hospitalization for heart failure (HF) is high. This study aims to identify predictive factors of one-year mortality.
Methods: This is a retrospective, single-center and observational study. All patients hospitalized for acute HF during one year were enrolled.
Results: A total of 429 patients were enrolled, mean age of 79 years. The in-hospital and one-year all-cause mortality rates were 7.9% and 34.3%, respectively. In the univariable analysis, the factors significantly associated with higher one-year mortality risk were: age ≥80 years (odds ratio (OR)=2.05, 95% confidence interval (CI) 1.35–3.11, p=0.001); active cancer (OR=2.93, 95% CI 1.36–6.32, p=0.008); dementia (OR=2.84, 95% CI 1.81–4.47, p<0.001); functional dependency (OR=2.63, 95% CI 1.65–4.19, p<0.001); atrial fibrillation (OR=1.86, 95% CI 1.24–2.80, p=0.004); higher creatinine (OR=2.03, 95% CI 1.29–3.21, p=0.002), urea (OR=2.92, 95% CI 1.95–4.36, p<0.001) and red cell distribution width (RDW; 4thQ OR=5.59, 95% CI 3.03–10.32, p=0.001); and lower hematocrit (OR=0.94, 95% CI 0.91–0.97, p<0.001), hemoglobin (OR=0.83, 95% CI 0.75–0.92, p<0.001) and platelet distribution width (PDW; OR=0.89, 95% CI 0.82–0.97, p=0.005). In the multivariable analysis, the independent predictors of higher one-year mortality risk were: age ≥80 years (OR=2.05, 95% CI 1.21–3.48); active cancer (OR=2.70, 95% CI 1.03–7.01); dementia (OR=2.69, 95% CI 1.53–4.74); higher urea (OR=2.97, 95% CI 1.84–4.80) and RDW (4thQ OR=5.24, 95% CI 2.55–10.76); and lower PDW (OR=0.88, 95% CI 0.80–0.97).

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Conclusions: Active cancer, dementia, and high values for urea and RDW at admission are predictors of one-year mortality in patients hospitalized for HF. These variables are readily available at admission and can support the clinical management of HF patients.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
Mortalidade;
Hospitalização;
Preditores;
Prognóstico

Fatores preditores da mortalidade no primeiro ano após hospitalização por insuficiência cardíaca aguda (subanálise do estudo PRECIC)

Resumo
Introdução e objetivos: A mortalidade no primeiro ano após a hospitalização por insuficiência cardíaca é alta. Este estudo tem como objetivo identificar fatores preditivos de mortalidade nesse período.
Métodos: Este é um estudo retrospetivo e observacional de um só centro. Todos os doentes hospitalizados por insuficiência cardíaca aguda durante o período de um ano foram incluídos.
Resultados: Foram incluídos 429 doentes com idade média de 79 anos. As taxas de mortalidade intra-hospitalar e por todas as causas após um ano foram de 7,9% e 34,3%, respetivamente. Na análise univariável, os fatores significativamente associados com maior risco de mortalidade a um ano foram: idade ≥ 80 anos (OR=2,05, IC 95% 1,35-3,11, p=0,001); neoplasia ativa (OR=2,93, IC 95% 1,36-6,32, p=0,008); demência (OR=2,84, IC 95% 1,81-4,47, p<0,001); dependência funcional (OR=2,63, IC 95% 1,65-4,19, p<0,001); fibrilhação auricular (OR=1,86, IC 95% 1,24-2,80, p=0,004); valores elevados de creatinina (OR=2,03, IC 95% 1,29-3,21, p=0,002), ureia (OR=2,92, IC 95% 1,95-4,36, p<0,001) e índice de distribuição de eritrócitos (RDW; 4Q OR=5,59, IC 95% 3,03-10,32, p=0,001); e valores baixos de hematócrito (OR=0,94, IC 95% 0,91-0,97, p<0,001), hemoglobina (OR=0,83, IC 95% 0,75-0,92, p<0,001) e índice de distribuição de plaquetas (PDW; OR=0,89, IC 95% 0,82-0,97, p=0,005). Na análise multivariável, os preditores independentes de maior risco de mortalidade a um ano foram: idade ≥ 80 anos (OR=2,05, IC 95% 1,21-3,48); neoplasia ativa (OR=2,70, IC 95% 1,03-7,01); demência (OR=2,69, IC 95% 1,53-4,74); ureia elevada (OR=2,97, IC 95% 1,84-4,80) e RDW (4Q OR=5,24, IC 95% 2,55-10,76); e PDW baixo (OR=0,88, IC 95% 0,80-0,97).
Conclusões: Neoplasia ativa, demência e valores elevados de ureia e RDW na admissão são preditores de mortalidade após um ano dos doentes hospitalizados por insuficiência cardíaca. Estes dados estão facilmente disponíveis na admissão e podem auxiliar na gestão clínica de doentes com insuficiência cardíaca.
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Introduction

Heart failure (HF) is a prevalent condition associated with high mortality and morbidity and reduced quality of life.[1] Comorbidities are frequent among HF patients, leading to increased hospitalization rates and mortality. The prevalence of comorbidities is higher in patients with more severe signs of HF.[2] According to international reports, one-year mortality and re-hospitalization rates for HF patients are 17% and 44%, respectively.[3,4] HF is the most common reason for hospitalization in people >65 years in economically developed countries.[5]

Little is known about the long-term prognosis and risk factors for a fatal outcome in patients hospitalized with acute HF (AHF).[6] The increasing incidence and associated morbidity and mortality of AHF mean there is an urgent need to better understand this population.[7] Risk stratification of HF patients is important to identify high-risk patients who may benefit from advanced treatments. Besides improving risk stratification, identifying new prognostic markers may also provide information about the pathophysiology of HF and support the clinical management of HF patients and decision-making as to the best therapeutic strategy.

This study reports the impact on one-year mortality of comorbidities and biochemical parameters of patients hospitalized for HF during one-year at an Internal Medicine Department of a large tertiary university hospital in Porto, Portugal.

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Methods

Study design and clinical setting

This is a retrospective, single-center, observational study. The study design and detailed characterization of the study population have been described elsewhere.[8] In short, all patients discharged from the Internal Medicine Department of Centro Hospitalar Universitário de Santo António, Porto, Portugal, over a one-year period were considered for enrollment. Based on the discharge summary review, patients were selected for enrollment if they had been hospitalized for AHF, either *de novo* or due to chronic decompensation. HF was diagnosed according to the European Society of Cardiology guidelines available at the time of study enrollment.[9] All patients without an echocardiogram presented the clinical syndrome of HF, relevant cardiac disease documented in their clinical record, and N-terminal-pro-B type natriuretic peptide (NT-proBNP) values >1000 pg/mL. For the purposes of this study, the first hospitalization for AHF during the one-year study period was considered the index hospitalization.

Data collection

Data was collected based on the hospital discharge summaries, clinical records, and telephone interviews. The following data were collected from the discharge summary: sex, age, risk factors for HF, comorbidities, functional status, and HF etiology. In addition, biochemical parameters and systolic blood pressure were collected from the admission clinical records and laboratory data records.

Comorbidities and conditions considered for analysis were hypertension, diabetes (DM), cerebrovascular disease, peripheral arteriopathy, atrial fibrillation (AF), active cancer, chronic lung disease, sleep disorder, and/or hypoventilation syndrome, dementia, and functional dependency. The occurrence of comorbidities was ascertained by the investigators through the critical analysis of each diagnosis after clinical record review and was considered if diagnosed before or at the index hospitalization.

Hospital admission biochemical parameters considered for analysis were blood plasma creatinine, urea, potassium, sodium, hemoglobin, hematocrit, platelet count, platelet distribution width (PDW), and red cell distribution width (RDW).

Other clinical records were reviewed for biometric, echocardiogram, follow-up, and re-hospitalization data. The etiology of cardiac disease was established through clinical data and echocardiogram. Only re-hospitalizations at the study center were considered, given the difficulty of accessing patients' health data in other public or private health organizations, which could underestimate re-hospitalizations. Mortality data were obtained from clinical records and telephone interviews.

Outcome

The main outcome was to characterize the factors associated with mortality in patients hospitalized for HF one-year after discharge from the index admission.

Study oversight

L.T. and D.M. performed the statistical analysis, I.M. and R.L.R. prepared the manuscript, and all authors reviewed and approved the final version of the manuscript. All authors vouch for the accuracy and completeness of the data and analysis.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are presented as means and standard deviation (SD) plus median and interquartile range (IQR). Differences in mortality related to clinical parameters and other factors were first analyzed using the Chi-Square test and *T*-test for categorical and continuous variables, respectively. Independent predictors of mortality within the first year after discharge were analyzed using multivariable logistic regression. The final multivariable model includes all the variables that remain statistically significant after adjusting for the remaining variables. This study reports the one-year follow-up outcomes for all patients. Statistical analysis was performed using SPSS for Windows, version 22.

Results

Patients and characteristics

A total of 429 patients were enrolled in this study, hospitalized for AHF, with an average stay of 11.7 days (median 10 days, range 1–117 days). The mean age was 79 years, and 62.5% were women. Ninety-six (22.4%) patients were functionally dependent for basic activities of daily living. Hypertension was the most prevalent comorbidity (86.7%), and 31.9% of all patients had more than three comorbidities.[8] Echocardiogram was available in 400 patients, and 70.5% of them had left ventricular ejection fraction (LVEF)>40%. In the 29 patients who did not have a detailed echocardiogram report, kidney disease did not seem to be responsible for the high values of NT-proBNP, as only four of these patients presented plasma creatinine levels >1.5 mg/dL. Ischemic etiology for HF was present in 34.6% of patients. Table 1 summarizes the baseline characteristics of the study cohort.

Mortality and re-hospitalization

The in-hospital and one-year all-cause mortality rates were 7.9% and 34.3%, respectively. One patient was lost to follow-up after discharge. Mortality data are summarized in Table 2. During the first year of follow-up after discharge, 33.2% of the 394 patients discharged alive and with follow-up data were re-hospitalized for HF.

Mortality predictors

Table 3 summarizes the univariable analysis. Factors significantly associated with higher one-year mortality risk were as follows: age ≥80 years, active cancer, dementia, functional dependency, and AF. Notably, a sleep disorder

Table 1 Baseline characteristics of the study cohort.

		n
Age (years), mean ± SD; median (IQR)	79±10; 81(11)	429
Females, %	62.5	429
Comorbidities		
Hypertension, %	86.7	429
Diabetes mellitus, %	47.8	429
Atrial fibrillation, %	51.7	429
Anemia, %	53.9	429
Cerebrovascular disease, %	19.1	429
Peripheral arterial disease, %	11.7	429
Pulmonary chronic disease, %	28	429
Active cancer, %	6.8	429
Sleep disorder/Hypoventilation syndrome, %	19.3	429
Dementia, %	24.7	429
Functional dependency, %	22.4	429
Admission SBP (mmHg), mean ± SD; median (IQR)	139.5±29.2; 136 (36)	420
Admission laboratory data		
Creatinine (mg/dL), mean ± SD; median (IQR)	1.3±0.6; 1.2 (0.78)	428
Urea (mg/dL), mean ± SD; median (IQR)	70.2±40.9; 59 (50)	427
Potassium (mmol/L), mean ± SD; median (IQR)	4.5±0.8; 4.4 (1)	424
Sodium (mmol/L), mean ± SD; median (IQR)	136.4±5.7; 137 (6)	428
Hemoglobin (g/dL), mean ± SD; median (IQR)	12±2.1; 12 (2.8)	429
Hematocrit (%), mean ± SD; median (IQR)	37.7±6.3; 38 (8.5)	429
Platelet count (×103/μL), mean ± SD; median (IQR)	225±97; 208 (92)	429
RDW (%), mean ± SD; median (IQR)	15.5±2.1; 15 (2.2)	428
PDW (%), mean ± SD; median (IQR)	13.7±2.6; 13.5 (3.1)	418
Ejection fraction>40%, %	70.5	400
First NT-proBNP (pg/mL), mean ± SD; median (IQR)	6698±10848; 2697 (6105)	366
Ischemic etiology, %	34.6	402

IQR: interquartile range; PDW: platelet distribution width; RDW: red cell distribution width; SBP: systolic blood pressure; SD: standard deviation.

Table 2 Mortality data.[a]

	n	%
Mortality		
In-hospital	34	7.9
On the first 30 days after discharge	15	3.5
One-year after discharge	147	34.3
Cause		
Cardiovascular	63	42.9
Other causes	73	49.7
Unknown	11	7.4

[a] Reports of 429 patients; one patient was lost to follow-up after discharge.

diagnosis and/or hypoventilation syndrome was associated with a lower one-year mortality risk.

The biochemical parameters associated with higher mortality risk were as follows: high levels of creatinine, high levels of urea, RDW in the fourth quartile (higher than 16.3%), low levels of hematocrit, and low levels of hemoglobin. High levels of PDW were associated with a lower one-year mortality risk.

Table 3 also summarizes the multivariable analysis. After adjusting the model for all clinically relevant characteristics (including age, sex, and ejection fraction), the independent predictors of higher one-year mortality risk were as follows: age ≥80 years, active cancer, dementia, high urea levels, RDW in the fourth quartile, and low PDW levels. These findings are also shown in the form of a graph in Figure 1.

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Table 3 One-year mortality predictors.

	Died[a]	Alive[a]	p	Univariable unadjusted OR (95% CI)	Multivariable adjusted OR (95% CI)	p
Age group						
<80 years	48 (25.5%)	140 (74.5%)	0.001	1	1	0.008
≥80 years	99 (41.3%)	141 (58.8%)		2.05 (1.35, 3.11)	2.05 (1.21, 3.48)	
Sex						
Female	90 (33.7%)	177 (66.3%)	0.800	1	1	0.159
Male	57 (35.4%)	104 (64.6%)		1.08 (0.72, 1.63)	1.47 (0.86, 2.49)	
Hypertension						
Yes	122 (32.8%)	250 (67.2%)	0.112	0.61 (0.34, 1.07)		
No	25 (44.6%)	31 (55.4%)		1		
Diabetes mellitus						
Yes	70 (34.1%)	135 (65.9%)	0.999	0.98 (0.66, 1.47)		
No	77 (34.5%)	146 (65.4%)		1		
Atrial fibrillation						
Yes	91 (41.0%)	131 (59.0%)	0.004	1.86 (1.24, 2.80)		
No	56 (27.2%)	150 (72.8%)		1		
Cerebrovascular disease						
Yes	31 (37.8%)	51 (62.2%)	0.546	1.21 (0.73, 1.99)		
No	116 (33.5%)	230 (66.5%)		1		
Peripheral arteriopathy						
Yes	17 (34.0%)	33 (66.0%)	0.999	0.98 (0.53, 1.83)		
No	130 (34.4%)	248 (65.6%)		1		
Chronic lung disease						
Yes	38 (31.7%)	82 (68.3%)	0.538	0.85 (0.66, 1.47)		
No	109 (35.4%)	199 (64.6%)		1		
Active cancer						
Yes	17 (58.6%)	12 (41.4%)	0.008	2.93 (1.36, 6.32)	2.70 (1.03, 7.01)	0.043
No	130 (32.6%)	269 (67.4%)		1	1	
Sleep disorder and/or hypoventilation syndrome						
Yes	18 (21.7%)	65 (78.3%)	0.010	0.46 (0.26, 0.82)		
No	129 (37.4%)	216 (62.6%)		1		
Dementia						
Yes	56 (52.8%)	50 (47.2%)	<0.001	2.84 (1.81, 4.47)	2.69 (1.53, 4.74)	0.001
No	91 (28.3%)	231 (71.7%)		1	1	
Functional dependency						
Yes	50 (52.1%)	46 (47.9%)	<0.001	2.63 (1.65, 4.19)		
No	97 (29.2%)	235 (70.8%)		1		
Systolic blood pressure	141.1/137.0	136.6/132	0.136	0.99 (0.98, 1.00)		
Creatinine[b]	1.26/1.12	1.45/1.31	0.002	2.03 (1.29, 3.21)		
Urea[b]	63/52	83/74	<0.001	2.92 (1.95, 4.36)	2.97 (1.84, 4.80)	<0.001
Potassium[b]	4.48/4.40	4.48/4.41	0.821	1.14 (0.36, 3.59)		
Sodium[b]	136.5/137.0	136.1/137.0	0.421	0.15 (0.002, 15.09)		
Hemoglobin	12.2/12.3	11.4/11.4	<0.001	0.83 (0.75, 0.92)		
Hematocrit	38.5/38.9	36.2/36.1	<0.001	0.94 (0.91, 0.97)		
Platelet count[b]	222.0/208.0	232.6/209.0	0.590	1.16 (0.68, 1.98)		
RDW						
Q1 (≤14.1)	21 (19.3%)	88 (80.7%)	0.001	1	1	<0.001
Q2 (>14.1–15.0)	30 (27.5%)	79 (72.5%)		1.59 (0.84, 3.00)	1.77 (0.84, 3.73)	
Q3 (>15.0–16.3)	36 (34.6%)	68 (65.4%)		2.22 (1.19, 4.14)	1.92 (0.91, 4.04)	
Q4 (>16.3)	60 (57.1%)	45 (42.9%)		5.59 (3.03, 10.32)	5.24 (2.55, 0.76)	
PDW	13.2/12.9	13.9/13.7	0.005	0.89 (0.82, 0.97)	0.88 (0.80, 0.97)	0.009

Table 3 (*Continued*)

	Died[a]	Alive[a]	p	Univariable unadjusted OR (95% CI)	Multivariable adjusted OR (95% CI)	p
Ejection fraction						
≤40%	44 (37.3%)	74 (62.7%)	0.266	1	1	0.246
>40%	87 (31.0%)	194 (69.0%)		0.75 (0.48, 1.18)	0.73 (0.43, 1.24)	
Re-hospitalization						
Yes	46 (35.1%)	85 (64.9%)	0.061	1		
No	67 (25.5%)	196 (74.5%)		1.58 (1.01, 2.49)		

CI: confidence interval; OR: odds ratio; PDW: platelet distribution width; Q: quartile; RDW: red cell distribution width.
[a] Categorical variables: absolute values (percentages); continuous variables: mean/median.
[b] Variable log transformed.

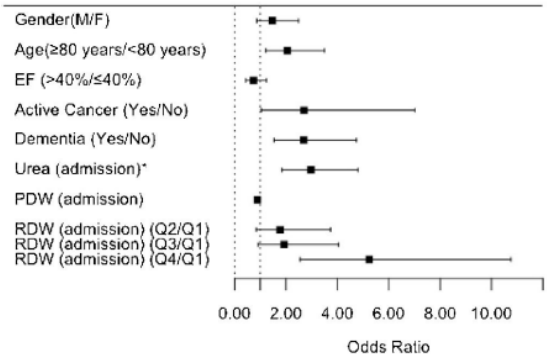


Figure 1 Multivariable analysis of predictors of one-year mortality: adjusted odds ratios. EF: ejection fraction; f: female; m: male; PDW: platelets distribution width; Q: quartile; RDW: red cell distribution width.

Discussion

This study reports the impact of multiple comorbidities and biochemical parameters on the one-year mortality rate in patients hospitalized for HF in an Internal Medicine Department. After adjusting the multivariable analysis model for all clinically relevant characteristics, the independent predictors of higher one-year mortality risk at admission were: age ≥80 years, active cancer, dementia, high urea levels, high RDW levels, and low PDW levels.

The characteristics of this study population were different from those of clinical studies addressing angiotensin-neprilysin inhibition in stabilized hospitalized patients with HF with reduced ejection fraction (HFrEF).[10,11] Our study population was older and predominantly female, with a higher prevalence of hypertension and a lower prevalence of ischemic etiology. This may be explained by the fact that our study included HF patients with and without reduced ejection fraction, which may preclude direct comparison with other studies. As previously discussed, the sex distribution of this study population reflects the fact that elderly patients hospitalized with HF are mainly women.[8]

The in-hospital and one-year all-cause mortality rates found in this study, 7.9% and 34.3%, respectively, are in accordance with those reported previously in the European database and registry studies,[4,5,12] as well as in a Portuguese study.[13] This observation confirms the general burden of HF, as expressed by the high one-year mortality rate, ruling out the hypothesis of poor clinical management of HF at local or national levels. Of note, we observed relatively low mortality in the first 30 days after discharge (3.5%). This may be due to the longer hospitalization stays for AHF patients (mean of 10 days in Europe *vs.* five days in USA), which gives the clinical teams more time to stabilize patients and thereby optimize the therapeutic strategy before hospital discharge.

These findings support the notion that there is still much room for improvement in the standard of care for AHF patients. The current international guidelines for the clinical management of HF need to be further implemented in order to promote better outcomes for HF patients. Under this rationale, risk stratification of HF patients using predictors of increased risk of mortality is a vital tool for ensuring that the most appropriate healthcare plan is implemented for each patient (*e.g.*, frequency of follow-up appointments, assignment to a telemonitoring program, among others).

Other studies have examined the contribution of multiple non-cardiac comorbidities to the mortality of patients with HF.[2,14–26] In a pioneer study conducted in 2014, van Dreusen et al. analyzed non-cardiac comorbidities of patients included in the observational Heart Failure Pilot Survey (ESC-HF Pilot) and found that diabetes, chronic kidney disease, and anemia were independent predictors of all-cause mortality risk in a multivariable analysis.[2] Since then, several reports, including sub-analyses from clinical studies, have confirmed this association, particularly for chronic kidney disease.[19–24] Other predictors for all-cause mortality were also found, such as chronic obstructive pulmonary disease (COPD) and peripheral artery disease.[25,26] We could not find any such association in our data, probably due to differences in the baseline characteristics of the population studied. In fact, compared to the pioneer study of Dreusen et al., our study population was older, with more females and fewer patients with HFrEF.[2,8]

In line with our findings, van Dreusen et al. did not identify sleep apnea as a predictor of mortality. However, in both studies, sleep apnea was not actively investigated; either it was mentioned on the clinical records or self-reported by patients. This may explain the contradiction with studies

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demonstrating that sleep apnea doubles the mortality risk of HF patients.[27] There has also been an increase in the number of studies advocating the importance of sleep-related disorders in patients with cardiovascular disease.[28,29] It is of note that van Dreusen et al. did not include dementia and cancer in their analysis.

In the ESC-HF Pilot study, the multivariable analysis found that predictors of one-year mortality in patients hospitalized for HF were: older age, high creatinine, low sodium, low systolic blood pressure, low EF, and other factors not included in our study.[4] An Italian observational study reported similar findings.[15] However, only older age had a similar result in our analysis. Likewise, we did not find a lower mortality risk in females or patients with higher LVEF, as reported elsewhere,[9] despite the higher use of beta-blockers and spironolactone in patients with lower LVEF.[8] These differences are probably due to the fact that our patients were all recruited after hospitalization for AHF, unlike those of the other studies, which were primarily outpatients from cardiology centers.

Emerging evidence suggests a relationship between cardiovascular disease and cancer.[30,31] HF and cancer are becoming increasingly more prevalent as the population ages, and both conditions are associated with significant mortality and morbidity. Accordingly, our findings that patients admitted for HF, those >80 years, and those with active cancer are more likely to die in the next year, were expected.

Cognitive impairment has a prevalence of 28–58% among HF patients, but little is known about mortality in patients with both diseases.[32] Braunstein et al. reported that Alzheimer's disease/dementia is associated with higher mortality risk.[14] These observations are in line with the findings of our study since, among the population studied, mortality risk increased with age, HF, and dementia. In fact, as demonstrated by the multivariable analysis, dementia is a robust independent predictor of mortality risk. This finding calls for a dramatic change in the clinical management of dementia patients.

Impairment in renal function is associated with significant morbidity and mortality in patients with chronic HF.[2,4,33] We found urea levels to be a strong predictor of one-year mortality. Indeed, blood urea nitrogen (BUN), another way of measuring urea, may increase independently of glomerular filtration rate (GFR) due to enhanced proximal and distal tubular reabsorption under HF neurohormonal activation.[33,34] This is especially important in patients with decompensated HF, in whom this mechanism plays a notable role in the clinical manifestations of the disease. Considering these mechanisms, BUN may be a better prognostic indicator than estimated GFR.[32] In fact, BUN has been established as a valid marker in HF mortality prediction risk models, both for in-hospital mortality and mortality during the first year after HF hospitalization.[35,36] Klein et al. also concluded that high BUN levels at admission are associated with poorer survival rates in HF patients.[33]

Red cell distribution width is a measure of the variability in the size of circulating erythrocytes and has been linked with a higher mortality risk in both HF patients and the general population.[37–39] Our results are consistent with those of previous reports, demonstrating a strong association between high levels of RDW and one-year mortality in patients with AHF, independently of other hematologic parameters, such as hemoglobin and hematocrit levels.[37] Remarkably, RDW in the fourth quartile (>16.3%) at admission was found to be a very strong predictor of one-year mortality. Since the evaluation of RDW levels consists of a simple, inexpensive, and widely available test, this finding may have substantial implications for the risk stratification and clinical management of patients with AHF.

Platelet distribution width levels are a widely available platelet activation marker. Very few studies have analyzed the possible effect of PDW on mortality risk in general or specifically in HF patients. The available data suggest that the risk increases with higher values of PDW.[40,41] However, we have found a contradictory result in this study, with lower PDW levels independently predicting higher one-year mortality. Thus, PDW may be an important prognostic marker in HF, but its role remains to be clarified in more extensive studies.

Our study has several limitations: (i) it is a retrospective study, (ii) it does not determine the presence and severity of chronic kidney disease, (iii) it does not determine the type, stage, or treatment for oncologic patients, and (iv) it does not examine the use of cardiac devices. Regarding this last point, it is important to stress that it was unlikely that a significant number of this study's patients had implanted such devices, considering their age and that only one-third of them had LVEF $\leq$40%. Moreover, it is possible that other factors with an impact on mortality have not been included in the analysis. Nevertheless, the findings of this study are sufficiently robust to prompt an improvement in the clinical management of HF patients and contribute to better health outcomes for this population.

Conclusions

The predictors of one-year mortality in a large cohort of patients hospitalized for HF in an Internal Medicine Department are: age $\geq$80 years, active cancer, dementia, high values of urea, and RDW at admission. The knowledge of such predictors allows clinicians to tailor both the treatment and follow-up of patients at higher risk of death. These data can be used to establish inexpensive and powerful lab results, such as RDW and urea, as predictors to choose not only the place where the treatment will be held (*e.g.*, cardiac and intensive care units) and the level of monitoring during hospitalization, but also to guide patients to specialized HF clinics and to an earlier post-discharge evaluation. Further studies are needed to corroborate our findings.

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Study oversight

L.T. and D.M. performed the statistical analysis, I.M. and R.L.R. prepared the manuscript, and all authors reviewed and approved the final version of the manuscript. All authors

vouch for the accuracy and completeness of the data and analysis.

Conflicts of interest

The authors have no conflicts of interest to declare.

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"O Melhor da RPC em 2023"

Artigo Vencedor

One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis)

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5.4. One-year rehospitalization and mortality after acute heart failure hospitalization: a competing risk analysis

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My contributions to this work were as follows: I designed the study, collected data, edited and revised the manuscript, and served as the corresponding author. To the best of my knowledge this article has not been included in any other thesis. This is an open access publication, with no financial, legal or technical barriers to accessing it.

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One-year rehospitalisation and mortality after acute heart failure hospitalisation: a competing risk analysis

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ABSTRACT

Objective To identify factors that independently predict the risk of rehospitalisation and death after acute heart failure (AHF) hospital discharge in a real-world setting, considering death without rehospitalisation as a competing event.

Methods Single-centre, retrospective, observational study enrolling 394 patients discharged from an index AHF hospitalisation. Overall survival was evaluated using Kaplan-Meier and Cox regression models. For the risk of rehospitalisation, survival analysis considering competing risks was performed: rehospitalisation was the event of interest, and death without rehospitalisation was the competing event.

Results During the first year after discharge, 131 (33.3%) patients were rehospitalised for AHF and 67 (17.0%) died without being readmitted; the remaining 196 patients (49.7%) lived without further hospitalisations. The 1-year overall survival estimate was 0.71 (SE=0.02). After adjusting for gender, age and left ventricle ejection fraction, the results showed that the risk of death was higher in patients with dementia, higher levels of plasma creatinine (PCr), lower levels of platelet distribution width (PDW) and at Q4 of red cell distribution width (RDW). Multivariable models showed that the risk of rehospitalisation was increased in patients with atrial fibrillation, higher PCr or taking beta-blockers at discharge. Furthermore, the risk of death without AHF rehospitalisation was higher in males, those aged ≥80 years, patients with dementia or RDW at Q4 on admission (compared with Q1). Taking beta-blockers at discharge and having a higher PDW on admission reduced the risk of death without rehospitalisation.

Conclusion When assessing rehospitalisation as a study endpoint, death without rehospitalisation should be considered a competing event in the analyses. Data from this study reveal that patients with atrial fibrillation, renal dysfunction or taking beta-blockers are more likely to be rehospitalised for AHF, while older men with dementia or high RDW are more prone to die without hospital readmission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hospitalisation due to acute heart failure (AHF) is the most common reason for hospitalisation in people older than 65 years, with 1-year rehospitalisation occurring in almost half of those patients.

⇒ Several risk factors for HF readmissions have been identified, namely being an older patient, having lower systolic blood pressure and estimated glomerular filtration rate, increased heart rate, sedentary lifestyle, depressive symptoms, high number of comorbidities, among others.

WHAT THIS STUDY ADDS

⇒ Atrial fibrillation, renal dysfunction and beta-blocker prescription at discharge were identified to be independent risk factors for 1-year rehospitalisation due to AHF.

⇒ After an index AHF hospital discharge, the risk of death without rehospitalisation was higher in men, patients ≥80 years of age, with dementia, or with red cell distribution width at Q4 on admission.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The analysis performed in this study allows for the stratification of patients by the identified risk factors for each event separately, granting us the possibility to personalise interventions and make clinical decisions effectively. This knowledge can guide clinicians in establishing the short- and medium-term prognosis of AHF patients discharged from the hospital.

INTRODUCTION

Hospitalisation due to acute heart failure (AHF) is a global public health problem of pandemic proportions,[1] representing the most common reason for hospitalisation in people older than 65 years in economically developed countries.[2] The first year after hospital discharge is a golden period of adverse events, with unacceptably high post-discharge readmission and mortality rates.[3] According to the European Society of Cardiology, the 1-year all-cause mortality among AHF patients is 23.6%, while the incidence of the combined outcome of death or HF hospitalisation within 1 year of discharge is 40.1%.[4]

Several studies have reported that the risk of being readmitted due to HF is higher in older patients, those who fail to comply with treatment, with longer index hospital stay (>7 days), lower systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR), heart rate over 70 bpm, high presence of comorbidities (such as renal or pulmonary dysfunctions), sedentary lifestyle, depressive symptoms, among others.[5–10] Older age, higher levels of blood urea nitrogen and N-terminal pro-B-type natriuretic peptide (NT-proBNP), lower haemoglobin (Hgb) values and not taking a beta-blocker were among the described risk factors for mortality.[7 11] However, most of these reports fail to consider competing risks in the data analysis, which may lead to an overestimation of the cumulative incidence and an inaccurate interpretation of data.[12]

Despite being independent, death and hospitalisation are closely related: death leads to the loss of sicker individuals, those more likely to be hospitalised and hospitalisation is associated with a higher risk of death.[13 14] Moreover, after an AHF index hospitalisation, rehospitalisation may be impossible to observe due to a previous occurrence of death, which defines rehospitalisation and death as competing risks, that is, when a certain event prevents the event of interest from happening.[12]

The use of more specific techniques, such as cumulative incident function or subdistribution function to estimate the probability of each event, and the model introduced by Fine and Gray to test covariates when competing risks are present, ensures that the results can be correctly interpreted. As a result, competing risk analysis has received increasing attention and is becoming more frequently used in clinical studies. This strategy allows to split of the contribution of a covariate from each event type separately and, hence, to gain a better understanding of the disease.[15]

Using competing risk analyses, this study aimed to identify independent predictive factors for rehospitalisation and death without rehospitalisation among patients with an index admission for AHF, considering rehospitalisation as the event of interest and death without rehospitalisation as the competing event. Additionally, we sought to determine the 1-year overall mortality risk, after an AHF hospitalisation.

METHODS

Study sample and clinical setting

This is a retrospective, single-centre and observational study conducted in the Internal Medicine Department of a tertiary university hospital in Portugal. The study design and detailed characterisation of the study population have been described elsewhere.[16] Briefly, all patients hospitalised for AHF and discharged between January and December 2012 were considered for enrolment and were followed for up to 1 year after discharge. For the purposes of this study, the first hospitalisation for AHF during the study period was considered the index hospitalisation. Of note, only rehospitalisations due to AHF at the study centre were considered.

Data collection and study outcomes

Hospital discharge summaries, clinical records and telephone interviews were used for data collection, as previously described.[16] The main outcomes of this subanalysis were the identification of risk factors for AHF rehospitalisation and death without rehospitalisation in the year following discharge from the index hospitalisation, considering death without rehospitalisation as a competing event.

Statistical methods

Categorical variables are described as absolute frequencies and percentages. Continuous variables are described in terms of mean, standard deviation (SD), median and interquartile range (IQR).

To analyse the overall mortality after discharge from AHF index hospitalisation, standard survival analysis methods were applied, considering death as the event of interest and the time between discharge and death as the follow-up time. Patients alive 1 year after discharge were censored, with a follow-up period of 365 days. Kaplan-Meier curves were obtained for the total sample and according to age groups (<80 years vs ≥80 years). Cox proportional hazards regression models were used to analyse the effect of covariates on the overall mortality after discharge.

To analyse the risk factors for rehospitalisation without bias, survival analysis methods taking competing risks into account were needed, considering rehospitalisation as the event of interest and death without rehospitalisation as the competing event. The follow-up period was considered the time between discharge and the occurrence of the first event (rehospitalisation or death without rehospitalisation). As previously, live patients were censored 1 year after discharge and after a follow-up period of 365 days. The cumulative incidence function (CIF) was estimated as the probability of failing from a given cause in the presence of competing events, given that a subject has survived or has already failed from different causes. Finally, the Fine and Gray model based on the subdistribution hazard function was used to analyse the effect of covariates in the rehospitalisation risk.

In both analyses, an exploratory evaluation was performed to decide which variables should be included in the multivariable models by fitting univariable models and considering all variables significant at the 0.05 significance level as candidates for the multivariable model. The final multivariable models were built, including all variables with p values lower than 0.05, after adjusting for age, gender, left ventricular ejection fraction (LVEF) and the remaining significant variables.

Statistical analysis was performed using SPSS V.26 and R softwares.

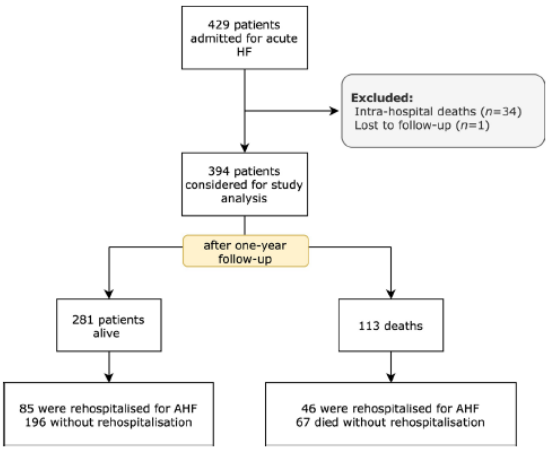


Figure 1 Flow chart of the study population. AHF, acute heart failure; HF, heart failure.

RESULTS

Patients' characteristics

This is a subanalysis of the previously reported population sample from the PRECIC study[16], which enrolled 429 patients discharged during the year of 2012 after hospitalisation for AHF. A total of 394 patients were alive at discharge (34 patients suffered intrahospital deaths and one was lost to follow-up) and were considered for this subanalysis (figure 1). Table 1 summarises the baseline characteristics of this study cohort. Briefly, patients' mean age was 79 years, and most of them were female (61.9%). Importantly, the majority of patients (70.5%) presented an LVEF >40%. At discharge, around half of the patients were prescribed a beta-blocker (52.9%) and an ACE inhibitor (ACEi) or an angiotensin receptor blocker (52.2%).

Table 1 Baseline characteristics of the study cohort

		n
Age (years), mean (SD); median (IQR)	79.1 (9.4); 80.5 (10)	394
Females, %	61.9	394
Ischaemic aetiology, %	35.5	372
LVEF >40%, %	70.5	370
Comorbidities		
Hypertension, %	87.8	394
AF, %	51.3	394
Diabetes mellitus, %	48.7	394
Chronic pulmonary disease, %	28.7	394
Dementia, %	22.6	394
Sleep disorder/hypoventilation syndrome, %	20.6	394
Need for caregiving, %	20.3	394
Stroke, %	18.5	394
Peripheral arterial disease, %	11.9	394
Active cancer, %	6.6	394
Admission		
SBP (mm Hg), mean (SD); median (IQR)	140.5 (29.0); 137.0 (38)	385
First NT-proBNP (pg/mL), mean (SD); median (IQR)	5931.3 (10062.8); 2485.5 (5279.8)	336
RDW (%), mean (SD); median (IQR)	15.4 (2.0); 14.9 (2.2)	393
Htc (%), mean (SD); median (IQR)	37.9 (3.6); 38.1 (8.4)	394
Hgb (g/dL), mean (SD); median (IQR)	12.0 (2.1); 12.1 (2.8)	394
Platelet count (x10^3/µL), mean (SD); median (IQR)	223.4 (88.2); 208.0 (93)	394
PDW (%), mean (SD); median (IQR)	13.7 (2.6); 13.5 (3.0)	385
Discharge		
ACEi/ARB, %	52.2	393
Beta-blocker, %	52.9	393
MRA, %	17.3	393
Oral anticoagulant, %	30.0	393
PCr, mean (SD); median (IQR)	1.3 (0.6); 1.1 (0.6)	388
PUr, mean (SD); median (IQR)	67.5 (34.8); 59.0 (41.5)	389
PK^+, mean (SD); median (IQR)	4.3 (0.5); 4.3 (0.7)	390
PNa^+, mean (SD); median (IQR)	139.2 (5.3); 140.0 (5)	389

ACEi, ACE inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; Hgb, haemoglobin; Htc, haematocrit; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-B type natriuretic peptide; PCr, plasma creatinine; PDW, platelet distribution width; PK^+, plasma potassium; PNa^+, plasma sodium; PUr, plasma urea; RDW, red cell distribution width; SBP, systolic blood pressure.

Overall mortality after discharge

One year after discharge, a total of 113 patients (28.7%) were dead, and 281 (71.3%) patients remained alive (figure 1). Figure 2A presents the Kaplan-Meier curve for overall mortality after discharge, for the total sample. Considering that in a previous report, we found that being ≥80 years was a significant predictor for a higher all-cause 1-year mortality risk,[17] Kaplan-Meier curves for overall mortality according to different age groups (<80 years vs ≥80 years) are also presented, independently of the occurrence of a rehospitalisation before death (figure 2B). The overall 1-year survival estimate was 0.71 (SE=0.02), being significantly lower (p=0.015, table 2) for patients aged ≥80 years [0.66 (SE=0.03) vs 0.77 (SE=0.03) if <80 years].

Table 2 includes information about the unadjusted and adjusted hazard ratio (HR) and 95% CI for overall mortality after discharge. The factors age, active cancer, dementia, need for caregiving, atrial fibrillation (AF), ACEi, plasma creatinine (PCr), plasma urea (PUr), platelet distribution width (PDW), red cell distribution width (RDW), haematocrit (Htc) and Hgb were identified as potential predictive factors of overall mortality after discharge. After adjusting for gender, age and LVEF, only dementia, PCr, PDW and RDW remained statistically significant. The risk of death was increased in patients with dementia (HR 2.43, 95% CI 1.56 to 3.79), with

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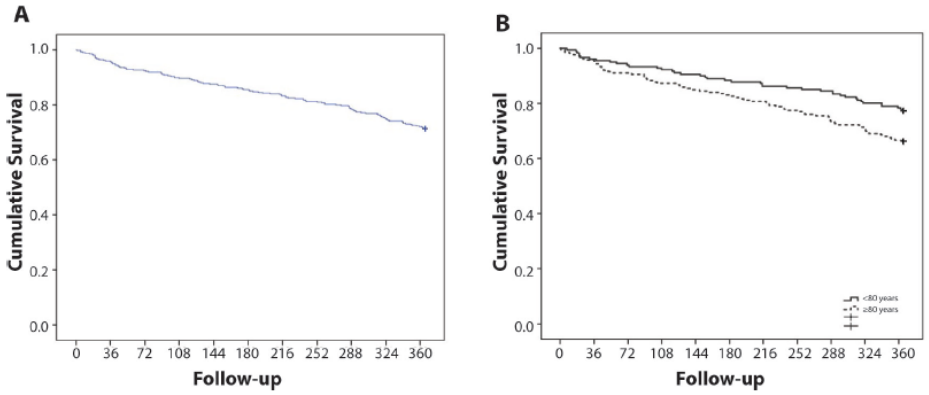


Figure 2 Kaplan-Meier curves for overall mortality after discharge (A) and overall mortality after discharge by age group (B).

higher levels of PCr (HR 3.28, 95% CI 2.05 to 5.25), with lower levels of PDW (HR 0.90, 95% CI 0.83 to 0.97), and at the Q4 of the RDW (HR 3.90, 95% CI 2.13 to 7.12).

AHF rehospitalisation after discharge

A total of 131 patients (33.3%) experienced rehospitalisation after discharge, and 67 (17.0%) died without being rehospitalised (figure 1). The remaining patients (n=196, 49.7%) were alive 1 year after discharge without any hospital readmission. Figure 3 presents the CIF for all possible events. The probability of rehospitalisation and death without rehospitalisation 1 year after discharge were 0.33 and 0.17, respectively.

Table 3 includes information about the unadjusted subdistribution HR (SHR) and 95% CI for all possible events. Hypertension, diabetes, AF, beta-blocker, PCr, PUr, PK^{+}, RDW and Hgb were identified as potential predictive factors of AHF rehospitalisation. Age, LVEF, active cancer, dementia, need for caregiving, ACEi, beta-blocker, PDW, RDW, Htc and Hgb were identified as potential predictive factors of death without rehospitalisation.

Table 4 displays the adjusted SHR and 95% CI for all possible events after AHF hospital discharge. Multivariable models, adjusting for age, gender and LVEF, showed that risk of rehospitalisation was increased in patients with AF (SHR=1.58, p=0.020), higher creatinine levels (SHR=2.00, p<0.001) or taking a beta-blocker at discharge (SHR=1.61, p=0.010). The risk of death without rehospitalisation was increased in males (SHR=1.72, p=0.040), those ≥80 years (SHR=1.87, p=0.030), patients with dementia (SHR=2.68, p<0.001) or RDW at Q4 on index admission (compared with the first, SHR=2.54, p=0.030). Taking a beta-blocker at discharge and high PDW levels at admission reduced the risk of death without rehospitalisation due to AHF (SHR=0.55, p=0.040 and SHR=0.89, p=0.009, respectively).

DISCUSSION

This is a 1-year follow-up study of a cohort of real-world AHF patients who were discharged after an index hospitalisation from an internal medicine department of a tertiary care hospital, in Portugal. Considering that there may be different risk factors for death and rehospitalisation in AHF patients after hospital discharge, the main goal of this study was to identify the independent predictors of rehospitalisation for AHF, considering death as a competing event. In addition, it was sought to determine the risk factors for 1-year overall mortality, independently of the occurrence of a rehospitalisation before death. Of note, our study reports data from a real-world geriatric HF population, predominantly having a LVEF >40%, which is largely underrepresented in clinical trials and cardiology-based registries.

After performing the competing risks analyses, we were able to identify which factors independently contribute to the risk of rehospitalisation 1 year after hospital discharge from AHF in our study population: AF, renal dysfunction or beta-blocker prescription at discharge. In addition, we have identified predictors of death without rehospitalisation: being a male patient, aged ≥80 years, with dementia, and RDW at Q4 on index admission were considered as high-risk factors, while taking beta-blockers at discharge and having higher PDW levels on the index admission were found to be low-risk factors. Interestingly, we have previously reported the predictors of 1-year overall mortality after AHF hospitalisation,[17] and identified those having ≥80 years of age, with active cancer, dementia, higher urea, RDW at Q4 and lower PDW levels as being at higher risk of mortality. Consistent with this, we are now reporting that, after adjusting for gender, age and LVEF values, having dementia, RDW at Q4 and lower PDW levels remain as independent risk factors for overall mortality after hospital discharge. Altogether, this knowledge will allow us to stratify patients by risk factors for each event (rehospitalisation or death) separately, at discharge of the index hospitalisation.

Hospital readmission is a key marker of healthcare quality, particularly when assessing AHF patient outcomes. However, despite its widespread use, there is some controversy regarding the statistical methods

Table 2 Univariable and multivariable Cox model for overall mortality after discharge

	Unadjusted			Adjusted		
	HR	95% CI	P value	HR	95% CI	P value
Gender			0.630			0.823
Male	1	-		1	-	
Female	1.1	0.75 to 1.60		1.05	0.69 to 1.60	
Age group			0.015			0.121
≤79 years	1	-		1	-	
≥80 years	1.61	1.10 to 2.36		1.39	0.92 to 2.11	
LVEF			0.209			0.470
≤40%	1	-		1	-	
>40%	0.77	0.51 to 1.16		0.86	0.56 to 1.31	
Hypertension			0.185			
No	1	-				
Yes	0.71	0.42 to 1.18				
Diabetes			0.749			
No	1	-				
Yes	1.06	0.73 to 1.54				
Active cancer			0.003			
No	1	-				
Yes	2.36	1.35 to 4.14				
Chronic pulmonary disease			0.600			
No	1	-				
Yes	0.9	0.59 to 1.35				
Stroke			0.801			
No	1	-				
Yes	1.06	0.67 to 1.69				
PAD			0.884			
No	1	-				
Yes	1.04	0.60 to 1.82				
Dementia			<0.001			<0.001
No	1	-		1	-	
Yes	2.08	1.41 to 3.07		2.43	1.56 to 3.79	
Need for caregiving			0.002			
No	1	-				
Yes	1.89	1.26 to 2.83				
AF			0.006			
No	1	-				
Yes	1.71	1.17 to 2.51				
Sleep apnoea/hypoventilation syndrome			0.064			
No	1	-				
Yes	0.61	0.36 to 1.03				
ACEi			0.004			
No	1	-				
Yes	0.58	0.40 to 0.84				

Continued

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Table 2 Continued

	Unadjusted			Adjusted		
	HR	95% CI	P value	HR	95% CI	P value
Beta-blocker			0.479			
No	1	-				
Yes	0.88	0.60 to 1.27				
MRA			0.475			
No	1	-				
Yes	1.19	0.74 to 1.89				
Oral anticoagulant			0.763			
No	1	-				
Yes	0.94	0.63 to 1.41				
PCr (discharge)*	2.55	1.68 to 3.89	<0.001	3.28	2.05 to 5.25	<0.001
PUr (discharge)*	2.13	1.45 to 3.12	<0.001			
PK^+ (discharge)	1	0.69 to 1.40	0.900			
PNa^+ (discharge)*	0.03	0.00 to 1.05	0.054			
SBP (admission)	1	0.99 to 1.00	0.463			
PDW (admission)	0.89	0.83 to 0.96	0.001	0.9	0.83 to 0.97	0.007
RDW (admission)*						
Q1	1	-	<0.001	1	-	<0.001
Q2	1.4	0.78 to 2.54	0.261	1.73	0.89 to 3.36	0.106
Q3	1.53	0.84 to 2.78	0.161	1.55	0.79 to 3.03	0.207
Q4	3.21	1.87 to 5.51	<0.001	3.9	2.13 to 7.12	<0.001
Platelet (admission)*	1.09	0.64 to 1.84	0.752			
Htc (admission)	0.96	0.93 to 0.98	0.002			
Hgb (admission)	0.87	0.80 to 0.95	0.001			

*Logarithm transformation.
ACEi, ACE inhibitor; AF, atrial fibrillation; Hgb, haemoglobin; HR, hazard ratio; Htc, haematocrit; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; PAD, peripheral arterial disease; PCr, plasma creatinine; PDW, platelet distribution width; PK^+, plasma potassium; PNa^+, plasma sodium; PUr, plasma urea; Q, quartile; RDW, red cell distribution width; SBP, systolic blood pressure.

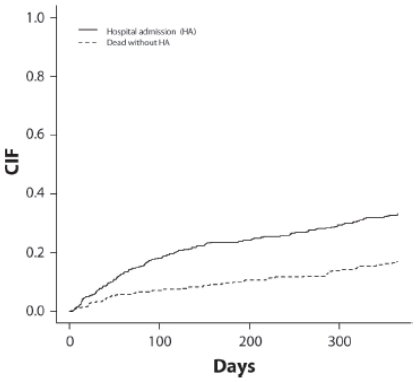


Figure 3 Cumulative incident function (CIF) for possible events: rehospitalisation and death without rehospitalisation due to AHF. AHF, acute heart failure.

employed to analyse the risk of rehospitalisation, as these analyses mostly do not consider patients who die before experiencing a readmission event within the period of interest.[18] Significantly, it has been estimated that 46% of studies in high-impact medical journals are susceptible to competing for risk bias,[19] highlighting the importance of considering death and rehospitalisation separately in the risk analysis of HF patients.

Many pivotal clinical trials included in the pharmaceutical and device development programmes for HF management have tested the benefit of the intervention on the composite primary endpoint of cardiovascular death and HF hospitalisation. However, several researchers have noted that the emphasis on the reduction of 30-day hospitalisation rates may have adverse consequences, such as an increased risk in the 30-day mortality,[20] and that risk-adjustment models do not account for the competing risk of mortality.[21] In fact, there is one report of increased

Table 3 Univariable Fine and Gray model for rehospitalisation (event of interest) and death without rehospitalisation (competing event) due to AHF

	Rehospitalisation			Death without rehospitalisation		
	SHR	95% CI	P value	SHR	95% CI	P value
Gender			0.360			0.170
Male	1	-		1	-	
Female	1.18	0.83 to 1.69		0.72	0.44 to 1.15	
Age group			0.410			0.004
≤79 years	1	-		1	-	
≥80 years	0.87	0.62 to 1.22		2.16	1.28 to 3.62	
LVEF			0.610			0.030
≤40%	1	-		1	-	
>40%	1.1	0.76 to 1.59		0.6	0.37 to 0.96	
Hypertension			0.020			0.200
No	1	-		1	-	
Yes	2.37	1.15 to 4.89		0.65	0.33 to 1.26	
Diabetes			0.040			0.280
No	1	-		1	-	
Yes	1.43	1.02 to 2.02		0.77	0.48 to 1.24	
Active cancer			0.800			0.010
No	1	-		1	-	
Yes	1.1	0.55 to 2.21		2.33	1.19 to 4.55	
Chronic pulmonary disease			0.650			0.880
No	1	-		1	-	
Yes	1.09	0.76 to 1.57		0.96	0.57 to 1.62	
Stroke			0.270			0.410
No	1	-		1	-	
Yes	0.76	0.47 to 1.23		1.27	0.72 to 2.23	
PAD			0.130			0.410
No	1	-		1	-	
Yes	1.55	0.87 to 2.74		1.33	0.68 to 2.59	
Dementia			0.220			<0.001
No	1	-		1	-	
Yes	0.76	0.49 to 1.17		2.58	1.59 to 4.20	
Need for caregiving			0.400			0.030
No	1	-		1	-	
Yes	1.19	0.79 to 1.77		1.78	1.06 to 3.00	
AF			0.002			0.350
No	1	-		1	-	
Yes	1.72	1.21 to 2.44		1.26	0.78 to 2.04	
Sleep apnoea/hypoventilation syndrome			0.400			0.150
No	1	-		1	-	
Yes	1.19	0.79 to 1.79		0.59	0.29 to 1.20	
ACEi			0.600			0.020
No	1	-		1	-	
Yes	1.1	0.78 to 1.55		0.55	0.34 to 0.89	

Continued

Table 3 Continued

	Rehospitalisation			Death without rehospitalisation		
	SHR	95% CI	P value	SHR	95% CI	P value
Beta-blocker			0.030			0.030
No	1	-		1	-	
Yes	1.49	1.05 to 2.10		0.59	0.37 to 0.96	
MRA			0.160			0.870
No	1	-		1	-	
Yes	1.36	0.89 to 2.10		1.05	0.56 to 1.96	
Oral anticoagulant			0.660			0.660
No	1	-		1	-	
Yes	0.917	0.63 to 1.34		0.89	0.53 to 1.50	
PCr (discharge)*	1.98	1.37 to 2.85	<0.001	1.6	0.86 to 2.97	0.140
PUr (discharge)*	1.81	1.27 to 2.57	0.001	1.23	0.73 to 2.05	0.440
PK^+ (discharge)	1.44	1.04 to 2.00	0.030	0.69	0.43 to 1.11	0.130
PNa^+ (discharge)*	0.09	0.00 to 4.78	0.240	0.35	0.01 to 25.5	0.630
SBP (admission)	1	1.00 to 1.01	0.370	1	0.99 to 1.00	0.300
PDW (admission)	1.01	0.94 to 1.09	0.770	0.88	0.80 to 0.96	0.004
RDW (admission)*						
Q1	1	-		1	-	
Q2	0.94	0.57 to 1.55	0.820	1.2	0.55 to 2.60	0.650
Q3	0.88	0.52 to 1.49	0.640	1.55	0.73 to 3.29	0.250
Q4	1.78	1.14 to 2.77	0.010	2.75	1.38 to 5.52	0.004
Platelet (admission)*	0.98	0.62 to 1.57	0.950	1.17	0.57 to 2.39	0.670
Htc (admission)	0.98	0.95 to 1.00	0.070	0.94	0.91 to 0.98	<0.001
Hgb (admission)	0.92	0.85 to 0.99	0.020	0.85	0.77 to 0.94	0.002

*Logarithm transformation.
ACEi, ACE inhibitor; AF, atrial fibrillation; AHF, acute heart failure; Hgb, haemoglobin; Htc, haematocrit; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; PAD, peripheral arterial disease; PCr, plasma creatinine; PDW, platelet distribution width; PK^+, plasma potassium; PNa^+, plasma sodium; PUr, plasma urea; Q, quartile; RDW, red cell distribution width; SBP, systolic blood pressure; SHR, subdistribution HR.

30-day and 1-year mortality after the successful implementation of a Hospital Readmissions Reduction Programme when competing risks analyses were used.[22]

These findings are particularly important considering the characteristics of our study population, a real-world cohort of geriatric patients with multiple comorbidities (having an average of three comorbidities per patient) and with the majority of patients having LVEF >40%.[16] We should not neglect that HF is regarded as the cardiovascular syndrome of ageing, resulting from the combination of cardiovascular conditions of older adults with age-related changes in cardiovascular structure and function[23], and that the mortality, hospitalisation and rehospitalisation rates are still high in this population.[2 24] Therefore, it is of utmost importance to find risk factors for these events in such patients.

AF has been associated with a worse prognosis for patients with chronic HF and is a classical trigger for HF decompensation. Herein, the more advanced age and HF severity of this group of patients justify the finding that AF is associated with a higher risk of rehospitalisation, in line with previous reports.[25] In the ESC-HF-LT Registry, the proportion of patients with AF varied widely among clinical profiles, with the highest prevalence of AF (34.7%) documented in patients with right HF. Curiously, this was also the group with the highest 1-year rehospitalisation rate (31.2%),[26] in accordance with what was observed in this study.

Other authors have also reported that risk predictors for rehospitalisation are different from those for mortality. For instance, SBP <120 mm Hg at the index hospitalisation predicts mortality, whereas an increase in body weight predicts rehospitalisation.[21] Although we included SBP in our risk analysis, it was not identified as an independent predictor of rehospitalisation or death without rehospitalisation.

Table 4 Multivariable Fine and Gray model for the two events: rehospitalisation (event of interest) and death without rehospitalisation (competing event) due to AHF

	Rehospitalisation			Death without rehospitalisation		
	SHR	95% CI	P value	SHR	95% CI	P value
Gender			0.370			**0.040**
Male	1	–		1	–	
Female	1.20	0.81 to 1.76		0.58	0.35 to 0.97	
Age group			0.720			**0.030**
≤79 years	1	–		1	–	
≥80 years	0.93	0.64 to 1.36		1.87	1.05 to 3.33	
LVEF			0.400			0.060
≤40%	1	–		1	–	
>40%	1.18	0.80 to 1.72		0.58	0.33 to 1.02	
Dementia			0.290			**<0.001**
No	1	–		1	–	
Yes	0.79	0.50 to 1.23		2.68	1.57 to 4.59	
AF			**0.020**			0.600
No	1	–		1	–	
Yes	1.58	1.09 to 2.31		1.17	0.65 to 2.12	
Beta-blocker			**0.010**			**0.040**
No	1	–		1	–	
Yes	1.61	1.12 to 2.32		0.55	0.32 to 0.96	
PCr (discharge)*	2.00	1.33 to 2.99	**<0.001**	1.65	0.88 to 3.09	0.120
PDW (admission)	1.02	0.95 to 1.10	0.580	0.89	0.81 to 0.97	**0.009**
RDW (admission)*						
Q1	1	–		1	–	
Q2	0.99	0.59 to 1.65	0.950	1.22	0.53 to 2.80	0.640
Q3	0.72	0.41 to 1.27	0.250	1.62	0.69 to 3.79	0.270
Q4	1.60	0.99 to 2.59	0.060	2.54	1.10 to 5.85	**0.030**

p-values with statistical significance are shown in bold.
*Logarithm transformation.
AF, atrial fibrillation; AHF, acute heart failure; LVEF, left ventricle ejection fraction; PCr, plasma creatinine; PDW, platelet distribution width; Q, quartile; RDW, red cell distribution width; SHR, subdistribution HR.

Renal dysfunction has been recognised as a risk factor for HF rehospitalisation and mortality,[25] and our data support this notion. Indeed, a previous report by Álvarez-García *et al* performed a competing risk analysis for risk prediction in hospitalised HF patients. They used competing risks analysis to develop the Redin-SCORE to predict the 1-month and 1-year risk of rehospitalisation due to HF acute episodes among ambulatory patients.[6] Similar to our findings, they found that renal dysfunction, defined as an eGFR below 60 mL/min/1.73m^2, among other clinical and laboratory parameters, were predictors of 1-year rehospitalisation.[6]

Interestingly, we found that higher levels of PCr at the index HF admission are: (1) a risk factor for overall mortality after discharge in the multivariable Cox model and (2) a risk factor for rehospitalisation, but not for death without rehospitalisation, in the competing risk analysis. Of note, this last finding does not weaken the impact of renal dysfunction on mortality, since patients are known to die during and after AHF rehospitalisations, and rehospitalisation for HF is a known risk factor for death.[27] In a systematic review of models for predicting mortality and/or hospitalisation in patients with HF, Ouwerkerk *et al* found that the strongest predictors were blood urea nitrogen and sodium levels.[28] Perkins *et al* have developed a prediction model for rehospitalisation derived from a cohort of 607 chronic kidney disease patients hospitalised for HF; 19.1% were rehospitalised within 30 days.[29]

In our study, 52.8% of patients had a prescription for a beta-blocker at hospital discharge,[16] and this was associated with a higher risk of rehospitalisation and a lower risk of death without rehospitalisation. These are in line with recent evidence from multiple studies reporting that the

uptitration of beta-blockers is associated with more HF hospitalisations in patients with a preserved ejection fraction.[30 31] Nevertheless, these results need to be addressed, given that the known mortality benefit of this class of drugs in HF patients seems limited to those with LVEF <40% and in sinus rhythm,[25 30] whereas our patients had mostly LVEF >40% (70.5%) and AF (51.7%).[16] Notably, 75.2% of patients with LVEF <40% were discharged with a beta-blocker,[16] following the guidelines in place at the time the study was conducted, and we adjusted the analysis for LVEF. Therefore, we can presume that the higher risk of rehospitalisation is related to the frequent side effects of beta-blockers—negative inotropism, bradycardia and hypotension—and the contribution of these factors to the decompensation of HF patients.[25] Recently, Stolfo *et al* performed a propensity score-matched analysis from the Swedish HF registry focusing on older patients (>80 years) with LVEF <40%, typically underrepresented in randomised control trials.[32] The authors concluded that the use of beta-blockers was high for those patients and was strongly associated with improved all-cause and cardiovascular survival.

HF is not only associated with an increased risk of all-cause dementia, as it may represent a risk factor itself for dementia. In a meta-analysis by Cannon *et al*, the prevalence of cognitive impairment among HF patients was estimated as 43%.[33] Adelborg *et al* reported in a large, nationwide cohort study in Denmark that HF was associated with an approximately 20% risk increase of all-cause dementia among patients surviving at least 1 year after HF diagnosis.[34] The possible mechanisms underlying this risk association are chronic cerebral hypoxia secondary to hypoperfusion or cerebral inflammation, and microvascular dysfunction due to neurohormonal HF activation mechanisms.[34] Our findings add new information to this interplay between HF and dementia, showing that dementia is: (1) a risk factor for overall mortality after discharge and (2) a risk factor for death without rehospitalisation, but not for rehospitalisation. These findings reinforce the relationship between dementia and death after AHF hospitalisation and prompt further investigation into the death causes of these patients.

The higher RDW level (at Q4; ie, higher than 16.3%) has been previously reported by us in the PRECIC study as an independent predictor of higher 1-year overall mortality risk in HF patients.[28] Here, a higher RDW level is again associated with a higher mortality risk, yet in patients discharged from an index hospitalisation. In addition, this association is reinforced by the finding that patients with higher RDW had an increased risk of death without rehospitalisation. Recently, Melchio *et al* reported that HF patients discharged for AHF with higher RDW (>14.8%) had more comorbidities and were at higher risk of death (HR for death from any cause=1.73).[35] The authors have also demonstrated that RDW adds prognostic information beyond that provided by well-established risk factors or biomarkers (eg, age, renal function, NT-proBNP levels, therapy) and is a powerful marker of worse long-term outcomes in AHF patients. Thus, there is a growing body of evidence that RDW can alert clinicians to the risk of death for individual patients in the first few hours of an AHF hospitalisation.

On the opposite, the prognostic impact of PDW, a specific marker of platelet activation, is still not yet well known. In a prospective observational study, which aimed to evaluate the prognostic impact of PDW among AHF hospitalised patients, Sato *et al* found an association between PDW levels and the prognosis of HF patients[36]: patients with higher PDW (>16.9) were at higher risk of all-cause death, cardiac death and a cardiac event (HR 1.72, 1.92 and 1.40, respectively).[36] In contrast, our results show that patients with lower PDW levels were at higher risk of overall mortality after discharge and death without rehospitalisation, and had no influence on the rehospitalisation incidence levels.

Study limitations

This study has a few limitations that might introduce bias in our conclusions: (1) the rehospitalisation episodes analysed were only those occurring at the study centre, given the difficulty in accessing patient health data in other public or private health organisations, and, because of this, rehospitalisation rates might have been underestimated; (2) due to the retrospective nature of the study, with secondary use of data, signs of congestion and other clinical and laboratory parameters, like NT-proBNP, could not be evaluated as risk factors for readmission or death; it was also not possible to provide a thorough description of the group, including the aetiology of AHF, as well as the NYHA class on admission (3) the implantation of cardiac devices was not examined, although it was unlikely that a significant number of patients had implanted such devices, considering their age and that only a minority had LVEF ≤40%; (4) other factors that could have contributed to rehospitalisation, such as poor compliance to medication, were also not considered in the risk analysis; (5) the causes of death after discharge were not studied in detail, although we have previously reported that 42.9% of patients from the PRECIC study died of cardiovascular causes.[16]

CONCLUSIONS

Predicting the risk of an event of interest is a matter of great relevance in clinical practice. In this study, we aimed to accurately estimate the predictors of AHF rehospitalisation and death in a real cohort of patients after hospital discharge for AHF, considering death without rehospitalisation as a competing event.

Our findings support that AF, renal dysfunction and beta-blocker prescription at discharge are strong predictors of rehospitalisation. When considering the overall risk factors for death without rehospitalisation, we found that being male, ≥80 years of age, having dementia or high RDW levels are considered as high-risk factors, while taking beta-blockers at discharge and having high

PDW levels at index admission represent a low risk. If confirmed in more extensive studies, these risk predictors may be used to guide clinicians about the short- and medium-term prognosis of AHF patients on hospital discharge and may help tailor clinical interventions to improve patients' clinical outcomes.

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5.5. Multidisciplinary Heart Failure Clinic: How to Implement?

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ARTIGOS DE REVISÃO
REVIEW ARTICLES

Clínica Multidisciplinar de Insuficiência Cardíaca: Como Implementar
Multidisciplinary Heart Failure Clinic: How to Implement

Irene Marques[1], Catarina Gomes[2], Sofia Viamonte[3], Gonçalo Ferreira[4], Catarina Mendonça[1]

Resumo

O objetivo deste artigo é fazer uma breve revisão do estado da arte sobre clínicas de insuficiência cardíaca e divulgar a implementação da nossa clínica, como exemplo possível em contexto português. Assim, é revista a evidência científica que suporta as recomendações para a implementação dessas clínicas, a sua estrutura, os domínios que devem abordar, as intervenções necessárias e também o impacto associado à sua implementação. Após a revisão da escassa evidência em território português, descrevemos a implementação da nossa clínica multidisciplinar de insuficiência cardíaca, a sua constituição, o seu programa estruturado de seguimento e os principais resultados obtidos nos três primeiros anos de atividade assistencial, nomeadamente a redução da mortalidade e dos reinternamentos. Concluímos que os cuidados aos doentes com insuficiência cardíaca em Portugal podem melhorar, com a implementação de mais clínicas como a nossa, e esperamos que este artigo estimule esse processo.

Palavras-chave: Cuidados Ambulatórios; Hospitalização; Insuficiência Cardíaca; Prestação de Cuidados de Saúde.

Abstract

The objective of this article is to briefly review the state-of-the-art about heart failure clinics and to report the implementation of our clinic, as an example in the Portuguese reality. Thereby, the evidence supporting the recommendations to implement those clinics is reviewed, as well as their structure, domains that need to be addressed, necessary interventions and the impact on outcomes after their implementation. After revision of the scarce evidence from Portuguese reality, we reveal how we implemented our multidisciplinary heart failure clinic. We present our team, the structured follow-up program and the impact in the major outcomes after the first three years of clinical practice, namely mortality and readmission reduction. In conclusion, we think that care to heart failure patients in Portugal can improve, if more heart failure clinics are implemented, and we hope this article can promote that process.

Keywords: *Ambulatory Care; Delivery of Health Care; Heart Failure; Hospitalization.*

Introdução

A insuficiência cardíaca (IC) é uma epidemia do século XXI, com prevalência ≥ 10% acima dos 70 anos.[1-3] De forma notável, representa o ponto de encontro das diversas doenças cardiovasculares no coração.

Nos países desenvolvidos é responsável por 1% - 2% dos custos globais em saúde, sobretudo à custa dos internamentos que acarreta. Estes internamentos têm aumentado, representando a causa mais frequente de internamento acima dos 65 anos.[3-7] A mortalidade no primeiro ano após internamento por IC é elevada, na nossa região da Europa e nosso Serviço de Medicina Interna, rondando os 30%. A taxa de reinternamento por IC nesse período é também cerca de 30%.[8,9] Estes reinternamentos têm um grande impacto na qualidade de vida e no prognóstico global dos doentes, assim como na saúde pública e na economia dos países desenvolvidos.[6,7,10]

As mais recentes recomendações internacionais deixam clara a importância da identificação dos doentes com pior prognóstico e da sua integração em programas de gestão multidisciplinar, também designadas Clínicas de IC. A atividade destas organizações centra-se no seguimento estruturado com educação dos doentes, otimização da terapêutica, suporte psicológico e acesso facilitado aos cuidados de saúde.[1,4,11-14]

O objetivo deste artigo é fazer uma breve revisão do estado da arte que suporta as recomendações relativas à criação de Clínicas de IC e dos domínios que devem abordar, assim como o impacto associado à sua implementação. Por outro lado, descrevemos a implementação da nossa Clínica multidisciplinar de IC no Centro Hospitalar do Porto, o

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GEstIC (Grupo de Estudo da Insuficiência Cardíaca), e os principais resultados obtidos após os três primeiros anos de atividade assistencial, no intuito de partilhar a nossa experiência e estimular a implementação de outras Clínicas de IC em Portugal.

Evidência científica

A implementação de Clínicas de IC como programas estruturados de gestão dos doentes com IC tem o mais elevado nível de evidência científica nas recomendações europeias publicadas em 2016.

Na última década, foram muitas as publicações que abordaram e definiram quais os doentes-alvo, os domínios de intervenção e as intervenções a incluir nestes programas, assim como a forma de avaliar o seu resultado.[1,4,11,15]

Destaca-se, contudo, um documento de consenso publicado em 2008 sob os auspícios da Heart Failure Society of America, que definiu claramente o que deve ser uma Clínica de IC.[15] Os peritos envolvidos definiram que os objetivos destas estruturas são reduzir as taxas de mortalidade e de reinternamentos e melhorar a qualidade de vida dos doentes com IC, através de cuidados personalizados. Ficou clara a noção de que, para serem bem-sucedidas, estas clínicas teriam que ter recursos e infraestruturas adequadas, aplicar as recomendações para a prática clínica em vigor e pautarem-se por uma cultura de avaliação da qualidade. Apesar de vários tipos de organização poderem cumprir os objetivos delineados, o documento estabelece à partida os componentes que devem incluir de forma a otimizar os cuidados ao doente com IC. Antes de mais, define quais os doentes candidatos, dos quais se destacam todos os recentemente hospitalizados por descompensação da IC e outros considerados de alto risco: idosos com múltiplas comorbilidades, com doença renal ou pulmonar grave, diabéticos, com IC classe III ou IV habitual da classificação New York Heart Association (NYHA) e os que têm história de reinternamentos frequentes, depressão, demência, má adesão à terapêutica e/ou contextos sociais e económicos desfavorecidos. Estes são os doentes que, em Portugal, são habitualmente tratados pelos internistas. Por fim, define onze domínios a desenvolver numa Clínica de IC:

1. gestão da IC;
2. avaliação funcional;
3. avaliação da qualidade de vida;
4. avaliação da terapêutica médica e farmacológica;
5. avaliação da indicação para dispositivos médicos;
6. avaliação nutricional;
7. seguimento;
8. definição do plano de cuidados;
9. comunicação,
10. educação do cuidador e
11. avaliação da qualidade. Para cada um destes domínios foi expressa a fundamentação e elencados os diversos componentes que o devem integrar.[15]

Mais recentemente, as recomendações europeias e americanas sobre IC consolidaram as ideias desse documento de consenso, estabelecendo quais as características dos doentes, componentes dos programas estruturados e recomendações para a gestão multidisciplinar e monitorização dos doentes incluídos nas Clínicas de IC. Salientam a importância da educação e auto-avaliação dos doentes, do desempenho de profissionais treinados, da monitorização dos idosos e da identificação atempada da necessidade de referenciação para cuidados paliativos.[1,12,13]

A chave para o sucesso destas organizações é a coordenação de cuidados, ao longo do trajeto da doença e dos diferentes níveis de cuidados de saúde prestados por diversos serviços. Isto só é possível através da estreita colaboração de profissionais destes serviços: cardiologistas, internistas, enfermeiros, nutricionistas, fisiatras, psicólogos, psiquiatras, assistentes sociais, farmacêuticos e profissionais dos cuidados de saúde primários e cuidados paliativos. A estrutura e conteúdo do programa podem variar conforme as realidades nacionais e locais. As Clínicas de IC devem ser facilmente acessíveis aos doentes e seus cuidadores, o que frequentemente é conseguido através de uma linha telefónica para aconselhamento.[1] Outros autores acreditam que existem três elementos essenciais para o sucesso: 1) todas as intervenções contarem com enfermeiros especializados em IC, 2) a educação dos doentes e/ou cuidadores sobre a IC e 3) haver acesso rápido a médicos com treino na área da IC.[16] As intervenções que levam à redução dos reinternamentos são tão mais bem-sucedidas quanto mais intensivo é o seguimento e maior o envolvimento de enfermeiros.[11,13,16,17]

Quanto à educação dos doentes e cuidadores, diversas organizações recomendam o método *Teach Back*, nomeadamente a American Medical Association,[17] como estratégia de melhorar a literacia em saúde. Esse método consiste em questionar informalmente o indivíduo previamente submetido a educação sobre o que compreendeu, estimulando-o a transmitir a informação recebida pelas suas próprias palavras. Se tiver havido falha na comunicação, pode rever-se a informação, assegurando-se que esta foi compreendida. Adicionalmente, o conceito de Zonas de IC pretende facilitar a compreensão de que existem áreas de perigo variável de descompensação, sendo a sua utilização recomendada por diversas sociedades científicas e sido adotado por diversos hospitais em todo o mundo, como facilmente se depreende após uma rápida consulta da *Internet*.

Para os doentes internados por IC descompensada é importante definir bem o plano para a alta. O agendamento de uma consulta após alta nesta altura mostrou reduzir a taxa de reinternamento e é uma das medidas de avaliação de qualidade dos hospitais pela American Medical Association.[1,19] A implementação de intervenções de cuidados de transição hospital-domicílio que visam reduzir os reinternamentos, onde se incluem as Clínicas de IC e também os telefonemas

estruturados, mostraram reduzir a mortalidade.[20-23] As mais recentes recomendações americanas para a IC sugerem que esses doentes sejam contactados telefonicamente nos primeiros 3 dias e tenham uma consulta presencial nos primeiros 7-14 dias após a alta.[12]

O conjunto de instrumentos de avaliação e intervenção integrados nas Clínicas de IC têm um impacto positivo no prognóstico dos doentes provavelmente superior ao que seria obtido pela sua utilização individual, mas a sua dimensão é de difícil quantificação.[14] Muitos deles estão diretamente relacionados com a mortalidade associada à IC, que continua a rondar os 50% aos 5 anos após diagnóstico, nas mais recentes estatísticas.[13,24] Referimo-nos nomeadamente à depressão, níveis de NT-proBNP e distância percorrida no Teste de 6 Minutos de Marcha (T6MM).[24] Neste âmbito, o T6MM mostra-se um instrumento valioso, uma vez que uma distância percorrida igual ou inferior a 300 metros é um indicador de risco de morte em doentes com IC ligeira a moderada.[25] Zotter-Tufaro e colaboradores mostraram que a distância percorrida é um fator preditor independente de internamento por IC e/ou morte de causa cardíaca em doentes com IC crónica e fração de ejeção preservada (FEp).[26]

A avaliação funcional e da qualidade de vida, tal como a promoção do exercício físico, são componentes essenciais das Clínicas de IC. A integração destes doentes em programas de reabilitação cardíaca mostrou melhorar a capacidade funcional e a qualidade de vida relacionada com a saúde, assim como reduzir os sintomas e os reinternamentos por IC[1,12], pelo que é especialmente recomendada. Apesar disto, no Reino Unido menos de 20% dos doentes hospitalizados por IC entre 2014 e 2015 foram referenciados para reabilitação cardíaca.[21] Por outro lado, a avaliação regular da qualidade de vida é especialmente importante nos doentes com IC e FEp, habitualmente idosos, muito sintomáticos e com elevada prevalência de comorbilidades, para os quais não existe terapêutica farmacológica que tenha mostrado impacto na mortalidade ou morbilidade.[1]

Em relação aos resultados obtidos, a implementação de Clínicas de IC mostrou reduzir a mortalidade e o tempo de internamento dos doentes internados por IC, melhorar a adesão terapêutica e reduzir os reinternamentos por IC.[1,4,17,20,21,23,27-29] Uma metanálise de 29 estudos aleatorizados mostrou que as estratégias multidisciplinares de gestão da IC reduziram em 43% o número total de internamentos por IC. Dessas, as que incluíam seguimento por uma equipa ou clínica multidisciplinar mostraram uma redução adicional da mortalidade por todas as causas em cerca de 25%, assim como dos internamentos por todas as causas em 20%. O impacto benéfico destas estratégias é semelhante à da prescrição de inibidores da enzima de conversão da angiotensina nos referidos indicadores, em populações similares.[16,23]

A favorável relação custo-efetividade destas estruturas é tanto mais importante quanto se reconhece o custo elevado da IC nas economias nacionais e sistemas de saúde, se prevê que esse custo nos Estados Unidos da América em 2030 sejam mais do dobro do atual e que os internamentos por IC aumentem em 50% no Reino Unido nos próximos 25 anos.[2,4,5]

Realidade portuguesa

Em Portugal, estima-se que existiam 380 000 doentes com IC[30] e o cenário da IC é preocupante, sendo necessário maior investimento nas redes de cuidados.[6,28]

Os dados disponíveis reportam escassa organização dos cuidados aos doentes com IC e ainda mais escassos recursos de enfermagem dedicados a esta patologia.[30-33] Ainda assim, num estudo observacional nacional, Azevedo e colaboradores constataram que os doentes integrados numa Clínica de IC em ambulatório tinham significativamente menor risco de morte ou reinternamento no primeiro mês após alta de internamento por IC. Estes doentes também mantinham um risco de morte significativamente menor e independente num seguimento longo, em média de 373 dias.[34] Noutro contexto, Fonseca e colaboradores demonstraram redução do resultado composto mortalidade e reinternamento a curto e longo prazo nos doentes integrados numa Unidade de IC Aguda.[35]

Em relação à reabilitação cardíaca, foram recentemente publicados dados sobre a sua cobertura nacional. Contudo, não encontramos dados que reportem qual a percentagem de doentes com IC que têm acesso a estes programas. Sabemos apenas que, entre 2013 e 2014, a IC foi o motivo de referenciação em apenas 12,7% dos doentes integrados.[36]

Sobre as características dos doentes de alto risco, citadas como motivos de integração em Clínicas de IC, estas estão disseminadas na população de doentes internados por IC no nosso Serviço de Medicina Interna[9] e, presumivelmente, na maioria dos seus congéneres nacionais. Por outro lado, estes doentes representam uma grande parte do total de internamentos nestes serviços. Assim, faz todo o sentido a implementação de Clínicas de IC, envolvendo à partida todas as áreas clínicas essenciais à abordagem multidisciplinar destes doentes, para cumprir a missão de oferecer os cuidados abrangentes, globais e integradores próprios da Medicina Interna.

Clínica Multidisciplinar de IC

A nossa Clínica multidisciplinar de IC nasceu no Serviço de Medicina Interna em 2009, após revisão da literatura, com uma Carta de Princípios que definiu os principais objetivos:

- Promover a formação de médicos, enfermeiros e doentes sobre a IC
- Envolver as áreas assistenciais com um papel relevante nos cuidados aos doentes com IC, nomeadamente Enfermagem, Cardiologia, Nefrologia, Medicina Física e de Reabilitação, Nutrição, Psiquiatria, Cuidados Paliativos e Serviço Social

- Promover o cumprimento das recomendações estabelecidas
- Desenvolver métodos de avaliação de prognóstico para os doentes tratados
- Promover estratégias de redução da mortalidade e dos reinternamentos por IC
- Implementar estratégias de melhoria do prognóstico
- Promover o relacionamento com os Cuidados de Saúde Primários
- Participar em estudos sobre novas terapêuticas para a IC
- Promover a atividade científica

Adotámos a designação de GEstIC - Grupo de Estudo da Insuficiência Cardíaca. Após apresentação pública da Carta de Princípios, a equipa multidisciplinar foi constituída por um elemento de cada serviço e enfermeiros do Serviço de Medicina Interna. Apresenta-se de seguida a organização atual, nomeadamente o programa estruturado aplicado aos doentes admitidos em 2017.

CONSTITUIÇÃO DA EQUIPA

Esta equipa integra duas internistas que asseguram a consulta de Insuficiência Cardíaca; uma cardiologista, uma fisiatra, uma psiquiatra, uma nutricionista, uma assistente social, uma fisioterapeuta e dez enfermeiros; neste momento não há nefrologista, o que aconteceu entre 2013 e 2015. Além deste núcleo, existe um enfermeiro-chefe e um grupo de internos da formação específica em Medicina Interna que colabora na atividade científica e de desenvolvimento do projeto.

A responsável pelo GEstIC é uma das internistas, que também coordena toda a equipa multidisciplinar. Um dos enfermeiros coordena a atividade da equipa de enfermagem.

Programa Estruturado de Gestão da IC

REFERENCIAÇÃO

A referenciação ocorre durante o internamento por IC aguda nos Serviços de Medicina Interna ou de Cardiologia ou por apresentação na Consulta de Grupo de IC. Os critérios de referenciação ao GEstIC apresentam-se na Tabela 1.

No internamento, a referenciação é formalizada informaticamente no Processo Clínico Eletrónico do doente, o que leva à inclusão do doente numa aplicação informática do GEstIC e gera atitudes e intervenções terapêuticas na visão de enfermagem do programa SClínico, desenvolvido pelos Serviços Partilhados do Ministério da Saúde.

GUIA E INTERVENÇÃO EDUCACIONAL SOBRE IC

Na primeira abordagem de educação é entregue um Guia sobre IC ao doente, familiar e/ou cuidador. O seu conteúdo resume a Intervenção Educacional sobre a IC e baseia-se em:

1. promoção de autocuidados em diversos domínios: alimentação, álcool, tabaco, medicação, exercício físico, restrição de sal e líquidos e peso corporal diário;
2. reconhecimento dos sinais de descompensação da IC, segundo Zonas da IC; e
3. atitudes a tomar perante a identificação das situações de descompensação da IC, como telefonar para um dos enfermeiros do GEstIC ou deslocar-se ao Serviço de Urgência.

A nossa versão das Zonas da IC foi adaptada[37] para incluir rostos que personalizam o nível de perigo de cada zona. (Fig. 1) Tem sido útil na educação de doentes daltónicos e como reforço visual da mensagem que se pretende transmitir.

Esta Intervenção Educacional é iniciada pelos enfermeiros da enfermaria onde se encontra internado o doente, os quais tiveram formação específica, e utiliza o método *Teach Back*.[18]

ALTA DE INTERNAMENTO POR IC

A responsável pelo GEstIC, quando contactada pelos médicos assistentes do doente no dia da alta, agenda um telefonema de um enfermeiro do GEstIC para o doente, 48 a 96 horas após a alta, assim como a primeira consulta externa de IC. Esta consulta é agendada sempre que possível nos 14 dias seguintes e por regra até 30 dias após alta.

TELEFONEMA PÓS-ALTA

Este telefonema é estruturado para cumprir objetivos:

1. deteção de sinais ou sintomas de descompensação da IC, nomeadamente qual a Zona da IC nesse dia;
2. esclarecimento de dúvidas;
3. revisão da medicação e
4. confirmação da data da primeira consulta de IC.

Tabela 1: Critérios de referenciação, exclusão e de alta do GEstIC *

	Critérios
Referenciação	1. Internamento por IC aguda, crónica descompensada ou de novo 2. Manifestações clínicas de IC em classe funcional III ou IV da NYHA 3. Internamentos prévios ou observações frequentes no Serviço de Urgência por IC aguda
Exclusão	1. Ausência ou escassez de vida de relação 2. Dependência total de terceiros 3. Ausência de condições para cumprir as medidas propostas por motivos sociais ou outros
Alta	1. Estabilidade clínica i.e. IC habitual não superior a II da NYHA, sob terapêutica estável, e ausência de hospitalizações por IC no último ano (doentes com FEp) 2. Ausência de condições para cumprir as medidas propostas, por motivos sociais, demência e/ou outros 3. Incumprimento

* FEp- fração de ejeção preservada, IC- insuficiência cardíaca, NYHA - New York Heart Association

Tabela 2: Cronograma de seguimento na consulta de IC e parâmetros mínimos avaliados*

	Admissão	3 meses	6 meses	9 meses	1 ano	16 meses	20 meses	2 anos e anualmente
Consulta IC†	X	X	X	X	X	X	X	X
Hemograma completo	X		X		X			X
Bioquímica de sangue	X	X	X	X	X	X	X	X
Glicose	X	X	X	X	X	X	X	X
Ácido úrico	X				X			X
Ureia	X	X	X	X	X	X	X	X
Creatinina	X	X	X	X	X	X	X	X
TFG ‡	X	X	X	X	X	X	X	X
Sódio	X	X	X	X	X	X	X	X
Potássio	X	X	X	X	X	X	X	X
Fósforo	X	X	X	X	X	X	X	X
Cálcio	X	X	X	X	X	X	X	X
Magnésio	X	X	X	X	X	X	X	X
TGO	X				X			X
TGP	X				X			X
Fosfatase alcalina	X				X			X
GGT	X				X			X
Desidrogenase lática	X	X	X		X			X
NT-proBNP	X	X	X	X	X	X	X	X
Colesterol LDL	X		X		X			X
Colesterol HDL	X		X		X			X
Triglicerídeos	X		X		X			X
HbA1c	X		X		X			X
TSH	X				X			X
Ferritina	X				X			X
Taxa saturação da transferrina	X				X			X
Vitamina D	X				X			X
Paratormona §	X							
Análise de urina tipo II	X		X		X			X
Sedimento	X		X		X			X
Creatinina	X		X		X			X
Relação proteínas totais/Creatinina	X		X		X			X

* GGT – gamaglutamiltransferase, HbA1c – hemoglobina glicosilada, HDL- lipoproteina de alta densidade, IC – insuficiência cardíaca, LDL – lipoproteina de baixa densidade, NT-proBNP – fragmento N-terminal do peptídeo natriurético tipo B, TFG – taxa de filtração glomerular, TGO- transaminase glutâmica oxaloacética, TGP - transaminase glutâmica pirúvica, TSH- hormona tireoestimulante. † A partir do 1º ano a consulta tem uma regularidade mínima de 4 meses. ‡ A TFG é estimada segundo a fórmula CKD-EPI (*Chronic Kidney Disease Epidemiology Collaboration*) § Apenas nos doentes com TFG ≤ 45 mL/min.

Tabela 3: Cronograma de seguimento na Consulta de IC e parâmetros mínimos avaliados (continuação)*

	Admissão	3 meses	6 meses	9 meses	1 ano	16 meses	20 meses	2 anos e anualmente
Consulta IC†	X	X	X	X	X	X	X	X
EXAMES								
Radiografia do tórax	X							
Ecocardiograna transtorácico	X							
Electrocardiograma	X				X			X
Ecografia renovesical	X							
Estudo do sono	X							
Densitometria óssea ‡			X					
TESTES								
Mini-Cog	X				X			X
MMSE §	X				X			X
DASI	X		X		X			X
T6MM	X		X		X			X
MLWHFQ		X		X				X
HADS			X					X
FRAX ‡		X						

*DASI - *Duke Activity Score Index*, FRAX - *Fracture Risk Assessment Tool* da Organização Mundial de Saúde, HADS - *Hospital Anxiety and Depression Scale*, IC – Insuficiência Cardíaca, MLWHFQ - *Minnesota Living with Heart Failure Questionnare*, MMSE - *Mini Mental State Examination*, T6MM – Teste de 6 Minutos de Marcha. †A partir do 1º ano a consulta tem uma regularidade mínima de 4 meses. ‡ Apenas nas situações indicadas no protocolo terapêutico do GEstIC. § Apenas se o teste *Mini-Cog* se mostrar a favor de défice cognitivo.

CONTACTO TELEFÓNICO DO DOENTE PARA O GESTIC

A posição na Zona da IC amarela deve motivar um telefonema do doente ou cuidador, através de um número de telemóvel dedicado, para um enfermeiro do GEstIC. Este serviço está disponível entre as 9 e as 12 horas dos dias úteis. Se necessário, este enfermeiro contacta uma das internistas, que orientará a situação.

CONSULTA DE IC

Em janeiro de 2013 foi criada a Consulta de Insuficiência Cardíaca, que inclui consulta médica e de enfermagem.

Na consulta de enfermagem é desenvolvida a Intervenção Educacional e avaliados diferentes domínios de acordo com os seguintes instrumentos:

1. capacidade funcional através do T6MM[38] e do Duke *Activity Score Index* (DASI),[39]
2. qualidade de vida pelo *Minnesota Living with Heart Failure Questionnaire*[40],
3. ansiedade e depressão pela *Hospital Anxiety and Depression Scale*[41],
4. capacidade cognitiva através do teste *Mini-Cog*[42] e, se positivo, do *Mini Mental State Examination*.[43]

O seguimento dos doentes na consulta inclui avaliação regular de diversos parâmetros. O cronograma de seguimento (Tabelas 2 e 3) determina a avaliação mínima em cada momento. Os problemas específicos de cada doente ditam o pedido de exames adicionais e a regularidade necessária do seguimento.

Em todas as consultas é entregue um calendário de autovigilância da IC, para preenchimento diário com os dados do peso corporal, edemas, Zona da IC e dose de furosemida (Fig. 2). Em cada consulta médica é revista a terapêutica e

Tabela 4: Impacto da atividade do GEstIC entre 2013 e 2015

	PRECIC* 2012	GEstIC 2013-2015
Nº doentes admitidos	429	259
Idade (mediana)	81	79
Relação homens:mulheres	1,8 : 3	2:3
Mortalidade no 1º ano pós-alta	16,1 %†	10,4 %
Rehospitalização por IC no 1º ano após alta ou 1ª Consulta	30,5%	25,9%

IC - insuficiência cardíaca, **PRECIC - Reality and Outcomes of Heart Failure hospitalization before a Heart Failure Clinic:* PRECIC study.(9), ¶ Resultados da atividade do GEstIC janeiro de 2013 e dezembro de 2015 (inclui 100 doentes com mais de um ano de seguimento), †Apenas foram considerados os doentes que não teriam critérios de exclusão para o GEstIC.



Figura 1: Zonas da Insuficiência Cardíaca - adaptado pelo GEstIC - Grupo de Estudo da Insuficiência Cardíaca a partir de Canada Heart and Stroke Foundation *Heart failure zones*.

elaborada uma folha de prescrição, que fica gravada no processo clínico eletrónico.

O tratamento é guiado por um protocolo terapêutico, que inclui a avaliação e o tratamento dos seguintes problemas:

1. IC crónica com Fração de Ejeção Reduzida,
2. IC crónica com Fração de Ejeção Preservada,
3. fibrilação auricular persistente ou permanente,
4. estratégia terapêutica diurética, refratariedade e intolerância aos diuréticos,
5. ferropenia,
6. doença óssea e osteoporose e
7. ansiedade e depressão.

CONSULTA DE GRUPO DE IC

Em maio de 2014 foi formalizada a Consulta de Grupo de Insuficiência Cardíaca. Semanalmente, durante uma hora, a equipa multidisciplinar reúne na Consulta de Grupo de IC. Estão presentes: a responsável pelo GEstIC, a outra internista, o enfermeiro-chefe responsável, pelo menos um dos enfermeiros e todos os elementos das áreas específicas. Discute-se a referenciação às áreas específicas e orientação diagnóstica e terapêutica dos doentes.

REFERENCIAÇÃO PARA PROGRAMA DE REABILITAÇÃO CARDÍACA

Os *doentes podem ser referenciados para Programa de Reabilitação Cardíaca* na Unidade de Reabilitação e Prevenção Cardíaca, onde trabalha a nossa fisiatra, sob a direção de um cardiologista. Um protocolo estabelecido entre o GEstIC e a Liga dos Amigos do Hospital de Santo António, permite que esta suporte os custos com as deslocações para reabilitação cardíaca dos doentes mais carenciados.

Os candidatos são todos os doentes em classe I a III da NYHA, clinicamente estáveis e com capacidade funcional. Após exclusão de contraindicações, os doentes são submetidos a uma prova de esforço convencional, visando a prescrição do exercício, efetuada de acordo com as recomendações atuais.[44] O Programa de Reabilitação Cardíaca é constituído por sessões de exercício com periodicidade bissemanal, sob supervisão médica, e tem a duração de 12 semanas.

GEstIC
Grupo de Estudo da Insuficiência Cardíaca

centro hospitalar do Porto

CALENDÁRIO DE AUTOVIGILÂNCIA DA INSUFICIÊNCIA CARDÍACA

1				
2				
3				
4				
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31				

Legenda:

Data | Peso | Zona de Perigo: Verde, Amarela, Vermelha | Edemas: + tornozelo, 1+ perna, 2+ joelho, 3+ acima joelho, 4+ anca, barriga | Número de comprimidos de Furosemida

Figura 2: Calendário de autovigilância domiciliária, a preencher pelo doente, cuidador ou familiar.

ALTA

Os critérios de alta do GEstIC apresentam-se na Tabela 1. Contudo, note-se que os doentes que cumpram o primeiro critério para alta, não terão alta se se prever a necessidade uma intervenção médica a curto ou médio prazo. Os destinos pós-alta mais frequentes são as consultas de Cardiologia, Medicina Interna, Nefrologia e de Medicina Geral e Familiar.

DIFICULDADES E SOLUÇÕES ENCONTRADAS NO PROCESSO DE IMPLEMENTAÇÃO

A estratégia organizacional do GEstIC tem uma perspetiva abrangente da população com IC e assenta na atividade dos enfermeiros. A sua implementação foi um processo longo e difícil, apenas possível devido à convicção e resiliência de uma equipa dedicada à melhoria da qualidade. A determinação e apoio das direções dos Serviços de Medicina Interna e de Cardiologia foram decisivos para a sua concretização. Apesar da grande dificuldade na angariação de recursos humanos e disponibilização de horário, esta organização tornou-se uma mais-valia em termos de cuidados assistenciais e de valorização profissional.

A estreita relação entre o Serviço de Medicina Interna e o Serviço de Cardiologia, com corresponsabilidade e complementaridade na gestão dos doentes, tem permitido a investigação e tratamento céleres dos doentes com maior risco de complicações. O papel relevante da cardiologista é claro nos dados que mostram que foi solicitada para decisão em mais de 50% dos casos discutidos na Consulta de Grupo de IC. A presença das outras áreas nesta consulta é também preciosa na discussão das situações mais difíceis. A assistente social tem um papel fundamental na garantia de condições para tratamento e adesão às recomendações.

RESULTADOS DA ATIVIDADE ASSISTENCIAL ENTRE 2013-2015

Entre 1 de janeiro de 2013 e 31 de dezembro de 2015 foram integrados 259 doentes no GEstIC. O internamento por IC aguda, de novo ou crónica descompensada, foi a origem de 95% deles. Estes doentes contactaram a equipa através de 204 telefonemas, dos quais apenas 28% foram motivados por sinais de descompensação da IC.

Nesse período, foram realizadas 1009 consultas de IC e discutidas 371 situações clínicas na Consulta de Grupo de IC, das quais 54% com a nossa cardiologista. Apesar de referenciação de um razoável número de doentes para Programa de Reabilitação Cardíaca, apenas 26 doentes terminaram esse programa. Cento e cinquenta e dois doentes tiveram alta.

Como principais resultados do impacto da nossa atividade no mesmo período, analisamos a mortalidade e o número de reinternamentos por IC. Para isso, comparamos dois grupos: os doentes integrados no GEstIC e os doentes internados por IC no nosso Serviço de Medicina Interna em 2012, o ano prévio à implementação do GEstIC, previamente caracterizados (estudo PRECIC).[9]

Na Tabela 4 encontra-se a caracterização segundo o género, a idade e as taxas de mortalidade e de reinternamento por IC. A comparação dos resultados mostra uma redução absoluta de 5,7% e relativa de 35,4% da mortalidade entre o grupo do estudo PRECIC e o grupo integrado no GEstIC. No mesmo sentido, encontra-se uma redução absoluta de 4,6% e relativa de 15,1% dos reinternamentos por IC.

OUTRAS ATIVIDADES

De modo a cumprir os seus objetivos, a equipa multidisciplinar do GEstIC têm-se envolvido noutras atividades, nomeadamente: 1) organização anual do Dia de Sensibilização para a IC, sob o lema "Siga o seu Coração" 2) participação em estudos internacionais multicêntricos e aleatorizados, 3) publicação de artigos científicos, 4) formação pós-graduada, 5) partilha de experiência com outros hospitais, 6) criação de brochuras para doentes com IC, sobre alimentação e exercício físico, e 7) organização de um curso multidisciplinar de IC, destinado aos médicos e enfermeiros dos cuidados de saúde primários. Algumas destas atividades podem ser acompanhadas na nossa página do *Facebook*.

Conclusão

A implementação de Clínicas multidisciplinares de IC representa uma recomendação para a prática clínica suportada por evidência científica de elevada qualidade, com o objetivo de reduzir a mortalidade e morbilidade e melhorar a qualidade de vida dos, cada vez mais numerosos, doentes com IC.

Neste artigo, fazemos a revisão dessa evidência e divulgamos o modo de implementação e o programa estruturado da nossa clínica, o GEstIC, assim como o seu impacto na redução da mortalidade e dos reinternamentos por IC nos três primeiros anos de atividade.

O GEstIC possui as características definidas para uma Clínica de IC, quer em relação ao tipo de doentes que inclui, quer em relação aos domínios que abrange e avalia.[1,15,45] Não temos conhecimento de outra clínica com estas características em Portugal. Contudo, temos um longo caminho a percorrer, no sentido de melhorar a articulação com os cuidados paliativos e com os cuidados de saúde primários, criar um Hospital de Dia de IC e um desenvolver um programa de Internamento Domiciliário.

Por fim, esperamos que a nossa experiência estimule a implementação de outras clínicas, ajude a ultrapassar barreiras locais e nacionais e a otimizar os recursos disponíveis, melhorando o panorama português na área da IC.

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A Dra. Sofia Viamonte trabalha atualmente no Centro de Reabilitação do Norte Dr. Ferreira Alves, Vila Nova de Gaia, Portugal. ■

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5.6. NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)- Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

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My contribution to this work was as follows: I was the principal investigator of the PRIMA II study at my hospital, collected data and revised the manuscript. This article was included in the PhD thesis of Susan Stienen presented in March, 2018, and the PhD thesis of Khibar Salah presented in November, 2018, both at the University of Amsterdam, the Netherlands. This is an open access publication, with no financial, legal or technical barriers to accessing it.

Circulation

ORIGINAL RESEARCH ARTICLE

NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)-Guided Therapy in Acute Decompensated Heart Failure

PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

Editorial, see p 1684

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BACKGROUND: The concept of natriuretic peptide guidance has been extensively studied in patients with chronic heart failure (HF), with only limited success. The effect of NT-proBNP (N-terminal probrain natriuretic peptide)-guided therapy in patients with acute decompensated HF using a relative NT-proBNP target has not been investigated. This study aimed to assess whether NT-proBNP-guided therapy of patients with acute decompensated HF using a relative NT-proBNP target would lead to improved outcomes compared with conventional therapy.

METHODS: We conducted a prospective randomized controlled trial to study the impact of in-hospital guidance for acute decompensated HF treatment by a predefined NT-proBNP target (>30% reduction from admission to discharge) versus conventional treatment. Patients with acute decompensated HF with NT-proBNP levels >1700 ng/L were eligible. After achieving clinical stability, 405 patients were randomized to either NT-proBNP-guided or conventional treatment (1:1). The primary end point was dual: a composite of all-cause mortality and HF readmissions in 180 days and the number of days alive out of the hospital in 180 days. Secondary end points were all-cause mortality within 180 days, HF readmissions within 180 days, and a composite of all-cause mortality and HF readmissions within 90 days.

RESULTS: Significantly more patients in the NT-proBNP-guided therapy group were discharged with an NT-proBNP reduction of >30% (80% versus 64%, *P*=0.001). Nonetheless, NT-proBNP-guided therapy did not significantly improve the combined event rate for all-cause mortality and HF readmissions (hazard ratio, 0.96; 95% confidence interval, 0.72–1.37; *P*=0.99) or the median number of days alive outside of the hospital (178 versus 179 days for NT-proBNP versus conventional patients, *P*=0.39). Guided therapy also did not significantly improve any of the secondary end points.

CONCLUSIONS: The PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) demonstrates that the guidance of HF therapy to reach an NT-proBNP reduction of >30% after clinical stabilization did not improve 6-month outcomes.

CLINICAL TRIAL REGISTRATION: URL: http://www.trialregister.nl. Unique identifier: NTR3279.

Key Words: biomarkers ■ heart failure ■ hospitalization ■ mortality ■ natriuretic peptide, brain ■ patient readmission ■ randomized controlled trial

Sources of Funding, see page 1681

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Clinical Perspective

What Is New?

- Although several studies have investigated the use of NT-proBNP (N-terminal probrain natriuretic peptide)-guided therapy in patients with chronic heart failure, guidance of therapy in patients with acute heart failure using a relative NT-proBNP target has never been investigated.
- We demonstrate that NT-proBNP-guided therapy targeting an NT-proBNP reduction of >30% did not improve clinical outcomes.

What Are the Clinical Implications?

- Our study does not support the use of serial NT-proBNP measurements for the guidance of therapy during admission for acute heart failure.

The prognosis of patients admitted for and discharged after acute decompensated heart failure (ADHF) is poor, with ≥50% of patients being readmitted or deceased within 6 months.[1–4] The immediate goal of treatment in patients with ADHF is to relieve congestion, for which several measures of effect are available.[5–7] As the main mechanism of congestion, elevated filling pressures at discharge have been related to a poor prognosis.[8] A subsequent effort to guide therapy in patients with ADHF with systolic HF toward lower filling pressures before discharge was successful in reducing filling pressures but did not improve prognosis after discharge.[9] Noninvasive assessment of preload and afterload by brain natriuretic peptide (BNP) or NT-proBNP (N-terminal probrain natriuretic peptide) may extend these earlier studies by showing that higher absolute levels and a lack of decrease of these BNPs are associated with worse outcomes in patients with ADHF.[4,10–12] The studies provide a new impetus for these biomarkers as attractive targets to guide in-hospital therapy because they reflect decongestion (preload reduction) and also mirror other mechanisms of heart failure in the measurable response of the biomarkers to several HF therapies that improve prognosis.[13–15] Current guidelines state that the usefulness of NT-proBNP-guided HF therapy to reduce hospitalization or mortality in patients with chronic HF is not well established.[16,17] For ADHF, a first attempt was made to use an absolute NT-proBNP cut-off level (>3000 ng/L predischarge) to randomize 280 patients to further optimization of HF medication (but without a prespecified NT-proBNP target) versus to proceed to discharge without any adjustments to therapy.[18] This study was unable to demonstrate a difference in 6-month outcomes between groups.

The PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) is the first prospectively randomized study on in-hospital guidance of ADHF treatment by targeting an NT-proBNP reduction of ≥30% at discharge, with the aim to decrease event rates 6 months after discharge.[19] Previous studies demonstrated that the target of a >30% decrease in NT-proBNP during admission for ADHF would be a robust predictor of prognosis[4,10,11]

METHODS

Study Design and Oversight

The study design has been reported previously.[19] Briefly, this investigator-initiated, multicenter, international, randomized controlled, prospective open 2-arm trial aimed to study the effect of in-hospital guidance of ADHF treatment by a predefined NT-proBNP target of >30% reduction from admission to discharge on the reduction of readmission and mortality rates in ≤180 days. Patients were included from 9 Dutch participating hospitals, 1 Portuguese hospital, and 1 Spanish hospital. The trial was approved by the Medical Ethics Committee of the University of Amsterdam and Academic Medical Center, The Netherlands, and registered in The Netherlands Trial Register (NTR3279). All patients provided written informed consent. The steering committee consisting of S.S., K.S., J.T., Y.P., and W.K. was responsible for the design, execution, and data analysis of the study. The trial was reviewed by an independent data and safety monitoring board. The first and subsequent drafts of the manuscript were prepared by the first and last authors. All authors approved the manuscript for publication and confirm that its contents adhere to the specifications in the protocol. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Patients, Group Assignments, and Interventions

Inclusion and exclusion criteria for participation in PRIMA II are listed in Table 1.

From the day of admission, HF treatment was started or continued at the discretion of the treating physician until clinical stability was achieved. Patients were defined clinically stable when they were admitted for ≥3 days and when a minimum of 3 out of 4 of the following criteria were present: target weight was reached, stable levels of serum creatinine (<25% increase from baseline) were obtained, improved symptoms and mobilization was possible, or adequate discharge medication was prescribed. When clinically stable, patients were randomized to either NT-proBNP-guided or conventional treatment (1:1). Although patients were included shortly after admission, they were randomized only after clinical stabilization. As described in our trial design,[19] the rationale for randomizing after clinical stabilization is as follows. First, the NT-proBNP target aimed at in our trial is derived from a discharge prediction model, not accounting for in-hospital mortality. By randomizing at the moment of clinical stability, we assumed that we could use the predictive value of the NT-proBNP discharge target taken from our

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Admission for acute decompensated heart failure
NT-proBNP levels of >1700 ng/L (>200 pmol/L) within 24 h of hospital admission
Exclusion criteria
Severe chronic obstructive pulmonary disease with forced expiratory volume in 1 s of <1 L
Pulmonary embolism within 1 mo before admission and pulmonary hypertension not caused by left ventricle dysfunction
Patients undergoing continuous ambulant peritoneal dialysis/patients on hemodialysis
Patients with planned coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery before admission (until 1 day before admission)
Patients with planned coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery during admission until the moment of randomization
Patients in cardiogenic shock at admission requiring invasive treatment
Patients with a history of ST-segment elevated myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, cardiac resynchronization therapy, or valvular surgery within 1 mo before admission
Signed informed consent for any current interventional study
Presence of severe noncardiac related life-threatening disease before inclusion with an expected survival of <6 mo after inclusion
Unwillingness to give or mental or physical status not allowing written informed consent
Circumstances that prevent follow-up (no permanent home address, transient, etc)

NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

previous study, and thus we did not randomize patients who died shortly after admission before randomization. Second, randomization at admission might introduce a bias by either undertreatment or intensified treatment of the conventional therapy group, whereas in the present study randomization was followed by either discharge or extra therapy. Third, some of the patients admitted for acute decompensated HF receive interventions (eg, percutaneous coronary intervention, coronary artery bypass graft, valvular surgery, etc) immediately or within a few days after admission. We decided to exclude these patients from our study if these interventions were planned before randomization in either an NT-proBNP-guided or a conventional treatment group. In this way, procedures would not influence results unless such interventions were intended to improve NT-proBNP levels after randomization. Randomizing patients predischarge (in a clinically stable state) avoids inclusion of these patients in the study. Randomization was stratified per center and HF severity (mild or severe HF).

After clinical stabilization, at the day of randomization, NT-proBNP levels were determined for all study patients. Levels were revealed to the treating physicians for patients in the NT-proBNP-guided group, and it was possible to plan discharge and follow-up when NT-proBNP had decreased >30% already at the day of randomization. Patients in the NT-proBNP group in whom NT-proBNP had not decreased ≥30% from the admission value entered a predefined algorithm consisting of several steps, including additional NT-proBNP measurements and suggested interventions to try to attain the desired >30% reduction in NT-proBNP levels. Briefly, suggested interventions were titration of HF medication (angiotensin converting enzyme [ACE]-inhibitors, β-blockers, and mineralocorticoid receptor antagonists [MRAs]) in eligible patients,[20] invasive therapies such as implantation of cardiac resynchronization therapy if indicated,[20] diagnostic coronary angiography when there was a suspicion of coronary ischemia, and electric cardioversion for patients with new-onset atrial fibrillation (see separately published design paper for details on the algorithm[19]). Further therapy adjustments were left at the discretion of the treating physician (ie, diuretics when it was felt that the patient was still or again became congested). When patients were randomized to NT-proBNP-guided therapy and had a reduction of <30% in NT-proBNP at randomization, the study coordinator contacted the site for therapy advice. In addition, reasons for not initiating or titrating HF medication had to be reported by the treating physician. For patients in the conventional therapy group, NT-proBNP levels determined at the day of randomization and discharge were blinded to the treating physicians. This was in contrast to NT-proBNP-guided patients, in whom discharge was further guided by NT-proBNP levels. Discharge and follow-up of conventionally treated patients were planned at the discretion of the treating physician. Discharge NT-proBNP measurements were reported as missing values when they were not determined ≤48 hours of discharge. In addition to NT-proBNP data, laboratory values on renal function and hemoglobin were collected. Hemoglobin levels at admission and discharge were used to determine the number of patients with hemoconcentration, which was defined as an absolute increase in hemoglobin levels and may serve as a measure of effective diuresis.[7] There was no predefined postdischarge program for follow-up, but patients who were included in The Netherlands were seen on a regular basis in dedicated HF outpatient clinics, similar to the previous outpatient study (PRIMA).[21]

Study Outcomes

The first primary end point was a composite end point of readmission for HF and all-cause mortality in 180 days after randomization, and the second primary end point was the number of days alive out of the hospital in 180 days after discharge. The secondary end points were readmissions for HF in 180 days, all-cause mortality in 180 days, and HF readmissions and mortality in the first 90 days. Adjudication of these end points was carried out in a blinded fashion by an independent committee of 2 cardiologists.

Statistical Analysis

The expected hazard ratio (HR) of experimental subjects relative to control subjects was 0.70 (ie, a reduction in the composite end point from 50% to 35%). Therefore, we estimated that we would need to randomize 340 patients (170 in each group) to provide the study with a power of 80% to detect a relative risk reduction of 30% in the first primary end point at an overall 2-sided α level of 0.05.

During the course of the study, we noticed that it was not possible to lower NT-proBNP levels to the target in ≈10% of patients in the NT-proBNP-guided group despite intensified therapy. To avoid a potential type 2 error, we increased our

sample size to 400 patients (2 x 200) to be able to detect an adapted relative risk reduction of 27% (ie, a reduction in primary end point from 50% to 36.5%).

Demographic characteristics are presented as frequencies and percentages when it concerns categorical data, and the Fisher exact test was used to make a comparison. Normally distributed, continuous variables are reported as mean±SD and were compared using Student *t* test. Other continuous data, expressed as median with interquartile range (IQR), were compared using the Mann–Whitney *U* test.

According to the intention-to-treat principle, we analyzed data of all patients who were randomized. Because this study had 2 primary end points, the Hochberg extension of the Bonferroni method for multiple comparisons was used to test for statistical significance.[22] Both end points are statistically significant if *P* of both end points is <0.05. If *P* is <0.05 for only 1 end point, then the *P* of this end point should be <0.025 to be declared statistically significant. Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional hazards models. HRs, 95% confidence intervals (CI), and 2-sided *P* values were calculated with the Cox models. We assessed the consistency of the treatment effect among 7 prespecified subgroups.

RESULTS

Study Population

From November 2011 through September 2015, 431 patients were included. Ten patients did not fulfill the criteria for randomization, 9 patients were discharged or deceased before randomization, 1 patient withdrew consent, and 6 patients were not randomized for other reasons. As a result, 405 patients were randomized to receive NT-proBNP-guided or conventional therapy (Figure 1). After randomization, 1 patient in the NT-proBNP-guided group withdrew informed consent and refused further data collection. Intention-to-treat analyses were hence performed in 404 patients. Baseline characteristics of these patients according to their study groups are displayed in Table 2.

Effect of Randomized Assignment on NT-proBNP

NT-proBNP levels at different time points during admission for patients in the NT-proBNP-guided and conventional therapy group are listed in Table 3. From admission to randomization, similar percentages of patients in the NT-proBNP-guided and conventional therapy groups attained the desired NT-proBNP reduction of ≥30% (64% versus 63%, *P*=0.75). Of the 71 patients who had not yet attained >30% NT-proBNP reduction at randomization, 3 patients did not have a discharge NT-proBNP measurement. From the remaining patients, 52% (35/68) of patients in the NT-proBNP-guided group eventually attained >30% NT-proBNP reduction at discharge, whereas in the group of conventional patients, only 14% (9/63) eventually attained >30% NT-proBNP reduction at discharge (*P*<0.001). At discharge, significantly more patients in the NT-proBNP-guided group attained a reduction of >30% in NT-proBNP (from admission to discharge) compared with patients in the conventional therapy group (80% [144/179] versus 64% [113/177], *P*<0.001). The number of patients attaining and not attaining the NT-proBNP target at randomization and discharge and missing NT-proBNP levels is depicted in Table I in the online-only Data Supplement.

In line with this, patients in the NT-proBNP-guided therapy group attained a significantly larger relative and absolute reduction in NT-proBNP from admission to discharge compared with patients in the conventional therapy group, although no significant difference in absolute NT-proBNP levels at discharge was observed (Table 3).

Effect of Randomization Assignment on HF Therapy

Seventy-one patients in the NT-proBNP-guided group had an NT-proBNP reduction of ≤30% at randomization and therefore were subjected to the study algorithm to increase guideline-based directives for the management of HF. In 48 of these patients (68%), ≥1 subset of the algorithm was followed (start or titration of ACE inhibitor or angiotensin II receptor blocker (ARB), β-blocker or MRA, and an intervention planned or performed). In 4 patients (6%), attempts were made to start or titrate HF medication but were stopped because of side effects. In 13 patients (18%), physicians documented that they were not able to titrate or start HF medication because of severe renal insufficiency, hypotension, bradycardia, or simply because patients had a left ventricular ejection fraction >40%, and HF medication was not indicated in these patients. In 6 patients (8%), the algorithm was not followed adequately, although diuretics were uptitrated in 4 of these patients.

Changes in HF medication in patients in both NT-proBNP-guided and conventional groups between randomization and discharge are listed in Table 4. Attempts to adjust HF medication in the NT-proBNP-guided group were also scored. ACE inhibitors or ARBs and diuretics were initiated significantly more often or increased in dosages in patients in the NT-proBNP-guided group compared with those in the conventional group (25% versus 16%, *P*=0.04 for ACE inhibitors and ARBs; 29% versus 19%, *P*=0.03 for diuretics). Therapy changes in β-blockers and MRAs did not significantly differ between patients in NT-proBNP-guided and conventional groups (Table 4). In selected patients with a left ventricular ejection fraction <40%, there were no significant differences in ACE inhibitors or ARBs, MRAs, and diuretics between treatment groups. β-blockers in

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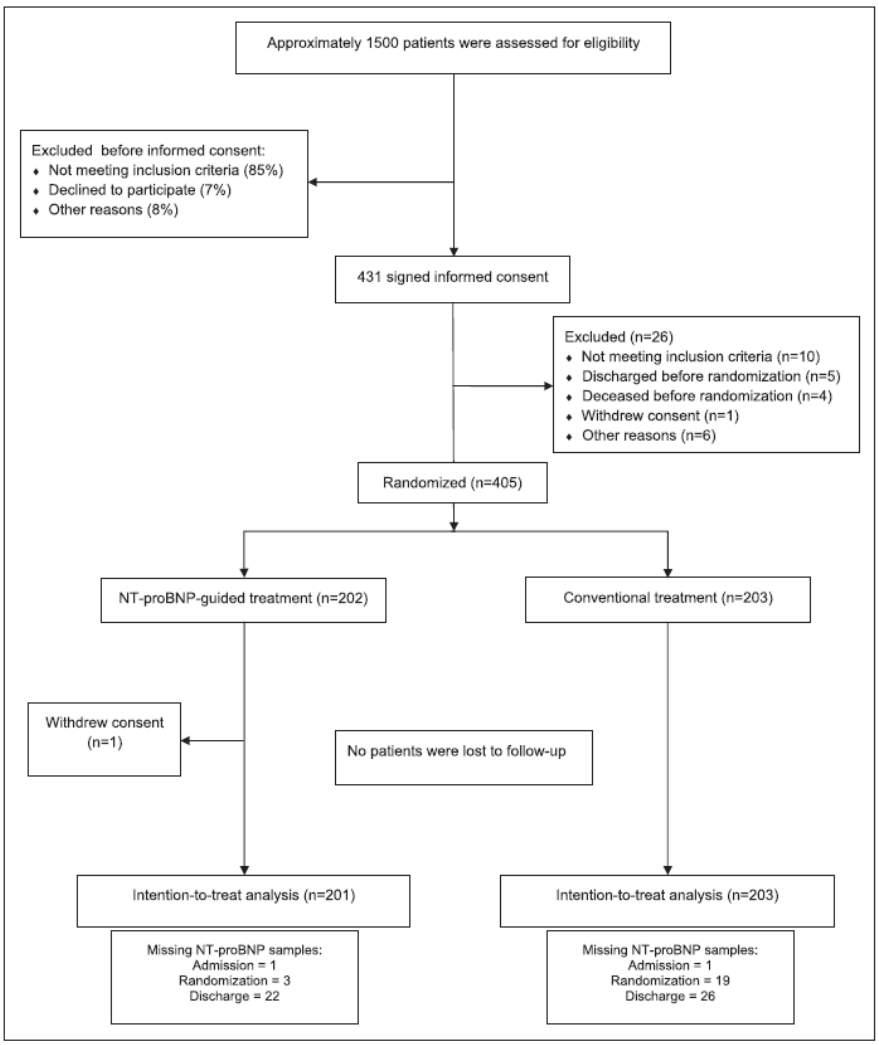


Figure 1. Outline of the PRIMA II trial.
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide; and PRIMA II, Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

patients with a left ventricular ejection fraction <40% were more often stopped or downtitrated in patients in the NT-proBNP-guided group compared with those in the conventional therapy group. Dosages of ACE inhibitors or ARBS, β-blockers, MRAs, and diuretics were similar at randomization and at discharge.

At discharge, no significant differences between patients in the NT-proBNP-guided and conventional groups were observed for the prescription rates and dosages of ACE inhibitors or ARBs, β-blockers, MRAs, and diuretics. This finding was not different between patients in the complete cohort and in selected patients with a left ventricular ejection fraction <40% (Table II in the online-only Data Supplement). There were no differences in discharge laboratory values, especially not in renal function (Table III in the online-only Data Supplement). The percentages of patients with hemoconcentration did not differ between the NT-proBNP-guided and conventional groups between admission and randomization (62% versus 55%, *P*=0.33), between randomization and discharge (32% versus 30%, *P*=0.77), and between admission and discharge (58% versus 58%, *P*=1.0).

Rates of electric cardioversion, coronary angiography, and cardiac resynchronization therapy ≤4 weeks after randomization were infrequent and did not differ between patients in the NT-proBNP-guided and conventional therapy groups (Table 4).

Table 2. Baseline Characteristics

Variable	NT-proBNP-Guided Therapy (n=201)	Conventional Therapy (n=203)	*P* Value
Age, y, median (IQR)	78 (69–85)	77 (68–84)	0.4
Male sex, n (%)	92 (47)	106 (54)	0.2
History of diabetes mellitus, n (%)	71 (35)	67 (33)	0.7
History of hypertension, n (%)	128 (65)	126 (62)	0.7
History of chronic obstructive pulmonary disease, n (%)	33 (17)	46 (23)	0.1
History of atrial fibrillation, n (%)	96 (48)	100 (50)	0.8
History of congestive heart failure, n (%)	120 (60)	126 (62)	0.7
Ischemic etiology, n (%)	53 (46)	49 (41)	0.4
Previous heart failure admission in the past 12 mo, n (%)	54 (45)	56 (44)	1.0
History of coronary artery disease, n (%)	75 (39)	69 (36)	0.5
History of cerebrovascular accident/transient ischemic attack, n (%)	35 (18)	33 (16)	0.8
LVEF, %, mean±SD	36±15	38±15	0.7
Preserved LVEF (>45%), n (%)	47 (27)	49 (30)	0.7
Mild-moderate reduced LVEF (25% to 45%), n (%)	89 (51)	78 (47)	
Severely reduced LVEF (<25%), n (%)	37 (21)	39 (24)	
Jugular venous pressure distended at admission, n (%)	68 (54)	74 (60)	0.4
Pulmonary rales at admission, n (%)	156 (79)	146 (76)	0.6
Peripheral edema at admission, n (%)	145 (74)	140 (72)	0.7
Systolic blood pressure at admission, mm Hg, median (IQR)	134 (115–158)	130 (116–156)	0.9
Diastolic blood pressure at admission, mm Hg, median (IQR)	78 (65–91)	79 (65–96)	0.6
Heart rate at admission, bpm, median (IQR)	86 (72–110)	90 (74–112)	0.3
Atrial fibrillation at admission, n (%)	71 (36)	83 (41)	0.3
New York Heart Association class at admission, n (%)			
I	3 (2)	3 (2)	0.7
II	34 (17)	41 (21)	
III	102 (52)	104 (53)	
IV	57 (29)	47 (24)	
Laboratory findings			
Hemoglobin at admission, mmol/L	7.6±1.2	7.8±1.2	0.2

(*Continued*)

Table 2. Continued

Variable	NT-proBNP-Guided Therapy (n=201)	Conventional Therapy (n=203)	*P* Value
Serum urea nitrogen at admission, mmol/l	9.5 (7.2–13.7)	9.5 (6.5–14.8)	0.7
Serum sodium at admission, mmol/l	139 (136–141)	139 (136–141)	0.6
Serum potassium at admission, mmol/L	4.2 (3.8–4.6)	4.3 (3.9–4.6)	0.3
Creatinine at admission, µmol/L	112 (87–157)	109 (82–150)	0.4
Estimated glomerular filtration rate at admission, ml/min/1.73m^2*	46 (33–60)	52 (35–67)	0.2
High-sensitivity cardiac troponin T at admission, µg/L	0.04 (0.02–0.07)	0.04 (0.03–0.09)	0.3
NT-proBNP at admission, ng/L	6293 (3949–11 438)	6122 (3252–11 371)	0.3
Medication at admission, n (%)			
Diuretics	136 (68)	136 (67)	0.9
Angiotensin-converting enzyme inhibitors or angiotensin receptor blocker	105 (52)	116 (57)	0.4
β-Blocker	125 (62)	135 (67)	0.4
Mineralocorticoid receptor antagonist	45 (22)	48 (24)	0.8
Triple heart failure medication (angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, BB, and mineralocorticoid receptor antagonist)	19 (10)	27 (13)	0.3
No heart failure medication	23 (11)	26 (13)	0.8

Values indicate n (%) or mean (IQR). Missing values (in NT-proBNP vs conventional patient, respectively): history of diabetes mellitus (0 vs 1), history of heart failure (3 vs 1), history of chronic obstructive pulmonary disease (2 vs 0), history of atrial fibrillation (1 vs 2), ischemic etiology of heart failure (87 vs 83), previous hospitalization for heart failure (81 vs 77), history of coronary artery disease (10 vs 9), history of cerebrovascular accident/transient ischemic attack (1 vs 0), jugular venous pressure at admission (75 vs 79), rales at admission (3 vs 11), peripheral edema at admission (6 vs 8), systolic blood pressure at admission (0 vs 3), diastolic blood pressure at admission (0 vs 3), HR at admission (2 vs 2), New York Heart Association class (5 vs 8), hemoglobin levels (4 vs 2), serum urea nitrogen levels (45 vs 43), sodium levels (1 vs 2), potassium levels (2 vs 2), hsTnT levels (80 vs 73), NT-proBNP levels (1 vs 1). BB indicates beta-blocker; IQR, interquartile range; LVEF, left ventricle ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Calculated as 186.3 × (creatinine mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if black).

Effect of Randomization Assignment on Duration of Admission

Between patients in the NT-proBNP and conventional groups, the number of days from admission to randomization (both median 5 days [IQR, 3–8], *P*=0.31) and

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Table 3. NT-proBNP Levels at Different Time Points and Changes in NT-proBNP Throughout Hospital Admission for Different Study Groups

	Admission (ng/L)	Randomization (ng/L)	Discharge (ng/L)	Reduction at Randomization		Reduction at Discharge	
				Percentage	Absolute (ng/L)	Percentage	Absolute (ng/L)
NT-proBNP median (IQR)	6350 (4152–11 327)	3498 (1833–5818)	2909 (1568–5340)	45 (16–64)	2411 (773–5414)	50 (34–67)*	2872 (1444–6687)†
Conventional median (IQR)	6013 (3711–11 113)	3286 (1922–7463)	3036 (1679–7092)	43 (8–63)	2130 (650–3963)	45 (9–66)*	2100 (651–5003)†

IQR indicates interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Statistical significant difference with $P<0.05$.
†Difference with $P<0.01$.

from randomization to discharge (both median 3 days [IQR, 1–7], $P=0.11$) was similar. Total duration of admission did not differ between patients in the NT-proBNP-guided compared to the conventional therapy group (both groups a median of 9 days [IQR, 6–15], $P=0.84$; and both groups a mean of 12 days±10, $P=0.9$).

Patients in the NT-proBNP-guided therapy group who failed to attain 30% NT-proBNP reduction at randomization had a significantly longer duration of admission (median of 11 days [IQR, 8–17 days]) compared with patients in the NT-proBNP-guided group who attained that target at randomization (median of 8 [IQR, 6–13] days, $P<0.001$) and compared with patients in the conventional therapy group (median of 9 [IQR, 6–15] days, $P=0.01$). There was no significant difference in duration of admission between conventionally treated patients who failed to attain an NT-proBNP reduction of 30% compared to those attaining a reduction >30% at randomization (respectively, 9 days [IQR, 6–14] versus 9 days [IQR, 6–15], $P=0.74$).

In patients in the NT-proBNP-guided group, we observed that a longer hospital stay after randomization (≥3 days after admission) was associated with a larger NT-proBNP reduction after randomization. This relationship was not present in patients in the conventional therapy group (Table IV in the online-only Data Supplement).

Outcomes

All-cause mortality or readmission for HF ≤180 days after randomization occurred in 72 patients (36%) in the NT-proBNP-guided group and in 73 patients (36%) in the conventional therapy group (HR for NT-proBNP-guided therapy, 0.96; 95% CI, 0.72–1.37; $P=0.99$) (Figure 2). Patients in the NT-proBNP-guided and conventional therapy groups were alive outside of the hospital a median of 178 (IQR, 153–180 and 179 (IQR, 160–180) days, respectively ($P=0.39$).

For the secondary end points, readmission for HF ≤180 days occurred in 49 patients (24%) in the NT-proBNP-guided therapy group and in 53 patients (26%) in the conventional therapy group (HR for NT-proBNP-guided therapy, 0.93; 95% CI, 0.63–1.38; $P=0.73$) (Figure IA in the online-only Data Supplement). All-cause mortality ≤180 days after randomization occurred in 39 (19%) and 35 (17%) of patients, respectively (HR for NT-proBNP-guided therapy, 1.12; 95% CI, 0.71–1.77; $P=0.63$) (Figure IB in the online-only Data Supplement).

Across all predefined subgroups, a consistently neutral treatment effect was observed for the first primary end point, except for sex, which showed a significant interaction (Figure 3).

Post Hoc Analyses

In the patients assigned to NT-proBNP-guided therapy, we analyzed event rates and NT-proBNP reduction percentages in subgroups of patients who were (1) successfully guided (from a reduction of ≤30% at randomization to >30% at discharge), (2) unsuccessfully guided (still ≤30% reduction at discharge), and (3) nonguided (including those patients randomized to NT-proBNP-guided therapy who attained >30% NT-proBNP reduction at randomization and remained at this level at discharge) (Figure 4). Event rates were significantly lower in nonguided patients compared with patients who needed guidance, and successfully guided patients had lower (although not statistically significant) event rates compared with unsuccessfully guided patients. Differences in event rates were reflected by differences in NT-proBNP reduction percentages: nonguided patients had a significantly larger reduction in NT-proBNP levels (from admission to discharge) compared with successfully and unsuccessfully guided patients (Figure 4).

In patients with an NT-proBNP reduction of ≤30% at randomization, there was no significant difference in event rate between patients randomized to the NT-proBNP-guided compared to the conventional therapy group (49% versus 55%, $P=0.5$; HR, 0.8, 95% CI, 0.5–1.3; $P=0.3$).

DISCUSSION

In our study involving patients with both de novo and acute-on-chronic ADHF, NT-proBNP-guided therapy

Table 4. Prescription of Heart Failure Therapy From Randomization to Discharge in Different Study Groups

	NT-proBNP (All LVEF %)	Conventional (All LVEF %)	*P* Value	NT-proBNP (LVEF <40%)	Conventional (LVEF <40%)	*P* Value
ACE inhibitor or ARB						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5	0.4 (0.3–0.7)	0.5 (0.3–0.7)	0.8
Randomization	0.3 (0.3–0.5)	0.5 (0.3–0.5)	0.2	0.3 (0.3–0.5)	0.5 (0.3–0.7)	0.08
Discharge	0.3 (0.3–0.5)	0.5 (0.3–0.5)	0.2	0.3 (0.3–0.5)	0.5 (0.3–0.6)	0.6
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	50 (25)	33 (16)	0.04	28 (26)	19 (21)	0.5
Stop or downtitration	30 (15)	37 (18)	0.4	15 (14)	20 (22)	0.2
No change in dosages	80 (40)	88 (44)	0.5	48 (44)	41 (45)	1.0
No ACE inhibitor/ARB at randomization and discharge	38 (19)	43 (21)	0.6	18 (17)	12 (13)	0.6
β-Blocker						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.3–0.5)	0.4 (0.3–0.5)	0.3	0.4 (0.3–0.5)	0.3 (0.3–0.5)	0.2
Randomization	0.4 (0.3–0.5)	0.3 (0.3–0.5)	0.3	0.3 (0.3–0.5)	0.3 (0.1–0.5)	0.3
Discharge	0.5 (0.3–0.5)	0.4 (0.3–0.5)	0.3	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.5
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	47 (24)	50 (25)	0.8	31 (28)	31 (34)	0.4
Stop or downtitration	33 (17)	26 (13)	0.3	18 (17)	6 (7)	0.03
No change in dosages	78 (39)	97 (48)	0.09	42 (39)	42 (46)	0.3
No ACE inhibitor/ARB at randomization and discharge	40 (20)	28 (14)	0.1	18 (17)	13 (14)	0.7
Mineralocorticoid receptor antagonist						
Proportion of target dose, median (IQR)						
Admission	0.5 (0.5–0.5)	0.5 (0.3–0.5)	0.3	0.5 (0.5–0.5)	0.5 (0.4–0.5)	0.7
Randomization	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.9	0.5 (0.5–0.5)	0.5 (0.4–0.5)	0.9
Discharge	0.5 (0.3–0.5)	0.5 (0.3–0.5)	0.8	0.5 (0.3–0.5)	0.5 (0.5–0.5)	0.4
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	26 (13)	32 (16)	0.5	14 (13)	16 (17)	0.4
Stop or downtitration	28 (14)	20 (10)	0.2	18 (17)	12 (13)	0.6
No change in dosages	71 (36)	80 (40)	0.5	43 (39)	41 (45)	0.5
No ACE inhibitor/ARB at randomization and discharge	72 (36)	69 (34)	0.7	33 (30)	23 (25)	0.4
Diuretics						
Proportion of target dose, median (IQR)						
Admission	40 (0–80)	40 (0–80)	0.8	40 (0–80)	40 (0–80)	0.8
Randomization	80 (40–143)	80 (40–125)	1.0	80 (40–160)	80 (40–125)	0.4
Discharge	80 (40–120)	80 (40–120)	1.0	80 (40–160)	80 (40–120)	0.5
Therapy changes between randomization and discharge, n (%)						
Initiation or uptitration	57 (29)	38 (19)	0.03	29 (27)	17 (19)	0.2
Stop or downtitration	48 (24)	58 (29)	0.3	23 (21)	28 (31)	0.1
No change in dosages	91 (46)	93 (47)	0.9	57 (52)	42 (46)	0.4
No ACE inhibitor/ARB at randomization and discharge	2 (1)	12 (6)	0.5	0 (0)	5 (5)	0.6
Coronary angiography, n (%)	21 (11)	24 (12)	0.8	NA	NA	NA
Electric cardioversion, n (%)	11 (6)	6 (3)	0.2	NA	NA	NA
Cardiac resynchronization therapy, n (%)	1 (1)	1 (1)	1.0	NA	NA	NA
ACE inhibitor/ARB, BB, and MRA initiated/uptitrated and intervention planned, n (%)	110 (56)	100 (50)	0.3	66 (61)	50 (54)	0.4
ACE inhibitor/ARB, BB, MRA, and diuretic initiated/uptitrated and intervention planned, n (%)	138 (70)	120 (60)	0.04	81 (74)	58 (63)	0.08

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NA, not available; and NT-proBNP, N-terminal pro-B-type natriuretic peptide. In-hospital deaths between randomization and discharge were excluded from these analyses (n=5). Proportion of target dose was calculated according to target doses in the ESC guidelines.[20]

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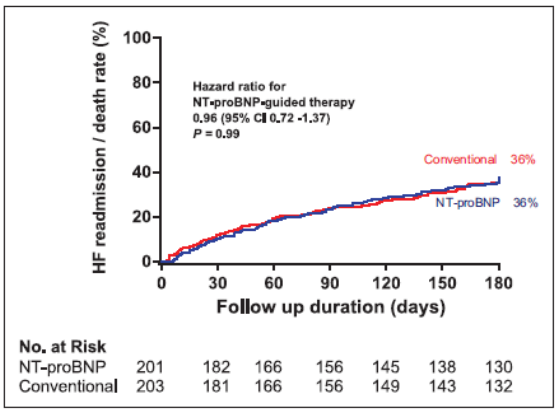


Figure 2. Kaplan–Meier curve for cumulative survival according to study group.
CI indicates confidence interval; HF, heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(targeting a reduction of >30% in NT-proBNP levels from admission to discharge) and conventional therapy demonstrated similar event rates for all-cause mortality and readmissions for HF within 180 days after randomization and a comparable number of days alive outside of the hospital within 180 days after discharge. This finding was despite a significantly higher percentage of patients achieving NT-proBNP target in the NT-proBNP-guided compared with the conventional group (80% versus 62%, *P*=0.001) and despite similar baseline NT-proBNP levels in both groups. The strength of our study is the focus on target NT-proBNP levels as discharge targets, in addition to using NT-proBNP levels as a selection criterion for patients at higher risk before guidance of therapy. Several explanations can be given for an apparent lack of benefit of guidance in our study.

First, the primary composite event rate of patients in the conventional therapy group was 36% and was much lower than the expected 50% event rate.[1–4] This finding was not caused by a difference in mortality rates between our and previous studies (18% versus 18%)[4] and therefore may be attributed to lower readmission rates in PRIMA II. A reduction in HF readmission rates by improvements in HF care may only partly explain the lower than expected readmission rates because mortality rates would also be expected to decrease with these efforts.[23] Another explanation for lower readmission rates may be the switch from readmission for cardiovascular reason as an end point in our preliminary calculations[4] to readmission for HF (in our trial).

Second, to explain why a demonstrable further reduction in NT-proBNP does not translate into a better outcome, one may argue that a longer duration of admission in the patients in the NT-proBNP-guided therapy group led to the desired drop in NT-proBNP, and it was not (solely) achieved by intensification of therapy. However, in contrast to patients in the NT-proBNP-guided therapy group selected to be guided from randomization (ie, with an NT-proBNP reduction of <30%

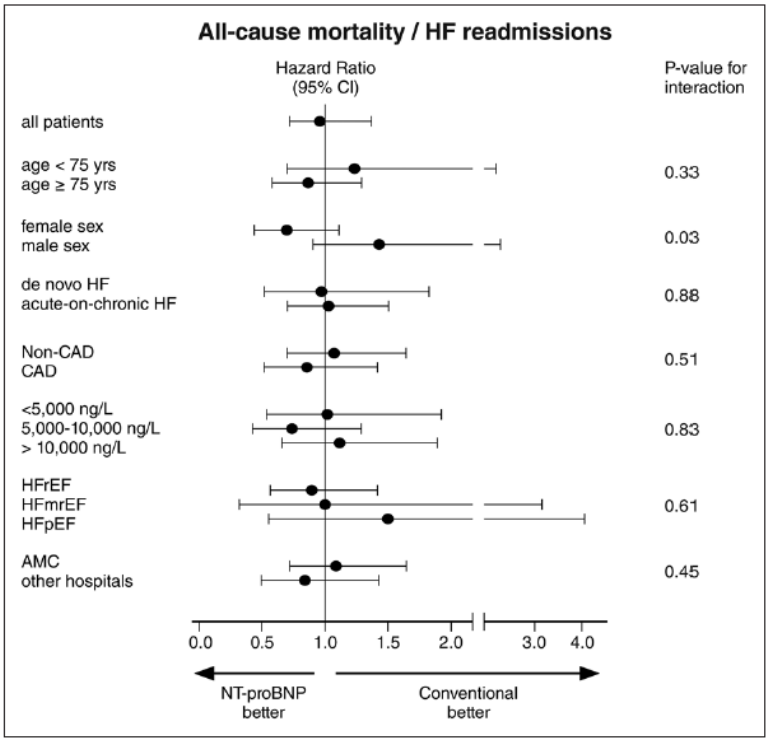


Figure 3. Subgroup analyses of primary end point.
AMC indicates Academic Medical Center; CAD, coronary artery disease; CI, confidence interval; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

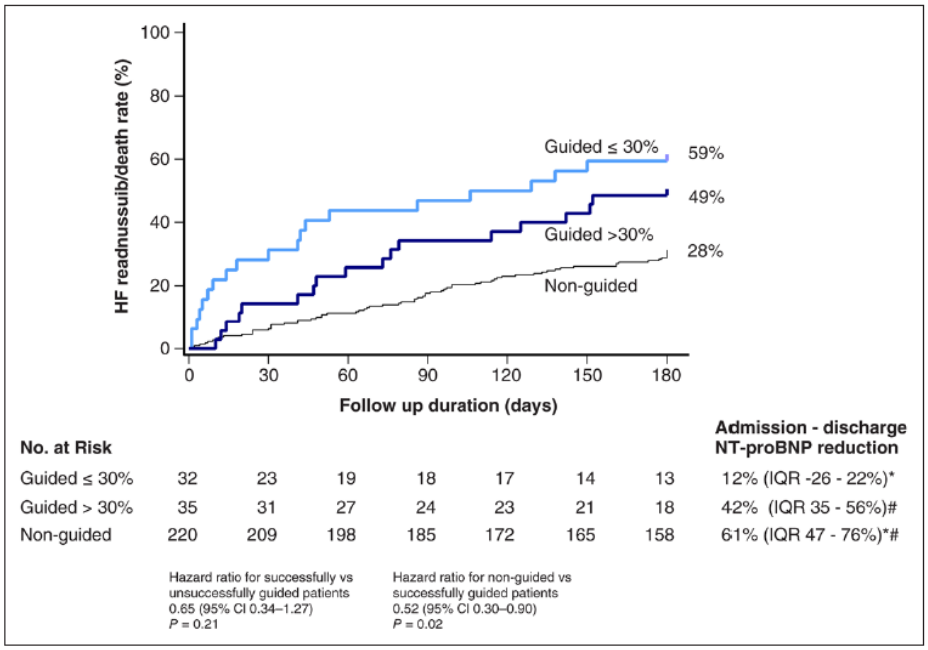


Figure 4. Kaplan–Meier curve for the primary end point for nonguided >30% NT-proBNP reduction, successfully guided, and unsuccessfully guided patients.
CI indicates confidence interval; HF, heart failure; IQR, interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.*Statistically significant difference with $P<0.001$ between nonguided and unsuccessfully guided patients. #Statistical significant difference with $P<0.001$ between nonguided and successfully guided patients.

at randomization), we did not observe a significantly greater percentage NT-proBNP reduction in conventional patients who also had a longer length of stay after randomization. Neither was this found in patients in the NT-proBNP-guided therapy group who already had a reduction of >30% at randomization and had a longer hospital stay. If a longer hospital stay would cause more patients to attain the NT-proBNP target of >30%, then we should have seen a relationship between length of stay and percentage NT-proBNP reduction in patients in nonguided NT-proBNP-guided and conventional therapy groups as well.

Third, although we accounted for an attainability of the NT-proBNP target of 90%, the attainability of 80% in the NT-proBNP-guided therapy group was still less than expected. Further study is needed to investigate why it was not possible to lower NT-proBNP levels in 20% of patients. When we correct the sample size to adjust for an attainability of 80%, we would have had to enroll 536 patients (2 x 268) to be able to detect an adapted relative risk reduction of 24% (ie, a reduction in primary end point from 50% to 38%). However, increasing the sample size to these numbers probably would not have led to a significant difference in outcome between patients in the NT-proBNP-guided versus conventionally treated groups because there were still other factors influencing the study outcome. One is the lower than expected primary event rate in the conventional therapy group (as mentioned earlier), and the other is our finding that a significantly smaller reduction in NT-proBNP was obtained in patients in the NT-proBNP-guided group who needed guidance compared with patients who achieved a >30% NT-proBNP reduction without guidance (Figure II in the online-only Data Supplement; respectively, a median NT-proBNP reduction from admission to discharge of 42% versus 61%). However, the latter were findings from our post hoc analyses and remain hypothesis-generating.

Implications for Future Research

In this study, we suggest that the outcome of patients who are successfully guided toward an NT-proBNP target of >30% reduction needs to be differentiated from the outcome of patients who attain an NT-proBNP reduction of >30% without guiding. Larger studies in selected high-risk patients (ie, with an NT-proBNP reduction of <30% at clinical stability) with sample sizes based on adapted event rates for patients in the intervention group are mandatory before we dismiss the idea of NT-proBNP guidance of therapy in patients with acute HF.

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Limitations

Some limitations to this study should be noted.

First, the criteria that we used for the definition of clinical stability are not evidence-based. To date, no clear, validated guidelines exist for what metrics should be used for adequate discharge of patients with ADHF. If by any rule, such a definition should be a composite of measures as previously suggested in the MEASURE-AHF study (An International, Prospective Registry to Evaluate the Evolution of Measures of Disease Severity in Acute Heart Failure).[24] Because our definition of clinical stability is not validated, it is possible that the moment of randomization slightly differed among patients, physicians, and hospitals.

Our criteria for clinical stability consisted of several measures reflecting (to some extent) clinical status and vital signs, but after this moment predischarge we did not collect data regarding clinical status, vital signs, or weight. As a measure of decongestion, we analyzed percentages of patients with hemoconcentration in both study groups at clinical stability and at discharge.[7,25] There was no difference in the percentage of patients with hemoconcentration, and percentages were comparable to percentages mentioned in previous publications.[7,25] Therefore, we believe that patients were equally decongested at clinical stability (randomization) and at discharge. However, it is possible that the continuing assessment of clinical signs of congestion after initial clinical stability would have helped physicians to make appropriate choices from the protocol. The possibility remains that patients again become congested between randomization and discharge.[26]

Second, although the study sites were contacted for therapy advice and physicians had to report reasons for not initiating or titrating HF medication for patients in the NT-proBNP-guided group who had an NT-proBNP reduction of <30% at randomization, the choice of which HF therapy to use was left to the treating physician. In addition, although ACE inhibitors, ARBs, and diuretics were more frequently initiated or titrated in patients in the NT-proBNP-guided therapy group, there were no differences in prescription rates and dosages at discharge between study groups. We cannot exclude the possibility that fewer than possible adjustments in therapy were made and that the changes in HF medication that were made during hospitalization were too small to result in significantly higher prescription rates and dosages at discharge.

Last, the relatively small number and exclusively European centers limit generalizability, and therefore the results of this study may not apply to countries with different healthcare systems. For example, it must be taken into account that the median length of stay in our study was 9 days, which differs from the length of stay in, for example, the United States (≈6 days).[27] In addition, because there is no evidence for NT-proBNP guidance after discharge, there were no study requirements for care after discharge (ie, care in all Dutch centers was delivered by a multidisciplinary HF team). Different care systems among countries may have resulted in different clinical outcomes among countries. However, differences in outcome were not detectable for patients in Dutch centers versus other European centers.

CONCLUSIONS

To our knowledge, this study is the first to evaluate the prognostic impact of NT-proBNP-guided therapy using an individualized selection target and discharge target in patients with ADHF. The PRIMA II demonstrates that guidance of HF therapy after clinical stability to increase the number of patients with an NT-proBNP target of >30% reduction in the present study did not improve outcomes.

ARTICLE INFORMATION

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Disclosures

Dr Ferreira reports receiving modest board fees from Novartis and modest speaker fees from Roche. Dr Marques reports receiving modest honoraria and

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Henry Ford Hospital

To serve the rapidly growing workforce and population in booming Detroit during the early 1900s, Henry Ford spearheaded the creation of a hospital, which first opened on October 1, 1915. From its inception, the mission of Henry Ford Hospital was to provide the best patient care, foster innovation through clinical research, and be a pillar in the community. This foundation was established by Drs Frank Sladen and Roy McClure, pupils of Sir William Osler and Dr William Halsted, respectively.

The hospital has provided innumerable contributions to the field of medicine and surgery, particularly in cardiovascular and cerebrovascular care. Dr Conrad Lam was the first physician to administer heparin to treat blood clots and also pioneered the creation of the heart-lung machine. In the 1990s, led by Drs KMA Welch and Barbara Tilley, the hospital was the lead coordinating center for the NINDS tPA trial. Most recently, Drs William O'Neill and Adam Greenbaum have pioneered techniques advancing the field of interventional cardiology. Currently, the hospital houses nearly 900 beds and boasts the largest number of intensive care unit beds in the state of Michigan.

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5.7. External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure

Salah K, Stienen S, Moons AHM, Bakx ALM, van Pol PE, Kortz RAM, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayes-Genis A, Pinto YM, Tijssen JG, Kok WE. J Am Heart Assoc. 2019;8:e010309. https://doi: 10. 1161/JAHA.118.010309 (original article)

My contribution to this work was as follows: I was the principal investigator of the PRIMA II study at my hospital, collected data and revised the manuscript. This article was included in the PhD thesis of Khibar Salah presented in November,2018 at the University of Amsterdam, the Netherlands. This is an open access publication, with no financial, legal or technical barriers to accessing it.

ORIGINAL RESEARCH

American Heart Association.

External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure

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***Background*—**Our aim was to calibrate and externally revalidate the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score, to confirm and improve on a previous external validation of the risk score.

***Methods and Results*—**The ELAN-HF score predicts 6-month all-cause mortality in patients hospitalized for acute decompensated heart failure using absolute and percentage change of NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels in addition to clinical variables. For the external validation, we used the PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial. For both data sets, observed versus predicted mortality was compared for the 4 risk categories; and the mean predicted mortality was plotted against the observed mortality with calculation of a correlation coefficient and SEE. The model discriminant ability was determined by comparing the C-statistics for both data sets. The predicted versus actual 6-month mortality values in the derivation cohort were 3.7% versus 3.6% for the low-risk category, 9.4% versus 9.2% for the intermediate-risk category, 24.2% versus 23.5% for the high-risk category, and 54.2% versus 51.1% for the very-high-risk category. The correlation between predicted and observed mortality by deciles was 0.92, with an SEE of ±4%. In the validation cohort, predicted versus actual 6-month mortality values were 3.0% versus 2.2% for the low-risk category, 9.4% versus 8.2% for the intermediate-risk category, 25.0% versus 22.9% for the high-risk category, and 56.8% versus 53.6% for the very-high-risk category. The correlation between predicted and actual mortality by quintiles was 0.99, with an SEE of ±2%. There was no significant difference in C-statistic between the derivation cohort (0.78; 95% CI, 0.74–0.82) and the validation cohort (0.77; 95% CI, 0.69–0.84; *P*=0.693).

Conclusions*—**Our study confirms that the ELAN-HF score predicts accurately 6-month mortality in patients hospitalized for acute decompensated heart failure with the use of easily obtained characteristics. (J Am Heart Assoc.* 2019;8:e010309. DOI: 10.1161/JAHA.118.010309.)**

Key Words: acute heart failure • external validation • NT-proBNP • prognosis • risk score

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Patients admitted for acute decompensated heart failure (ADHF) are diverse in age, type of heart disease, comorbidities, and patterns of disease progression, which creates important challenges in patient management.[1–4] A common denominator of treatment success is decongestion; however, decongestion is not the only prognostic factor,

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010309

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Clinical Perspective

What Is New?

- This external validation study of the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score confirms the excellent predictive proportional value of the risk score and shows that 6-month mortality increases with increasing score.

What Are the Clinical Implications?

- The ELAN-HF score is a statistically robust risk score predicting 6-month all-cause mortality in patients after hospitalization for acute decompensated heart failure, using NT-proBNP (N-terminal pro-B-type natriuretic peptide) values in addition to easily obtained clinical and laboratory characteristics, making it an easy to use and reliable bedside score to be used in the clinic practice.

and it is well established that patients with ADHF differ from one another substantially on their risk estimate.[5–7] A reliable risk stratification before discharge from the hospital may be used to further intensify therapies or intensify follow-up of those patients at higher risk and, in addition, provides extra information to the clinician as a performance measure.[7] To be usefully applied in the clinic, prognostic scores/models must be robust, simply applicable, and generalizable.

The ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score is such a bedside score, predicting 6-month all-cause mortality in patients after hospitalization for ADHF.[8] This easy-to-use score offers several promising applications for clinical use as it does not exclude any particular ADHF population.[8] The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America focused update of the 2013 guideline for heart failure recommends that "during a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis," for which the ELAN-HF score has been cited.[9]

The score has been validated previously in an external cohort,[10] which confirmed the predictive proportionality of the model.[8] However, in the original article, we did not calibrate the score and there were limitations about the validation cohort.[8] First, although discharge NT-proBNP (N-terminal pro-B-type natriuretic peptide) values were available in all patients, the NT-proBNP values at admission were not available; therefore, NT-proBNP values obtained 3 days before discharge were used as a proxy to calculate the change of NT-proBNP during hospitalization.[8,10] Second, assuming similar hazard ratios for NT-proBNP categories and other variables for shorter and longer follow-up durations, the follow-up duration of the validation cohort was extended to 1 year because of the small sample size, whereas the follow-up in the derivation cohort was 6 months after discharge.[8,10]

Therefore, the purpose of this study was to calibrate and revalidate the ELAN-HF score[8] in the recently published PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial cohort, a multicenter, international, randomized, controlled, 2-arm trial that aimed to study the effect of in-hospital guidance of ADHF treatment by a predefined NT-proBNP target.[11] Results of the PRIMA II trial were not different between the 2 treatment arms, and both treatment arms were included in the validation cohort.

Methods

Source/Study Populations

The ELAN-HF score was developed from 7 prospective cohorts of patients hospitalized for ADHF. The selection of the risk markers and construction of the model has been published previously.[8] Briefly, the score was developed using the multivariable Cox regression model, and variables were selected on the basis of the strongest predicting value for 6-month mortality after discharge. Thereafter, a simplified model was constructed by assigning weights to individual risk markers proportional to their regression coefficients.[8] The ELAN-HF score consisted of the following variables: absolute NT-proBNP levels at discharge of 1500 to 5000 pg/mL (1 point), 5001 to 15 000 pg/mL (3 points), and >15 000 pg/mL (4 points). Other risk markers (1 point each) were as follows: NT-proBNP reduction of ≤30% from admission to discharge, aged ≥75 years at admission, presence of peripheral edema at admission, systolic blood pressure ≤115 mm Hg at admission, hyponatremia (sodium <135 mmol/L) at admission, serum urea of ≥15 mmol/L at discharge, and New York Heart Association class III or IV at discharge. The risk groups were categorized in the following manner: low (≤2 points), intermediate (3–4 points), high (5–7 points), and very high (≥8 points).[8]

To perform an external validation, we used the cohort of the PRIMA II trial, an investigator-initiated, multicenter, randomized, prospective, 2-arm trial with either NT-proBNP–guided therapy or conventional therapy for patients with ADHF.[11] The design and study population and the primary outcomes of the trial were reported previously.[11,12] Briefly, patients admitted for ADHF (either de novo or acute-on-chronic HF) and with NT-proBNP levels of ≥1700 pg/mL measured within 24 hours of hospital admission were eligible for the PRIMA II trial.[11,12] From NT-proBNP measurements that were performed during hospitalization, we used only

admission and discharge NT-proBNP measurements. Follow-up visits for event registration were performed after discharge at 1 week and at 1, 3, and 6 months, where event registration was performed. The primary end point was a composite end point of all-cause mortality and readmission for HF at 6 months.[11,12] Results of the PRIMA-II trial were not different between the 2 treatment arms, and both treatment arms were included in the validation cohort.

Both trials (ELAN-HF and PRIMA-II) were approved by the institutional review committees in their respective centers, and all subjects gave informed consent.[8,11,12] The data that support the findings of this study are available from the corresponding author to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request, ensuring data deidentification.

Statistical Analysis

The primary end point for model calibration and discrimination was all-cause mortality at 6 months. Demographic characteristics were published previously.[8,11] We compared the baseline demographics and clinical characteristics between the derivation and validation cohorts using the Fisher exact test to make a comparison for categorical data and the independent *t* test to make a comparison for normally distributed continuous variables; the independent-sample Mann-Whitney *U* test was used to make a comparison for all other continuous variables. The distribution of ELAN-HF score predictors in the derivation and validation data sets is presented as frequencies and percentages.

To assess the discriminatory accuracy of our model, we calculated 6-month mortality in the validation cohort (PRIMA II) by the Kaplan-Meier method (Kaplan-Meier curves) with log-rank test for each of the 4 categories of the ELAN-HF risk score. To calculate the ELAN-HF score, each variable in the multivariate model was multiplied by its regression coefficient[8]; and the products were summed and prospectively applied to each patient in both the derivation cohort as well as in the validation cohort to provide individual estimates of survival at 6 months.[13,14]

First, the baseline survival function (B_0) was estimated at the observed time of 6 months in the derivation cohort (B_0=0.983). For a given value of the ELAN-HF score, we calculated the predicted mortality function (M_{pred}) in the derivation and validation data sets by the following equation[13]: $M_{pred}(t)=1-[B_0(t)^{exp(ELAN\text{-}HF)}]$.

Thereafter, calibration was assessed by calculating the actual mortality using Kaplan-Meier curves and the expected mortality in each risk group by calculating the mean predicted mortality at 6 months over all members of each aforementioned risk group in both the derivation (ELAN-HF) and the validation (PRIMA II) cohorts. Moreover, to further asses the accuracy of the calibration of our model, we also plotted the mean predicted mortality against the observed mortality (Kaplan-Meier) by deciles of predicted mortality for the derivation cohort and by quintiles (because of the smaller sample size) of predicted mortality for the validation cohort.[14] Calibration was assessed by a correlation coefficient and SEE. The model discriminant ability was determined by the 6-month receiver-operating characteristic area under the curve for both data sets, using the categorized model. We used the method of Hanley and MacNeil to compare the C-statistics.[15]

To accommodate for the different cohorts, separate baseline hazard functions were used to adjust for between-study differences. For the multivariable model, we performed multiple imputation pooling algorithms (n=10) to correct for missing values using predictive mean matching. All patient, medical history, and treatment variables (including outcome variables) were used when creating the multiple imputation data sets. All probability values were 2 sided and considered significant if $P<0.05$. Statistical analyses were conducted using SPSS 24.0.0.0 (SPSS IBM, New York, NY).

Results

Demographic Characteristics

The detailed demographics table for both the derivation cohort as well as for the validation cohort has been reported previously in the original articles.[8,11] Briefly (Table S1), the patients in the PRIMA II (validation) cohort were older than those in the ELAN-HF (derivation) cohort (77 versus 74 years; $P<0.001$), with more female patients (51% versus 40%; $P<0.001$) and patients more frequently with hypertension (64% versus 51%; $P<0.001$), peripheral edema (73% versus 62%; $P<0.001$), and a higher mean systolic blood pressure at admission (137 versus 133 mm Hg; $P=0.028$) and fewer patients admitted with New York Heart Association class III/IV (79% versus 96%; $P<0.001$). For routine laboratory measurements, patients in the validation cohort had significantly lower mean levels of urea nitrogen at admission (12 versus 13 mmol/L; $P=0.024$), lower serum sodium levels at admission (138 versus 139 mmol/L; $P=0.005$), and lower estimated glomerular filtration rate levels at admission (52 versus 57 mL/min per 1.73 m^2; $P=0.002$). There was no significant difference between validation and derivation cohorts for median NT-proBNP level at admission (6182 versus 6447 pg/mL; $P=0.433$) as well as at discharge (2910 versus 3252 pg/mL; $P=0.096$). The median NT-proBNP reduction percentage during hospitalization was significantly higher for the validation cohort compared with the derivation cohort (47% versus 43%; $P=0.007$). At discharge, significantly fewer patients in the validation cohort received diuretics compared with patients in the derivation cohort (92% versus

95%; P=0.010), but more patients received β blockers (75% versus 57%; P<0.001).

The Distribution Predictors

The distribution of the predictors between the derivation and validation cohorts is shown in Table 1. The distributions happen to be broadly similar between the derivation and validation data sets, although this is not a requirement for successful validation.[13]

Adverse Events

In both studies, no patients were lost to follow-up, and follow-up data were 100% complete. In the PRIMA II trial, 74 died of any cause within 6 months, which was equal to an all-cause mortality of 18%. In the ELAN-HF trial, 195 died of any cause within 6 months, which was equal to an all-cause mortality of 15% (P=0.118).

Calibration and Validation of the ELAN-HF Score

Figure 1 shows Kaplan-Meier curves for 6-month all-cause mortality in the validation cohort, according to the 4 risk groups. The figure shows that the curves are increasing significantly in a stepwise manner across the risk groups, confirming our earlier conclusion that the model has excellent discriminatory ability.[8] The predicted and observed mortality rates in the derivation and the validation cohorts are presented in tabular (Table 2) form for the 4 risk groups. The stepwise increase in all-cause mortality for the 4 risk groups for the derivation cohort increased with a rate of 3.6%

Table 1. Distribution of Predictors in the Derivation and Validation Data Sets

Predictors	ELAN-HF Cohort		PRIMA II Cohort		*P* Value
NT-proBNP value at discharge, pg/mL					0.509
1500–5000	471	(37)	171	(48)	
5001–15 000	334	(26)	80	(22)	
>15 000	132	(10)	27	(8)	
NT-proBNP reduction ≤30%	494	(39)	102	(29)	<0.001
Aged ≥75 y at admission	575	(44)	244	(60)	<0.001
Peripheral edema at admission	674	(62)	285	(73)	<0.001
Systolic blood pressure ≤115 mm Hg at admission	411	(32)	103	(26)	0.018
Hyponatremia (sodium <135 mmol/L) at admission	204	(17)	77	(19)	0.287
Serum urea ≥15 mmol/L at discharge	377	(33)	78	(25)	0.019
NYHA class III/IV at discharge	216	(18)	81	(21)	0.215

Data are given as number (percentage) of each group. ELAN-HF indicates European Collaboration on Acute Decompensated Heart Failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PRIMA II, Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

Table 2. Observed Mortality and Expected Mortality in the Derivation (ELAN-HF) and Validation (PRIMA II) Cohorts

Demographics	ELAN-HF Cohort		PRIMA II Cohort	
Follow-up, d	180		180	
Death, n (%)	195 (15)		74 (18)	
Risk Categories	Actual, %	Predicted, %	Actual, %	Predicted, %
Low (≤2)	3.6	3.7	2.2	3.0
Intermediate (3–4)	9.2	9.4	8.2	9.4
High (5–7)	23.5	24.2	22.9	25.0
Very high (≥8)	51.1	54.2	53.6	56.8

ELAN-HF indicates European Collaboration on Acute Decompensated Heart Failure; PRIMA II, Can NT-proBNP (N-terminal Pro-B-Type Natriuretic Peptide)–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

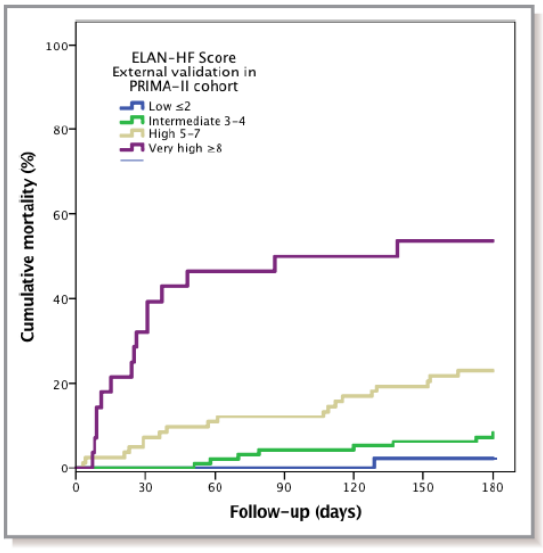


Figure 1. Kaplan-Meier curve of ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score in the external validation (PRIMA II [Can NT-proBNP {N-terminal Pro-B-Type Natriuretic Peptide}-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?]) cohort.

for the low-risk patients, 9.2% for the patients with an intermediate risk, 23.5% for the patients with a high risk, and 51.1% for the very-high-risk patients.[8] This was in complete agreement with the results in the validation cohort, after the ELAN-HF model was applied prospectively to the validation cohort, with mortality rates in the 4 risk categories of 2.2%, 8.2%, 22.9%, and 53.6%, respectively.

In the derivation cohort, the predicted 6-month mortality rates, according to the risk categories, were 3.6% for the low-risk category, 9.4% for the intermediate-risk category, 24.2% for the high-risk category, and 54.2% for the very-high-risk category; there was a correlation coefficient of 0.92, with a SEE of ±4%, between predicted and observed mortality by decile (Figure 2). In the validation cohort, predicted 6-month mortality rates, according to the risk categories, were 3.0%, 9.4%, 25.0%, and 56.8%, respectively; there was a correlation coefficient of 0.99, with a SEE of ±2%, between predicted and observed mortality by quintiles.

ELAN-HF Score Discriminant Ability

Table 3 shows the 6-month receiver-operating characteristic for the derivation cohort was 0.78 (95% CI, 0.74–0.82). In the validation cohort, the 6-month receiver-operating characteristic was 0.77 (95% CI, 0.69–0.84), not different from the C-statistic of the derivation cohort (P=0.693).

Discussion

The ELAN-HF score is a bedside score predicting 6-month all-cause mortality in patients after hospitalization for ADHF, for patients with both preserved ejection fraction and reduced ejection fraction, with a wide range of heart failure symptoms at discharge (New York Heart Association class I to IV).[8] The ELAN-HF score was previously validated in an external cohort.[8,10] However, because of limitations of the validation data set, we set out to calibrate and revalidate the ELAN-HF score prospectively in the PRIMA II cohort.[11] Our data show that the score is statistically robust in that both the calibration and external validity of the risk score were confirmed in the validation cohort using 4 risk categories. The model shows an excellent predictive proportional value and confirms the increasing 6-month mortality with increasing score using NT-proBNP values in addition to easily obtained clinical and laboratory characteristics.

Revalidating the ELAN-HF Score

External validation is a crucial step toward acceptance of a risk score into clinical practice. If a prognostic model predicts outcome well on a derivation cohort, but weakly on an independent cohort, it is clearly not fit for use. There are 2 fundamental aspects of validating model performance: discrimination and calibration.[13] Discrimination is the ability

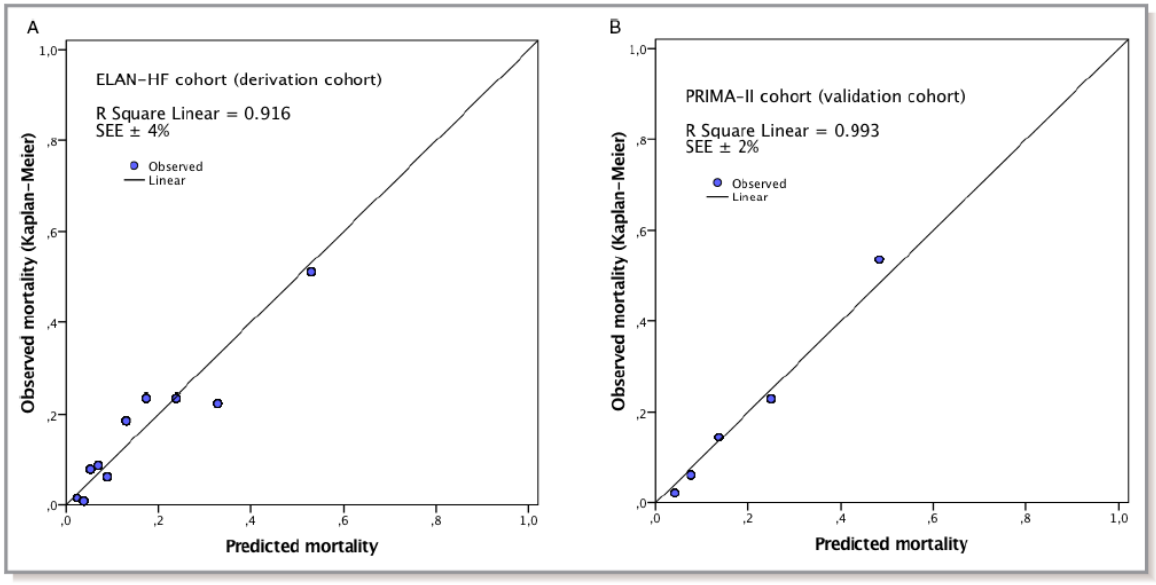


Figure 2. Calibration plots of mean predicted mortality vs observed mortality (Kaplan-Meier) by deciles of predicted mortality for the derivation cohort (ELAN-HF [European Collaboration on Acute Decompensated Heart Failure] cohort; **A**) and by quintiles of predicted mortality for the validation cohort (PRIMA II [Can NT-proBNP {N-terminal Pro-B-Type Natriuretic Peptide}-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?] cohort; **B**).

Table 3. Comparison of C-Statistics Between the Derivation (ELAN-HF) Cohort and the Validation (PRIMA II) Cohort

	C-Statistic for the Simplified ELAN-HF Score	
Cohort	AUC (95% CI)	*P* Value*
ELAN-HF	0.78 (0.74–0.82)	0.693
PRIMA II	0.77 (0.69–0.84)	. . .

AUC indicates area under the curve; ELAN-HF, European Collaboration on Acute Decompensated Heart Failure; PRIMA II, Can NT-proBNP (N-terminal Pro-B-Type Natriuretic Peptide)–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?
*AUCs were compared using the method of Hanley and MacNeil.[15]

of a model to predict that patients at higher risk should exhibit higher event rates than those at lower risk. Calibration reflects the prediction accuracy, where the correct event probability is assigned at all levels of predicted risk, without underpredicting or overpredicting the event probability.[13] The ELAN-HF score performs excellent on both departments. The model shows an excellent discriminative proportional value and confirms the increasing 6-month mortality with increasing score. Furthermore, our data showed that the calibration is excellent for the 4 risk categories for both data sets. The observed and predicted all-cause mortality rates in the 2 data sets are almost identical, reflecting the similarity in the distributions of the ELAN-HF score in each risk group across the data sets. In our previous study,[8] we only performed the external validation with level 2 information available.[13] With this study, we were able to externally validate the risk score with level 3 information available,[13] which shows that it is a reliable risk score to be used in the clinic practice.

Discriminative Ability

The risk score performed as well in the derivation cohort (ELAN-HF) as in the validation cohort (PRIMA II), as evidenced by the C-statistics. There was no difference between the C-statistics, with values of the C-statistic of 0.76 (95% CI, 0.71–0.80) and 0.77 (95% CI, 0.69–0.84) for the derivation and validation cohorts, respectively. The strength of the ELAN-HF model is its broad applicability and its easy calculation. Moreover, variables in the model can be easily ascertained when a patient has been hospitalized for ADHF.

Other Risk-Predicting Models for Patients With ADHF, Using Natriuretic Peptide Levels

The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) study showed that a model using clinical variables plus discharge BNP appropriately reclassifies risk in tertiles of 1-year mortality in a mixed population of patients with ADHF, aged ≥65 years, and improves discrimination compared with a model with clinical variables alone, with a final C-statistic of 0.69.[16] Calibration of the model was done; however, the model was not externally validated.[16] ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) was used to derive a clinical model, including natriuretic peptides (BNP) at discharge, with a C-index of 0.76 for predicting 6-month mortality.[17] The patient population consisted of patients with severe left systolic heart failure. The model was externally validated with clinical variables only, although BNP levels were the most important prognostic variable.[17] The COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) risk engine was previously published, using clinical and laboratory variables and discharge NT-proBNP levels, in a mixed population with ADHF, similar to our populations with ADHF. From a multistate model, the COACH risk engine predicts 18-month mortality and/or hospital readmissions for heart failure.[18] Their C-index for mortality was 0.73 in the derivation cohort and (with 48-hour NT-proBNP levels in place of discharge levels) was 0.70 in the validation cohort.[18] The prediction is for 18 months, which may make it less useful for earlier assessments, as risk weans off with time and other risk predictors may come into play. The program can be downloaded from the internet, which makes its clinical use more convenient. The ADHF/NT-proBNP risk score for 1-year mortality, heart transplantation, or left ventricular assist device implantation, in patients with ADHF with left ventricular ejection fraction ≤40% well treated with an implantable cardioverter defibrillator and a cardiac resynchronization therapy defibrillator, performs well, with a C-statistic of 0.84 in the derivation cohort and 0.77 in the validation cohort.[19] Apart from its selected population, a critique may be the use of admission NT-proBNP levels, which have lower predictive ability than discharge NT-proBNP levels, although their contribution to the final risk assessment was high in this particular score.[19] The more recent risk models, such as the BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure), include patients after discharge as well as patients at the outpatient clinic, necessitating the incorporation of having been hospitalized for heart failure as an added risk variable, which was also externally validated.[20] However, the C-statistic for the compact model was lower compared with the C-statistic of our simple bedside model (0.69 versus 0.76), possibly because of the interference of the outpatient population.

Limitations

The derivation cohort was an individual patient data analysis of 7 cohorts, which was conceived after publication of the

original studies.[8] Apart from some variation in NT-proBNP assays used, treatment and inclusion criteria in the different centers should be considered. Nevertheless, the range in markers and therapeutic approach of patients, as observed, reflects the day-to-day clinical practice. Missing data should be considered as a limitation in our study. However, we did correct for the bias from data missing at random by using multiple imputation pooling algorithms. Furthermore, the use of all-cause mortality instead of cardiovascular mortality as the primary outcome is a limitation. It is, however, clear that cardiovascular mortality explains 63% to 87% of mortality after ADHF.[21,22]

Conclusions

External validation of the ELAN-HF risk score in the PRIMA II cohort confirms its excellent accuracy and discriminative ability. The score allows accurate prediction of 6-month mortality of patients hospitalized for ADHF with the use of easily obtained clinical and laboratory characteristics, including absolute natriuretic peptide levels at discharge and a relative change in natriuretic peptide of ≤30% from admission values. The risk stratification, as predicted in our bedside model, is in complete agreement with that in the external validation cohort, which shows that it is a reliable score to be used in the clinic practice.

Author Contributions

Drs Salah and Kok had the idea for the project, designed the collaborative analysis, and undertook searches of published work. Drs Salah and Stienen collected the individual patient data and prepared for analysis. Statistical analysis and elaboration of figures was done by Drs Salah, Kok, and Tijssen. Dr Salah wrote the article, with important contribution from Drs Kok and Tijssen and input from Drs Pinto, Stienen, Ferreira, and Moons, who provided valuable comments on the article. All coauthors had an opportunity to contribute to the interpretation of results and to the redrafting of the article. All authors reviewed and revised the article and approved the final version.

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Disclosures

Pinto received research funding for their original study from the Dutch Heart Foundation, Dutch Organization for Scientific Research, the Royal Dutch Academy of Arts and Sciences–Interuniversity Cardiology Institute of the Netherlands, Pfizer, Astra-Zeneca, Medtronic, and Roche Diagnostics. Dr Pinto is a recipient of payments for lectures, including service on speakers' bureaus, and research grants from Roche Diagnostics. Dr Pinto has an unrelated biomarker patent and stocks in a university spinoff company. Dr Kok received a grant from the Dutch Heart Foundation for the PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial (grant 2010B97) and has participated in advisory board meetings of Roche Diagnostics and Novartis. Dr Ferreira reports receiving modest board fees from Novartis and modest speaker fees from Roche Diagnostics. Dr Marques reports receiving modest honoraria and expert witness fees. Dr Bayes-Genis reports receiving significant research grants, significant research support, and modest honoraria from Roche Diagnostics. The remaining authors have no disclosures to report.

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Table S1. Baseline demographics.

	ELAN-HF cohort N=1301	PRIMA II cohort N=404
Variables		
Age, years, median (IQR)	74 (64-80)	77 (69-85)
Male sex, n (%)	775 (60)	198 (49)
History of DM, n (%)	422 (33)	138 (34)
History of Hypertension, n (%)	661 (51)	254 (64)
History of COPD, n (%)	209 (18)	79 (20)
Ischemic etiology, n (%)	631 (51)	102 (43)
LVEF, %, mean ± SD	35 ± 16	36 ± 15
JVP distended at admission, n (%)	635 (62)	142 (57)
Pulmonary rales at admission, n (%)	821 (76)	302 (77)
Peripheral edema at admission, n (%)	674 (62)	285 (73)
SBP at admission, mmHg, median (IQR)	133 ± 32	137 ± 30
DBP at admission, mmHg, mean ± SD	81 ± 20	81 ± 22
Heart rate at admission, bpm, mean ± SD	93 ± 25	94 ± 28
Atrial fibrillation (AF) at admission, n (%)	513 (43)	154 (39)
NYHA class at admission, n (%)		
I/II	48 (4)	81 (21)
III/ IV	1134 (96)	310 (79)
Laboratory findings, mean ± SD		
Hemoglobin at admission, mmol/L	7.9 ± 1.3	7.7 ± 1.2
Serum urea nitrogen at admission, mmol/l	13 ± 7.8	12 ± 6.8
Serum sodium at admission, mmol/l	139 ± 4.8	138 ± 4.8
eGFR at admission, ml/min/1.73m²	57 ± 33	52 ± 25
NT-proBNP at admission, pg/ml, median (IQR)	6447 (3057-12632)	6182 (3945-11146)
NT-proBNP at discharge, pg/ml, median (IQR)	3252 (1419-7291)	2910 (1643-5779)
NT-proBNP reduction during hospitalization, median (IQR)	43 (13-67)	47 (22-66)
Duration admission, days, median (IQR)	9 (6-14)	9 (6-15)

Medication at discharge, n (%)		
Diuretics	1156 (95)	370 (92)
ACE-inhibitors or ARB	806 (66)	287 (71)
Beta-blocker	685 (57)	304 (75)

5.8. Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study

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Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study

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Introduction: Heart failure (HF) is the leading cause of hospitalization in the elderly in developed countries and significantly impacts public health expenditures. Patients with HF usually have associated comorbidities that require multidisciplinary management. This study aims to demonstrate the benefits of a multidisciplinary clinic in reducing all-cause hospitalizations and HF events (HF hospitalizations and urgent HF visits) in a real-world setting. Finally, the study evaluates the associated costs of HF events.

Methods: This observational study included patients admitted to GEstIC, a multidisciplinary Portuguese HF clinic, from January 2013 to February 2019, who had one-year follow-up. Hospitalizations and HF events, total days spent in the hospital during HF hospitalizations, and HF events-related costs, in the year before and the year after GEstIC admission, were compared.

Results: Of the 487 patients admitted to the GEstIC, 287 were eligible for the study sample. After one year of HF patients' multidisciplinary management at GEstIC, there was a 53.7% reduction in all-cause hospitalizations (462 vs. 214), a 71.7% reduction in HF hospitalizations (392 vs. 111), and a 39.1% reduction in urgent HF visits (87 vs. 53). As a result, there was a significant decrease of 12.6 days in the length of hospital stay due to HF per patient (15.6 vs. 3.0, $p < 0.001$). This translated into the release of 9.9 hospital beds in the year following admission to GEstIC. The average total savings associated with the reduction of HF events was €5,439.77 per patient (6,774.15 vs. 1,334.38, $p < 0.001$), representing a total cost reduction of €1,561,213. Furthermore, the significant reduction in the number of all events was independent of the patient's left ventricular ejection fraction (LVEF).

Discussion: Significant reductions in all-cause and HF hospitalizations and urgent HF visits were observed with the implementation of this multidisciplinary clinic for HF patients' management. This was particularly important for patients with LVEF >40%. Before GEstIC, there was no medical intervention to improve the prognosis of these patients. The reduction of over one million euros in health-related costs after only one year of person-centered multidisciplinary management highlights the need to replicate this approach in other national healthcare institutions.

KEYWORDS

heart failure events, multidisciplinary management, heart failure clinic, hospitalization, urgent heart failure visit, healthcare utilization

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1. Introduction

Heart failure (HF) is the cardiovascular pandemic, affecting more than 60 million people worldwide, and is associated with significant morbidity and mortality (1). It is currently the leading cause of hospitalization in the elderly (>65 years) and a major cause of emergency hospital admissions (2, 3). In Portugal, there were 18,752 hospitalizations and 2,327 deaths for HF in 2016 (4). The in-hospital mortality rate, in 2014, was 12.5% (5). By 2035, the number of HF patients is expected to increase by 30%, mainly due to the aging of the population (6). Globally, HF represents a total economic burden of approximately $108 billion per year (7, 8). In Portugal, the total cost associated with HF reached €405 million in 2014, accounting for an economic burden of 2.6% of the public health expenditure (9).

Clinically, HF is often connected with a group of comorbidities, such as hypertension, diabetes, chronic kidney disease (CKD), atrial fibrillation, chronic obstructive pulmonary disease (COPD), cognitive dysfunction, anemia, and iron deficiency (10, 11). These conditions and their associated treatments may not only contribute to the progression of HF but also influence patients' response to treatment, thereby affecting their prognosis and quality of life (12). Thus, management and improvement of the associated comorbidities are crucial.

To address the complexity of HF patients' management, most guidelines from cardiology societies advocate that patient care should be provided in a multidisciplinary manner, namely by establishing multidisciplinary clinics (2, 3, 13, 14). These clinics should be staffed by specialist physicians, nurses, pharmacists, nutritionists, psychologists, physiotherapists, and social workers, among others, so that they can guarantee adequate treatment and psychological support to patients while educating them about their disease (2, 3, 15–17). Managing HF patients through this multidisciplinary approach has been shown to reduce the mortality and number of HF hospitalizations while improving patients' quality of life and reducing HF-associated healthcare costs (17, 18).

The multidisciplinary HF clinic GEstIC (*Grupo de Estudo da Insuficiência Cardíaca*, meaning Heart Failure Study Group) was implemented at *Centro Hospitalar Universitário de Santo António* in 2013 and is composed of several healthcare professionals, including physicians from different specialties (internal medicine, cardiology, nephrology, psychiatry, physical medicine and rehabilitation and palliative care), nurses, a physiotherapist, a social worker, and a nutritionist. Most patients admitted to GEstIC proceed from the Internal Medicine Department after HF hospitalization and are managed according to a structured program, as per the guidelines of the cardiology societies for multidisciplinary clinics and HF management (2, 3, 16, 19). The GEstIC organization and HF management program was published previously (16). Briefly, like similar HF clinics, GEstIC has a comprehensive and multidisciplinary approach consisting of structured follow-up, patient education, therapy optimization, psychological support, and efficient access to healthcare. Patients are identified through electronic medical records after hospitalization for HF and, upon discharge, a GEstIC nurse initiates contact, providing education and a direct line to the team. The program encourages self-management and healthy habits and instruct patients and caregivers to notify the team of worsening symptoms. Regular patient monitoring includes hospital visits and evaluation of laboratory values, patient-reported outcomes, and tests such as the 6-Minute Walking Test. Notably, GEstIC also collaborates with a cardiac rehabilitation unit, allowing eligible patients to access tailored rehabilitation programs. The main aim of this study was to characterize the impact of the GEstIC multidisciplinary clinic on the improvement of specific healthcare indicators, namely the number of all-cause hospitalizations, HF events (hospitalizations and urgent visits), as well as their associated costs, in a Portuguese public hospital. With this work, it is expected that policymakers and other healthcare organizations will recognize the benefits of this model of care and promote the implementation of similar solutions in other units. Ultimately, this will contribute to the improvement of the quality and sustainability of the national healthcare system.

2. Materials and methods

2.1. Study design and study population

This single-center, observational, retrospective study included all patients admitted to the GEstIC clinic at *Centro Hospitalar Universitário de Santo António*, a university hospital in Porto, between January 1, 2013, and February 28, 2019, with at least one year of follow-up. The COVID-19 pandemic period was excluded; in Portugal, first COVID-19 patient was diagnosed in March 2020. To be admitted to GEstIC, patients had to be 18 years of age or older and either be recently hospitalized for HF or have history of previous HF hospitalization or frequent urgent HF visits. Exclusion criteria included complete dependence on caregivers for activities of daily living and inability to communicate. The study protocol was approved by the local ethics committee and institutional review boards.

2.2. Study outcomes

The primary outcome of this study was to evaluate the impact of GEstIC on all-cause hospitalizations and HF events. The latter includes HF hospitalizations and urgent HF visits. An HF hospitalization was defined as an event in which the patient is admitted to the hospital for at least 24 h with a primary diagnosis of HF (new or worsening symptoms of HF on presentation and objective evidence of new or worsening HF by physical examination and/or laboratory criteria) and initiates or intensifies HF treatment. An urgent HF visit was defined as an emergency department visit with a primary diagnosis of HF, receiving intravenous diuretics, but does not meet the criteria for HF hospitalization.

The number of events and total days of HF hospitalization in the year before and the year after GEstIC admission were determined and compared. In addition, the impact of HF hospitalizations on the number of hospital beds released annually was estimated.

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The impact of the GEstIC multidisciplinary clinic on the total cost of HF events was calculated based on the number of events and number of days spent in the hospital due to HF, considering €428.55 as the average daily cost of one patient hospitalized in the Internal Medicine Department and €239.64 the average cost of one visit to the Emergency Department of *Centro Hospitalar Universitário de Santo António* (average costs were provided by the Health Information Management Department of the hospital).

2.3. Data collection

The number of all-cause hospitalizations, HF hospitalizations, urgent HF visits, and days hospitalized due to HF, during the year before and the year after the first GEstIC visit, were retrospectively collected from the clinical records and hospital databases. Data collected at the time of GEstIC admission included age, sex, HF etiology, presence and type of comorbidities, New York Heart Association (NYHA) class, N-terminal-pro-B type natriuretic peptide (NT-proBNP) levels, estimated glomerular filtration rate (eGFR), and left ventricular ejection fraction (LVEF) values. HF diagnosis and classification followed the Universal definition and classification of HF consensus statement (18).

2.4. Statistical analysis

Continuous variables were summarized using mean, standard deviation (SD), median, and 25th and 75th percentiles (P25 and P75). Absolute and relative frequencies were used for categorical variables. The number of events before and after first GEstIC admission was compared using the nonparametric Wilcoxon signed rank test with continuity correction for paired samples.

The correlation between the variation in the number of HF hospitalizations and LVEF values at GEstIC admission was assessed using the nonparametric Wilcoxon rank-sum test with continuity correction (Mann–Whitney) for independent samples.

Total savings from HF-associated hospitalizations and urgent visits were determined based on the average cost of each event per day provided by the Health Information Management Department, which was in place in 2021.

A 5% significance level was used. Statistical analysis was performed with R® software version 4.2.3 (Vienna, Austria).

3. Results

3.1. HF patients demographic and clinical characterization at GEstIC admission

A total of 487 patients were admitted to the GEstIC HF clinic between January 2013 and February 2019. Of these, 68 patients (14.0%) died within the first year and 132 (27.1%) did not complete a minimum of 365 days of follow-up. The remaining 287 patients (58.9%) met all inclusion criteria and constituted the study sample (Figure 1).

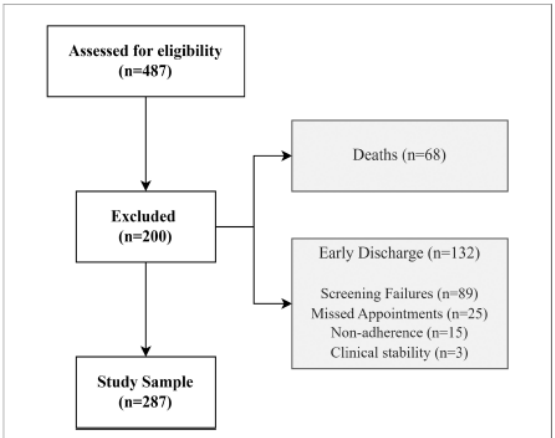


FIGURE 1
Flowchart of the study population.

The patients' demographic and clinical characteristics at the time of admission to GEstIC are shown in Table 1. The median age of the study participants was 77 years, and the majority were female (56.8%).

TABLE 1 Patients' demographic and clinical characteristics at GEstIC admission.

Characteristics	Value	*n* total
Age (years), median (P25; P75)	77 (68; 83)	287
Female, *n* (%)	163 (56.8)	287
Comorbidities		
Hypertension, *n* (%)	238 (82.9)	287
Iron deficiency, *n* (%)	96 (58.2)	165
CKD (eGFR <60 mL/min/1.73 m^2), *n* (%)	162 (56.4)	287
eGFR 30–59	134 (46.7)	
eGFR 15–29	26 (9.1)	
eGFR <15	2 (0.7)	
Anemia, *n* (%)	148 (51.7)	286
Diabetes *mellitus*, *n* (%)	156 (54.9)	284
Atrial flutter/fibrillation, *n* (%)	140 (48.8)	287
COPD, *n* (%)	72 (25.1)	287
Cognitive decline, *n* (%)	27 (9.4)	287
HF etiology, *n* (%)		287
Hypertensive	119 (41.5)	
Ischemic	109 (38.0)	
Valvular	97 (33.8)	
Others	83 (28.9)	
NYHA functional class, *n* (%)		278
I	43 (15.5)	
II	187 (67.3)	
III	46 (16.5)	
IV	2 (0.7)	
LVEF, *n* (%)		287
≤40%	119 (41.5)	
41–49%	29 (10.1)	
≥50%	139 (48.4)	
NT-proBNP (pg/mL), median (P25; P75)	2,135 (789; 4,719)	261

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated Glomerular Filtration Rate; HF, heart failure; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal-pro-B type natriuretic peptide; NYHA, New York Heart Association.

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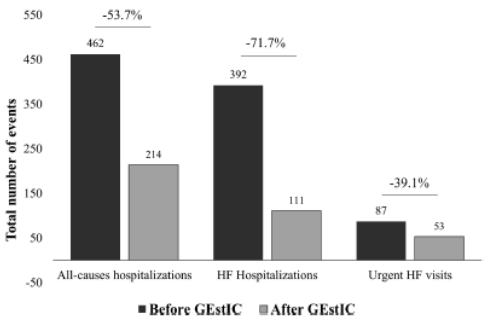


FIGURE 2
Number of events registered before and after GEstIC admission. Number of total all-cause hospitalizations, HF hospitalizations, and urgent HF visits registered for 287 HF patients one year before and one year after GEstIC first visit. *p*-values were determined using the Wilcoxon signed rank test with continuity correction.

In terms of HF etiology, patients were primarily diagnosed with hypertensive (41.5%), ischemic (38.0%), and/or valvular (33.8%) heart disease, of which the latter were further identified as having aortic (64.9%) and/or mitral (54.3%) valvular disease. Most patients had NYHA functional class II symptoms (67.3%). According to the Universal definition and classification of Heart Failure and the 2021 ESC HF Guidelines classification, 48.4% of the patients had preserved ejection fraction (LVEF ≥50%) and 41.5% presented reduced LVEF (≤40%). Laboratory analyses revealed a median NT-proBNP level of 2,135 pg/mL. Hypertension (82.9%), iron deficiency (58.2%), and CKD (56.4%) were the most frequent comorbidities. Atrial flutter or fibrillation was present in 48.8% of patients.

3.2. Number of hospitalizations and urgent HF visits

In the year before GEstIC admission, a total of 462 all-causes hospitalizations, 392 HF hospitalizations, and 87 urgent HF visits were registered. At the end of the first year of follow-up in GEstIC, the number of such events significantly decreased to 214 (−53.7%), 111 (−71.7%), and 53 (−39.1%), respectively (Figure 2).

For all-cause hospitalizations, the mean number of events per patient decreased significantly ($p < 0.001$) from 1.61 (SD ± 1.04) in the year before to 0.75 (SD ± 1.18) in the year after GEstIC admission (Table 2). Specifically, of the 287 patients, 195 decreased, 65 maintained, and 27 increased the number of hospitalizations. In addition, the number of patients who did not require all-cause hospitalizations increased from 13 (4.5%) to 164 (57.1%) (Figure 3A).

TABLE 2 Average number of all-causes hospitalizations and HF events per patient in the study population.

Events	Before GEstIC	After GEstIC	Variation	*p*-value*
All-causes hospitalizations, mean (SD)	1.61 (1.04)	0.75 (1.18)	0.86 (1.33)	<0.001
HF hospitalizations, mean (SD)	1.37 (0.88)	0.39 (0.91)	0.98 (1.07)	<0.001
Urgent HF visits, mean (SD)	0.30 (0.70)	0.18 (0.51)	0.12 (0.67)	0.005

*Wilcoxon signed rank test with continuity correction for paired samples.

The mean number of HF hospitalizations per patient decreased significantly ($p < 0.001$) from 1.37 (SD ± 0.88) before and 0.39 (SD ± 0.91) after GEstIC admission (Table 2). The total number of HF hospitalizations decreased in 229 patients, remained unchanged in 41 patients, and increased in 17 patients. The number of patients without HF hospitalizations between the two periods under comparison increased from 15 (5.2%) to 222 (77.4%) (Figure 3B).

Finally, the mean number of urgent HF visits per patient decreased significantly ($p = 0.005$) from 0.30 (SD ± 0.70) before to 0.18 (SD ± 0.51) after GEstIC admission (Table 2). Fourty-six patients reduced, 219 maintained, and 22 increased the number of urgent HF visits. The number of patients who did not require an urgent HF visit slightly increased from 228 (79.4%) to 247 (86.1%) (Figure 3C).

Next, we investigated the link between the number of all-cause hospitalizations, HF hospitalizations, and urgent HF visits per patient and the patient's LVEF at admission (Figure 4 and Supplementary Table S1). Results show that presenting a LVEF ≤40% or >40% did not affect the magnitude of the reduction in all-cause hospitalizations ($p = 0.573$, Figure 4A), HF hospitalizations ($p = 0.341$, Figure 4B), and urgent HF visits ($p = 0.988$, Figure 4C). Such observation was also valid when considering LVEF <50% and ≥50% (all-causes hospitalizations: $p = 0.771$, Figure 4D; HF hospitalizations: $p = 0.459$, Figure 4E; urgent HF visits: $p = 0.467$, Figure 4F). Regardless, within each group of patients, the mean number of registered events decreased in the year following GEstIC admission (Figure 4 and Supplementary Table S1), with the exception of the number of urgent HF visits in patients with LVEF ≤40% ($p = 0.177$, Figure 4C) and LVEF ≥50% ($p = 0.058$, Figure 4F), which was similar to the previous year.

3.3. Length of HF hospitalizations

The 392 HF hospitalizations registered in the year prior to GEstIC admission lasted for 4,488 days. Considering all days of HF hospitalizations, each patient spent on average (±SD) 15.6 ± 15.8 days hospitalized (Table 3). In contrast, during the first year of follow-up in GEstIC, the total days in hospital due to HF reduced to 864 days, corresponding to an 80.7% decrease. The mean (±SD) length of stay was reduced to 3.0 ± 7.8 days per patient, corresponding to a significant reduction of 12.6 days of hospital stays per patient ($p < 0.001$, Table 3). This reduction of 3,624 days of hospitalization due to HF translates into the release of 9.9 hospital beds in the year following admission to GEstIC. Of note, if we consider only the patients that had HF hospitalizations in the two periods (272 patients with HF hospitalizations before vs. 65 after GEstIC admission), the average length of stay decreased from 16.5 days to 13.3 days.

3.4. Cost of HF events

After determining the impact of the GEstIC on the number and length of HF hospitalizations, the costs associated with these events

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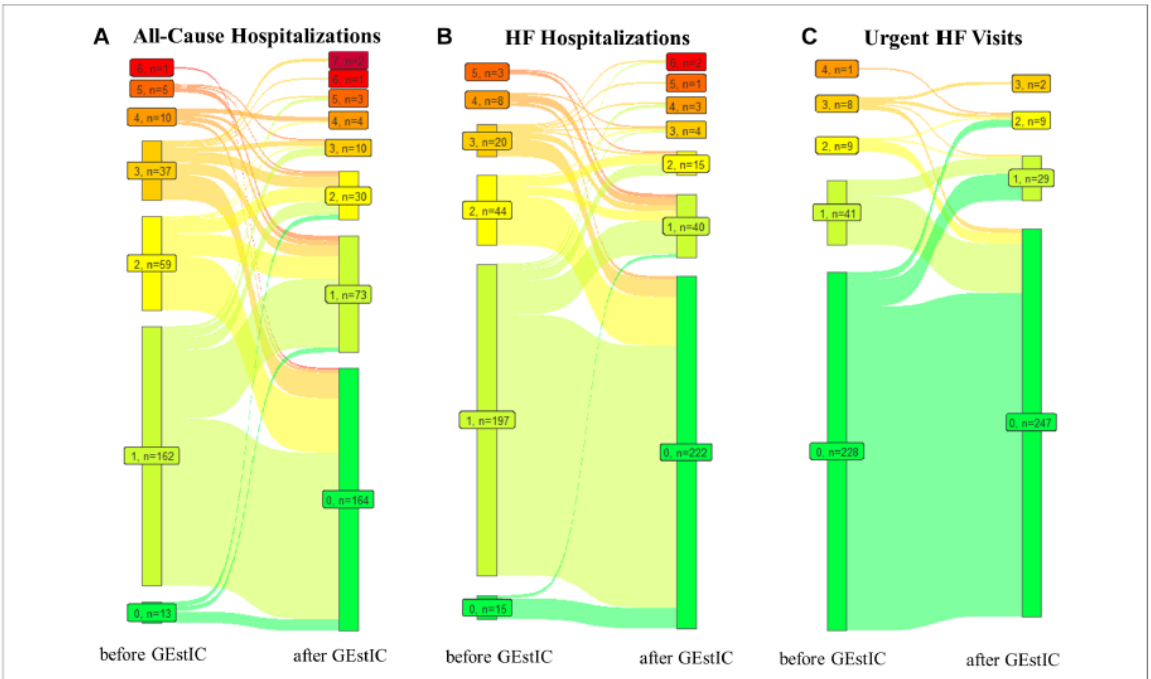


FIGURE 3
Number of patients with a certain number of all-cause hospitalizations, HF hospitalizations, and urgent HF visits registered before and after GEstIC admission. (A) Number of patients with zero to seven all-cause hospitalization events in the one year before GEstIC and one year after GEstIC admission. (B) Number of patients with zero to six HF hospitalization in the one year before GEstIC and one year after GEstIC admission. (C) Number of patients with zero to four urgent HF visits in the one year before GEstIC and one year after GEstIC admission. Data are presented as 0 events (■), 1 event (■), 2 events (■), 3 events (■), 4 events (■), 5 events (■), 6 events (■), and 7 events (■).

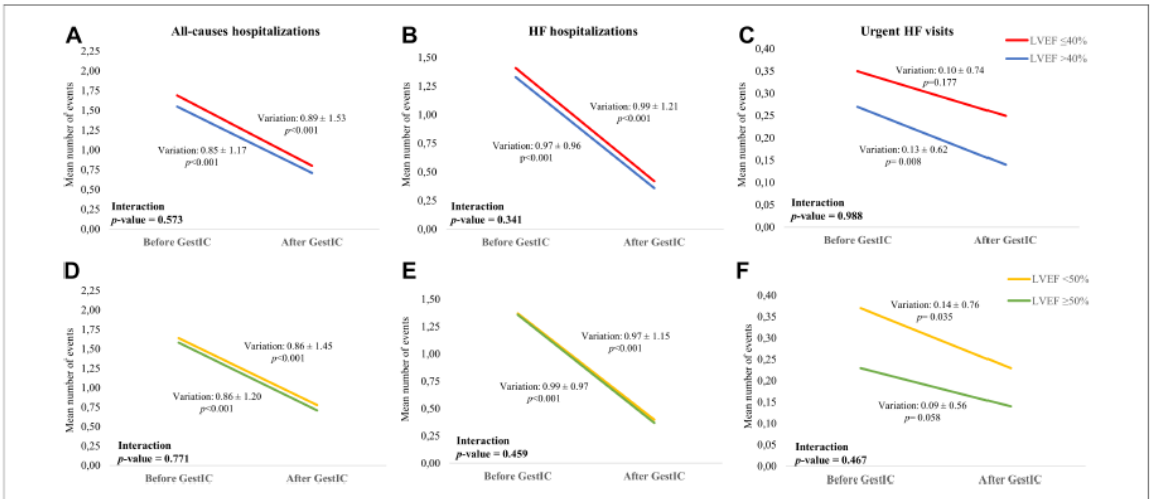


FIGURE 4
Mean number of all-causes hospitalizations and HF events per patient according to LVEF. (A) Mean number of all-cause hospitalizations, (B) HF hospitalizations, and (C) urgent HF visits during the one year before and one year after GEstIC admission in patients with LVEF ≤40% and >40%. (D) Mean number of all-cause hospitalizations, (E) HF hospitalizations, and (F) urgent HF visits during the one year before and one year after GEstIC admission in patients with LVEF <50% and ≥50%. *p*-values for the variation within each LVEF group were determined using the Wilcoxon signed rank test with continuity correction for paired samples; *p*-values for the comparison of the variation between LVEF groups were determined using the Wilcoxon rank-sum test with continuity correction (Mann-Whitney) for independent samples.

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TABLE 3 Characterization of HF hospitalization length and cost of HF events of the study population before and after GEstIC admission.

Study population				
HF hospitalization	Before GEstIC	After GEstIC	Variation	*p*-value*
Total length, days	4,488	864	3,624	
Average length of stay/ patient, days (SD)	15.6 (15.8)	3.0 (7.8)	12.6 (15.0)	<0.001
Total cost, €	1,923,332.40	370,267.20	1,553,065.20	
Average cost/patient, € (SD)	6,701.51 (6,770.01)	1,290.13 (3,331.21)	5,411.38 (6,423.61)	<0.001
Urgent HF visits				
Total cost, €	20,848.68	12,700.92	8,147.76	
Average cost/patient, € (SD)	72.64 (166.84)	44.25 (121.25)	28.39 (161.55)	0.005
HF events#				
Total cost, €	1,944,181.08	382,968.12	1,561,212.96	
Average cost/patient, € (SD)	6,774.15 (6,808.27)	1,334.38 (3,347.76)	5,439.77 (6,446.71)	<0.001

#HF Events = HF hospitalizations + urgent HF visits.
*Wilcoxon signed rank test with continuity correction for paired samples.

were estimated. A total saving of €1,553,065.20 was observed based on an average daily cost of €428.55 per hospitalization and a reduction of 3,624 days of HF hospitalization days between the two study periods. A significant average cost reduction of €5,411.38 per patient in HF hospitalizations was achieved ($p < 0.001$, Table 3).

As for urgent HF visits, their average cost was estimated by the hospital to be €239.64 per visit. Thus, the reported reduction of 34 urgent HF visits translated into a saving of €8,147.76 in these events ($p = 0.005$, Table 3).

When the overhead costs are added together, the total saving associated with reducing HF events (hospitalizations and urgent visits) over the first year of follow-up of the 287 patients in the GEstIC was €1,561,212.96. This represents an average saving of €5,439.77 per patient ($p < 0.001$, Table 3).

4. Discussion

This study aimed to characterize the impact of the GEstIC multidisciplinary clinic on specific HF healthcare indicators and their associated costs. Here we present real-world evidence showing, for the first time in Portugal, that the multidisciplinary management of HF patients significantly reduces the number of all-cause hospitalizations and HF events (HF hospitalizations and urgent HF visits), the length of HF hospitalizations, and, consequently, the costs associated with such events.

The demographic and clinical analysis of the study sample showed that this was an elderly population (median age 77 years), predominantly female, with a high number of comorbidities. Around half of the patients had LVEF ≥50% and almost two-thirds had a mild limitation in their physical activity (NYHA II). This profile aligns with what has been reported as the European reality (20).

Substantial reductions in HF hospitalizations (−71.7%) and urgent HF visits (−39.1%) were observed after admission to GEstIC. Moreover, 77.4% of the patients did not require any hospitalization for HF during the one-year after admission to the clinic, compared to the 5.2% in the preceding period. Other reports have described similar findings, although not as significant as this. A systematic review examining the effect of multidisciplinary strategies on the outcomes of HF patients indicated a 26% reduction in HF hospitalizations under randomized clinical trial conditions (15). More satisfactory values were reported by McMurray et al. and Packer et al., who observed a reduction in HF hospitalizations of around 30% when investigating the effect of new therapeutic options for HF (21–23). Data from a 3-month period of enrollment in a multidisciplinary community paramedicine program demonstrated a 25% reduction in the number of emergency department visits by patients with HF (24). In addition to the impact on the number of events, the length of stay for HF hospitalizations was also significantly shorter (−12.6 days of hospitalization/patient) during the first year of follow-up in GEstIC compared to the year before admission. This is particularly remarkable considering the patient demographics in a Portuguese internal medicine unit—predominantly elderly individuals with a variety of non-medical complexities (e.g., frailty, social isolation) and additional factors, such as hospital-acquired infections, that typically contribute to longer stays.

Considering these findings within their context, the main HF event in this population was hospitalization rather than urgent HF visits, which may be since most HF-related emergency visits ultimately lead to hospital admission. The implementation of multidisciplinary care had a positive impact mainly on reducing hospitalizations and, to a lesser extent, urgent HF visits. In addition, this multidisciplinary clinic did not significantly change the number of urgent HF visits in patients with LVEF ≤40% and ≥50%. Notably, during the study period, there was no alternative to the emergency department for the evaluation of HF decompensation events, as the GEstIC work was based in an outpatient ambulatory setting. Altogether, it is reasonable to speculate that HF events after GEstIC admission were probably less severe than those occurring in the previous year, leading to a lower number of hospitalizations. This idea is further supported by the significantly shorter length of stay for HF hospitalization after GEstIC admission.

The multidisciplinary management of these patients also led to a 53.7% reduction in all-cause hospitalizations. In the first year after GEstIC admission, 57.1% of patients did not require any hospitalization, opposed to 4.5% in the previous year. McAlister et al. observed a similar trend and reported a 19% reduction in all-cause hospitalizations upon implementation of multidisciplinary management for HF patients (15). In fact, multidisciplinary follow-up of HF patients by a cardiologist and a geriatrician significantly reduced all-cause hospitalizations compared with follow-up by a cardiologist only, as demonstrated by Herrero-Torrus et al. (25).

In this study, the multidisciplinary management of HF patients was beneficial for all patients, including those with preserved LVEF, who reported fewer all-cause hospitalizations and HF events one-year after admission to GEstIC. Until the publication of the

results from the EMPEROR-Preserved study in 2021, no drug treatment had been shown to significantly improve the prognosis of HF patients with LVEF >40% (26). Nevertheless, data from the present study, which reports up to February 2020 and before the knowledge that empagliflozin and dapagliflozin can reduce mortality and HF events in patients with HF and LVEF >40%, showed that admission to GEstIC reduced the number of all-cause hospitalizations and HF events in this group of patients in the first year of follow-up. These findings emphasize the importance of an all-encompassing, patient-centered, and multidisciplinary approach to HF patient management. Our results indicate that the implementation of such a program contributes significantly to the reduction in hospitalizations and HF-related events, thereby contributing to an overall improvement in patients' health status and quality of life.

One of the most significant outcomes of reducing hospitalizations and urgent HF visits is the financial impact on the public healthcare system. In 2014, the direct cost of HF to the Portuguese public healthcare system was €299 million. Here we show that the reduction of HF-related events (hospitalizations and urgent visits) after the admission of 287 patients to the GEstIC during the first year of follow-up represented an economic saving of €1,561,212.96 in a single hospital. Of note, if the costs of all-cause hospitalizations had been included in this estimate, the total savings would have been substantially higher. Other studies have reported a reduction in costs after implementing multidisciplinary clinics. Weinstein et al. demonstrated a 27% decrease in hospitalization costs after a one-year follow-up of a community-based HF multidisciplinary clinic (27). Ledwidge et al. calculated an overall cost/saving of €586 per hospitalization prevented and €729 per patient treated during a 3-month period of multidisciplinary care of HF patients (28). Despite variations in study implementation and design, daily hospitalization costs, and multidisciplinary clinic costs, the consensus is that replication of GEstIC in other Portuguese public institutions would reduce the economic burden on the public health system, saving millions of euros, while reducing the use of healthcare resources, being human or logistical.

In addition to the beneficial effects of physical exercise, regular assessment of health and quality of life, and adherence to treatment, among other factors, in reducing mortality and improving patients' well-being and quality of life, multidisciplinary clinics also have an important role in achieving these results, similar to angiotensin-converting enzyme inhibitors (14, 15, 19). In Portugal, although not extensively described, multidisciplinary clinics for HF patients were shown to reduce the risk of mortality and short-term hospitalization (16).

Following the introduction of GEstIC, 487 individuals were admitted within the initial six-year period, corresponding to this study period. Notably, during the first year of follow-up, the mortality rate was recorded at 14%, significantly lower than the 34.4% that we reported in an unselected HF population admitted to our Internal Medicine Department in the year before GEstIC implementation and the 22.8% reported in a recent real world study of HF patients from Sweden (29, 30).

Further analysis would be important to better understand the full potential of this HF multidisciplinary clinic, particularly on clinical and patient-reported outcomes. In addition, the long-term follow-up benefits in terms of HF complications and comorbidities, patients' overall survival, and human and economic resources use should be evaluated. Finally, a continuous re-evaluation of the results of this study would be desirable to include more patients in this analysis and thus contribute to more robust conclusions.

The major strength of the study lies in its design, which involves comparing the same group of patients before and after their admission to GEstIC. This approach minimizes the potential for bias. In addition, the researchers used real-world data collected from medical records. However, there are several limitations to acknowledge. The study did not provide a comprehensive characterization of additional costs associated with patients' treatments, interventions, or follow-up visits within the GEstIC program, including cardiovascular medications, iron supplementation, or cardiac rehabilitation, which could have influenced the observed positive outcomes. While our study aimed to assess the direct impact on hard clinical events, future cost-benefit analyses should consider incorporating these elements to provide a more holistic understanding of the program's economic implications. Secondly, this study did not evaluate the frequency of patients with LVEF ≤40% receiving prognostic modifying drugs or patients with LVEF >40% undergoing empagliflozin or dapagliflozin treatment for diabetes. Despite these limitations, it is important to note that the primary objective of the HF multidisciplinary clinic is to optimize treatment, ensuring that patients receive the best possible care. Lastly, the cost estimate considered the average cost of treating any patient, with any disease, in the Internal Medicine Department and the Emergency Department, which may be higher or lower than treating a HF patient, *per se*.

Future research is important to explore the combined effects of specialized multidisciplinary care and improved organizational aspects in HF clinics like GEstIC. This exploration will allow for a better understanding of their respective influences on patient outcomes, in addition to characterizing patient pathways and evaluating potential enhancements in health-related quality of life, exercise capacity, and mental health.

In conclusion, multidisciplinary clinics have shown great benefits in the diagnosis, treatment, and follow-up of HF patients. In addition to improving clinical outcomes by reducing the number of events (hospitalizations and urgent visits), these clinics also have the added value of helping healthcare institutions and other stakeholders better manage human, logistical, or financial resources. Therefore, replicating this model in other hospitals would certainly contribute to the sustainability of health systems.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Ethics statement

The studies involving humans were approved by the local ethics committee and institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

RR, AP, SP and IM collected the data. RR, NP and IM performed the statistical analysis. RR and IM prepared the manuscript. All authors vouch for the accuracy and completeness of the data and analysis. All authors contributed to the article and reviewed and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1232291/full#supplementary-material

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5.9. conTemporary reflectiOns regarding heart failure management - How to ovERcome the PorTuguese barriers (TOGETHER-PT)

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ORIGINAL ARTICLE

conTemporary reflectiOns regarding heart failure manaGEmenT – How to ovERcome the PorTuguese barriers (TOGETHER-PT)

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KEYWORDS
Heart failure;

Abstract
Introduction and objectives: Heart failure (HF) is a complex clinical syndrome that is a significant burden in hospitalisations, morbidity, and mortality. Although a significant effort has been

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Cardiology;
Internal medicine;
Primary healthcare;
Nursing awareness;
Diagnosis;
Treatment;
Healthcare organization;
Portugal

made to better understand its consequences and current barriers in its management, there are still several gaps to address. The present work aimed to identify the views of a multidisciplinary group of health care professionals on HF awareness and literacy, diagnosis, treatment and organization of care, identifying current challenges and providing insights into the future.
Methods: A steering committee was established, including members of the Heart Failure Study Group of the Portuguese Society of Cardiology (GEIC-SPC), the Heart Failure Study Group of the Portuguese Society of Internal Medicine (NEIC-SPMI) and the Cardiovascular Study Group (GEsDCard) of the Portuguese Association of General and Family Medicine (APMGF). This steering committee produced a 16-statement questionnaire regarding different HF domains that was answered to by a diversified group of 152 cardiologists, internists, general practitioners, and nurses with an interest or dedicated to HF using a five-level Likert scale. Full agreement was defined as ≥80% of level 5 (fully agree) responses.
Results: Globally, consensus was achieved in all but one of the 16 statements. Full agreement was registered in seven statements, namely 3 of 4 statements for patient education and HF awareness and 2 in 4 statements of both HF diagnosis and healthcare organization, with proportions of fully agree responses ranging from 82.9% to 96.7%. None of the HF treatment statements registered full agreement but 3 of 4 achieved ≥80% of level 4 (agree) responses.
Conclusion: This document aims to be a call-to-action to improve HF patients' quality of life and prognosis, by promoting a change in HF care in Portugal.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
Cardiologia;
Medicina interna;
Cuidados de saúde primários;
Enfermagem;
Consciencialização;
Diagnóstico;
Tratamento;
Organização dos cuidados de saúde;
Portugal

Reflexões contemporâneas sobre a gestão da insuficiência cardíaca – Como ultrapassar as barreiras em Portugal

Resumo
Introdução e objetivos: A insuficiência cardíaca (IC) é uma síndrome clínica complexa que representa uma carga significativa em termos de hospitalizações, morbilidade e mortalidade. Apesar do esforço significativo para melhor compreender as suas consequências e as atuais barreiras na sua gestão, ainda existem várias lacunas a colmatar. O presente trabalho teve como objetivo identificar os pontos de vista de um grupo multidisciplinar de profissionais de saúde sobre sensibilização e educação, diagnóstico, tratamento e a organização dos cuidados na IC, identificando os desafios presentes e proporcionando perspetivas futuras.
Métodos: Foi criada uma comissão coordenadora, que incluiu membros do Grupo de Estudo da Insuficiência Cardíaca da Sociedade Portuguesa de Cardiologia (GEIC-SPC), do Núcleo de Estudos de Insuficiência Cardíaca da Sociedade Portuguesa de Medicina Interna (NEIC-SPMI) e do Grupo de Estudo Cardiovascular (GEsDCard) da Associação Portuguesa de Medicina Geral e Familiar (APMGF). Esta comissão coordenadora elaborou um questionário contendo 16 afirmações relativas a diferentes domínios da IC que foi respondido por um grupo diversificado de 152 cardiologistas, internistas, especialistas de medicina geral e familiar e enfermeiros com interesse na IC, através da utilização de uma escala de Likert de 5 pontos. A concordância total foi definida como ≥80% de respostas de nível 5 (concordo totalmente).
Resultados: Globalmente foi alcançada uma concordância simples dos respondentes em todas as 16 afirmações, exceto numa. A concordância total foi registada em sete afirmações, nomeadamente, 3 de 4 afirmações sobre educação do doente e consciencialização sobre IC e 2 em 4 afirmações sobre diagnóstico de IC e sobre organização de saúde, com percentagens de respostas de totalmente de acordo variando entre 82,9% a 96,7%. Nenhuma das afirmações sobre tratamento de IC registou concordância total, mas 3 de 4 atingiram ≥80% de respostas de nível 4 (concordo).
Conclusão: Este documento pretende ser um apelo à ação para melhorar a qualidade de vida e o prognóstico dos doentes com IC, através da promoção de uma mudança dos cuidados prestados aos doentes com IC em Portugal.
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Introduction

Heart failure (HF) is a complex clinical syndrome characterised by debilitating symptoms and signs, caused by multifactorial structural and/or functional abnormalities of the heart, resulting in elevated intracardiac pressures and/or inadequate cardiac output at rest or during exercise.[1–3] It affects 1–2% of the general adult population in high-income countries[4] and is the leading cause of hospitalisation in individuals above 65 years old.[3,5] A significant proportion of patients with HF die within five years after diagnosis,[6] making HF mortality higher than most of common cancers, both in men and women,[7] which is contrary to common belief.

Beyond the negative impact of HF on patients' quality of life, this syndrome is a major burden for patients and caregivers and has a significant economic impact due to the escalating costs of hospitalisations and to the substantial loss of patients' and caregivers' productivity.[3,6,8,9]

In Portugal, HF prevalence estimates date back to 1998, with a global estimation of 4.36% based on the EPICA study.[5] This study showed a progressive prevalence increase with age, from 1.36% in the group between 25 and 49 years old to 16.14% in those over 80.[5]

Currently, to address knowledge gaps on HF epidemiology, characteristics and burden of disease, a new study is ongoing in Portugal. PORTHOS study[10] aims to determine the prevalence of HF and its subtypes, the distribution of comorbidities among patients with HF, and patients' health-related quality of life. The first study results are expected by the end of 2023.

Nevertheless, today we know that due to the population ageing and the increasing prevalence of cardiovascular risk factors such as obesity and diabetes, HF prevalence is expected to rise by 30% in 2035[11] and HF-associated deaths by 73% in 2036, further increasing HF economic burden, which is expected to grow by 28% in 2036.[2]

In 2002, Fonseca et al. suggested that HF was only satisfactorily managed in Portugal and should be a national priority.[12] More recently, another consensus statement also highlighted the need to increase awareness and improve HF management in Portugal.[13] In the past two decades, there has been significant innovation in the available therapies that triggered a transversal evolution in managing HF patients, namely in the HF disease awareness, diagnosis, treatment, and organization of healthcare. However, significant gaps in each of these areas have yet to be identified and acted upon for a more effective response.

Objectives

TOGETHER-PT (conTemporary reflectiOns regarding heart failure manaGEmenT – How to ovERcome the PorTuguese barriers) intends to be a call-to-action document to improve HF care in Portugal. This is a project of the Heart Failure Study Group of the Portuguese Society of Cardiology (GEIC-SPC), the Heart Failure Study Group of the Portuguese Society of Internal Medicine (NEIC-SPMI) and the Cardiovascular Study Group (GEsDCard) of the Portuguese Association of General and Family Medicine (APMGF) that aims to identify the views of a multidisciplinary group of Portuguese cardiologists, internists, general practitioners and nurses, on HF different domains, such as awareness and literacy programs, early diagnosis implementation policies, guideline-oriented treatment implementation and organization of care.

Methods

A panel of twelve Portuguese HF experts, including cardiologists, internists, and general practitioners, was invited to join the study Steering **Committee.** This Committee designed a questionnaire to collect the opinion of a group of HF experts on how to improve HF management in Portugal. The methodology used to build this questionnaire is summarised in Figure 1.

Components of the questionnaire on heart failure management

The European Society of Cardiology (ESC) Guidelines on Heart Failure 2021[3] and other relevant contemporary literature were considered to be the current gold standard of HF management and they were taken into consideration to build the questionnaire. Four independent groups of the Steering Committee members were constituted. Each of these groups elaborated a set of four to six statements concerning each of the four dimensions of the TOGETHER-PT project:

1. HF awareness and literacy.
2. HF early diagnosis.
3. HF guideline-oriented treatment.
4. HF organization of care.

These statements were later analysed and voted on by all Study Steering Committee members, resulting in a final selection of 16 statements, four regarding each of the four dimensions mentioned above (Supplementary Table 1).

Questionnaire

A questionnaire was created with the selected 16 statements. It was used to quantify the level of agreement with each statement among the invited respondents. The questionnaire for physicians included the 16 statements regarding the four dimensions mentioned above. The questionnaire for nurses included the eight statements pertaining to two dimensions: HF awareness and literacy and HF care organization.

A five-level Likert scale was used for answering to each statement: level 1 – fully disagree, level 2 – disagree, level 3 – equipoise, level 4 – agree, and level 5 – fully agree. An additional free-text comment was allowed for each statement.

Participants

GEIC-SPC, NEIC-SPMI and GEsDCard-APMGF identified a convenience sample of 174 health care professionals (HCP). This group included cardiologists, general practitioners,

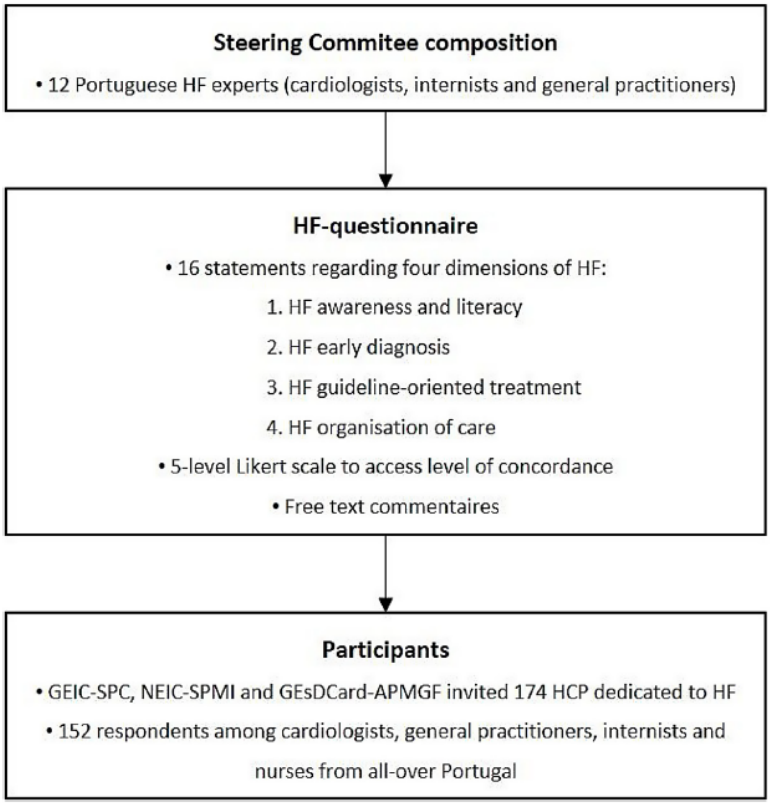


Figure 1 Questionnaire development method. GEIC-SPC: Heart Failure Study Group of the Portuguese Society of Cardiology; GEsDCard-APMGF: Cardiovascular Study Group of the Portuguese Association of General and Family Medicine; HCP: health care professionals; HF: heart failure; NEIC-SPMI: Heart Failure Study Group of the Portuguese Society of Internal Medicine.

internists, and nurses working at primary healthcare facilities, regional or central hospitals all over Portugal with interest, expertise, and experience in HF care. The 174 professionals were invited by e-mail and phone call to answer the questionnaire via an online form. After the first contact, two kind reminders by e-mail were sent.

Data analysis

Agreement with each statement was classified as follows:

- ''Full agreement'' – when ≥80% of level 5 responses obtained;
- ''Agreement'' – when ≥80% of level 4 or 5 responses obtained;
- ''No agreement'' – when none of the above results was met.
- Free-text comments were qualitatively analysed.

Ethics

This study involves the analysis of documents without direct or indirect intervention of participants. The prior review and approval by the competent Ethical Committee was waived. This study complied with the ethical principles for clinical research, specifically the confidentiality of respondents' choices.

Table 1 Distribution of respondents.

	n (%)	Response rate
Cardiologists	36 (23.7)	97.5%
General practitioners	39 (25.7)	100.0%
Internists	38 (25.0)	74.5%
Nurses	39 (25.7)	83.7%
Total	152 (100.0)	87.4%

Results

The questionnaire was available online between 20 July and 20 September 2022.

Among the 174 invited professionals, 152 (87.4% response rate) answered the questionnaire.

Response rate was balanced among the different professional groups (Table 1).

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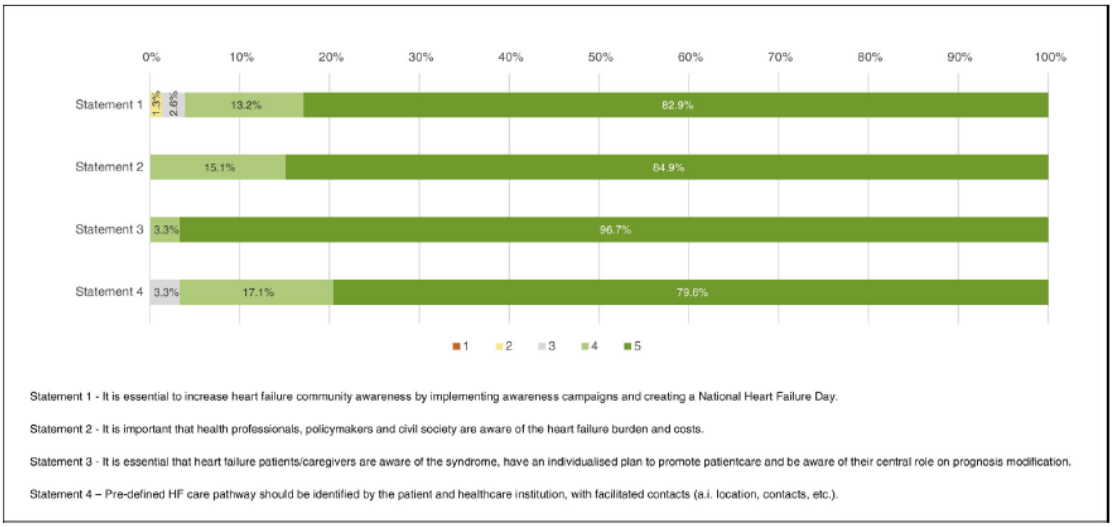


Figure 2 Level of agreement with patient education and awareness in heart failure.

Patient education and heart failure awareness

''Full agreement'' was recorded for three of the four statements with concordance proportions of 82.9% (Statement 1 – ''It is essential to increase heart failure community awareness by implementing awareness campaigns and creating a National Heart Failure Day.''), 84.9% (Statement 2 – ''It is important that health professionals, policymakers and civil society are aware of the heart failure burden and costs.'') and 96.7% (Statement 3 – ''It is essential that heart failure patients/caregivers are aware of the syndrome, have an individualised plan to promote patientcare and be aware of their central role on prognosis modification.''), and one statement obtained ''Agreement'', with 96.7% of respondents answering 4 or 5 (Statement 4 – ''Pre-defined HF care pathway should be identified by the patient and healthcare institution, with facilitated contacts (i.e. location, contacts, etc.).'') (Figure 2).

Participants strongly support national HF awareness campaigns among the general population and the health care community. They reinforced the utility of cardiovascular risk factors and HF preventive campaigns rather than the institution of a national day that would have little impact on population literacy. National HF awareness campaigns for the general public, and HF education campaigns conducted at primary healthcare facilities, nursing homes and schools, might also play an important role. Additionally, the development of HF awareness and education programs all year round was suggested. Respondents considered that an information campaign on HF's financial, social and disease burden should be developed targeting politicians and civil society. It was suggested that every healthcare institution should report their HF hospitalisations and/or HF outpatient care costs and establish targets to reduce them. This could be used to compare costs among different strategies and promote multidisciplinary care.

Experts provided suggestions on how to implement HF patient education: (1) to create a standard HF education package; (2) to use the ''Heart failure zones'', a visual colour scale on HF signs and symptoms to encourage HF patients/caregivers to take action, namely, by contacting HF professionals; (3) to discuss with each patient/caregiver HF trajectory and prognosis; (4) to use a patient-centred approach in order to discuss HF treatment individual goals; and (5) to always involve caregivers and family physicians in HF patients' education process.

Finally, participants highlighted the need to implement multidisciplinary teams at every level of care within the Portuguese National Health System. This would be essential to attend HF patients' needs, thus overcoming the current absence of these programs in most hospitals and primary healthcare facilities. The relevance of nurse outpatient visits was underlined, as well as the need to implement digital health solutions to improve patient access to healthcare.

Heart failure diagnosis

''Full agreement'' was achieved regarding echocardiography (Statement 6 – ''Accessibility to echocardiography for heart failure diagnosis must be ensured equitably in primary healthcare and hospital settings.'', 92.2% and Statement 7 – ''Echocardiographic reports must include minimum parameters for reaching a diagnosis, namely the quantification of ejection fraction and Doppler analysis.'', 90.5%). ''Agreement'' was achieved regarding the role of natriuretic peptides (NPs) (Statement 5 – ''B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide [BNP/NT-ProBNP] are essential diagnostic tools in primary and hospital healthcare, and must be equitably accessible throughout Portugal.'', 93.1% and Statement 8 – ''In patients with cardiovascular risk factors (diabetes, hypertension, smoking habits and/or obesity) the presence of cardiac dysfunction (structural and functional) should be

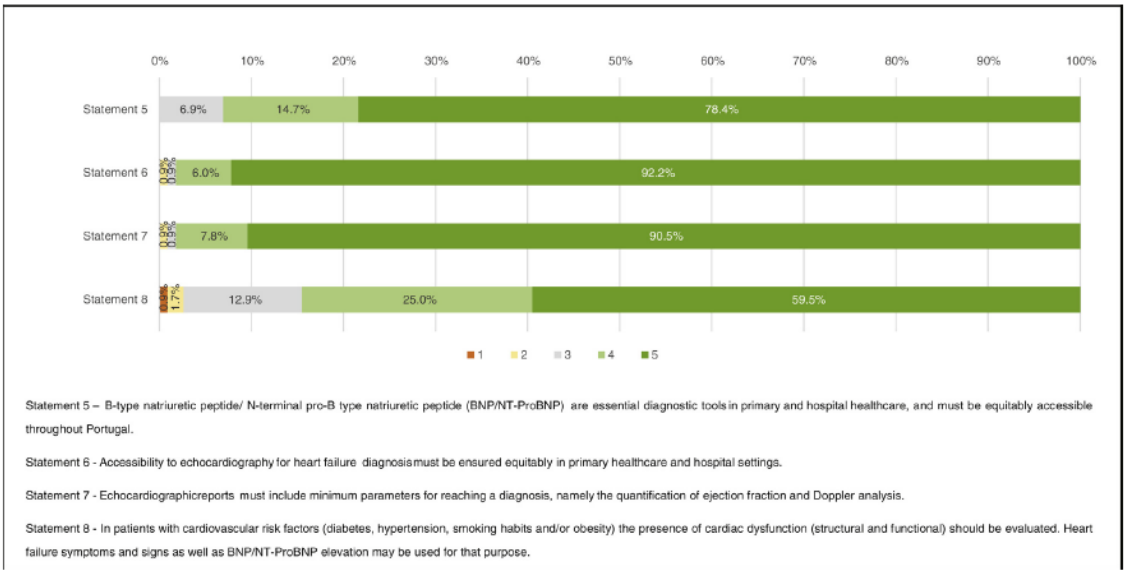


Figure 3 Level of agreement with heart failure diagnosis statements.

evaluated. Heart failure symptoms and signs as well as BNP/NT-ProBNP elevation may be used for that purpose.'', 84.5%) (Figure 3).

Respondents agreed on the relevance of echocardiography for establishing HF diagnosis. They also considered that access to good quality echocardiograms should be assured equitably both in outpatient and hospital settings. Essential echocardiographic parameters, such as ejection fraction and Doppler evaluation should always be included in the echocardiogram report. This was considered fundamental for a ''comprehensive'' and appropriate diagnosis.

Equitable access to NPs in the ambulatory and hospital setting at a national level was deemed crucial. NP testing reimbursement among primary care physicians, as well as education on its appropriate use, was considered necessary.

In asymptomatic patients at risk of developing HF (e.g., patients with diabetes, obesity or hypertension), the utility of NP gathered less level of agreement.

Heart failure treatment options

Responses regarding treatment options are presented in Figure 4. ''Agreement'' was obtained in Statement 9 – ''The initial approach to HF with reduced ejection fraction (HFrEF) therapy, should include as many of the four pillars of disease-modifying drug classes recommended in the European Guidelines. In some patients, there may be room for the simultaneous initiation of the four therapeutic pillars.'' (94.8%), 10 – ''Sodium-glucose cotransporter 2 inhibitors should be the first-line for heart failure with preserved ejection fraction (HFpEF) treatment.'' (93.1%) and 12 – ''In previous HFrEF patients with recovered ejection fraction above 50%, disease-modifying therapy should be maintained.'' (97.4%).

The fundamental relevance of implementing the four pillars of disease-modifying therapy in all HF with reduced ejection fraction patients was highlighted. Drug initiation and dose titration should be done as soon as possible. However, in some patients, simultaneous initiation of all the above drugs may not be possible. The occasional occurrence of drug intolerance during up-titration may be a barrier in some cases. This is also true concerning drug costs in those economically fragile.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i; dapagliflozin and empagliflozin) were accepted as the first-line treatment for HFpEF.

Participants agreed that disease-modifying treatment should be maintained in HF patients with improved left ventricular ejection fraction (LVEF). Improved LVEF is defined by an increase $\geq$10-point from baseline in patients with previous LVEF $\leq$40%. A second measurement of LVEF >40% is necessary for diagnosis. In cases of LVEF improvement, when in doubt of a reversible cause, most experts would agree to maintain disease-modifying therapy.

The 11th Statement (''Delaying devices implementation more than three months after medical therapy optimisation is acceptable, particularly in patients with non-ischemic dilated cardiomyopathy.'') did not gather ''Agreement''. Commentary suggested that this issue is not to be approached by non-cardiologist physicians.

Healthcare organization

Figure 5 presents the results regarding healthcare organization. ''Full agreement'' was obtained in Statement 14 – ''The proper patient management involves a well-defined referral network. This includes in hospital level multidisciplinary teams (cardiologists, internists, and nurses) engaged

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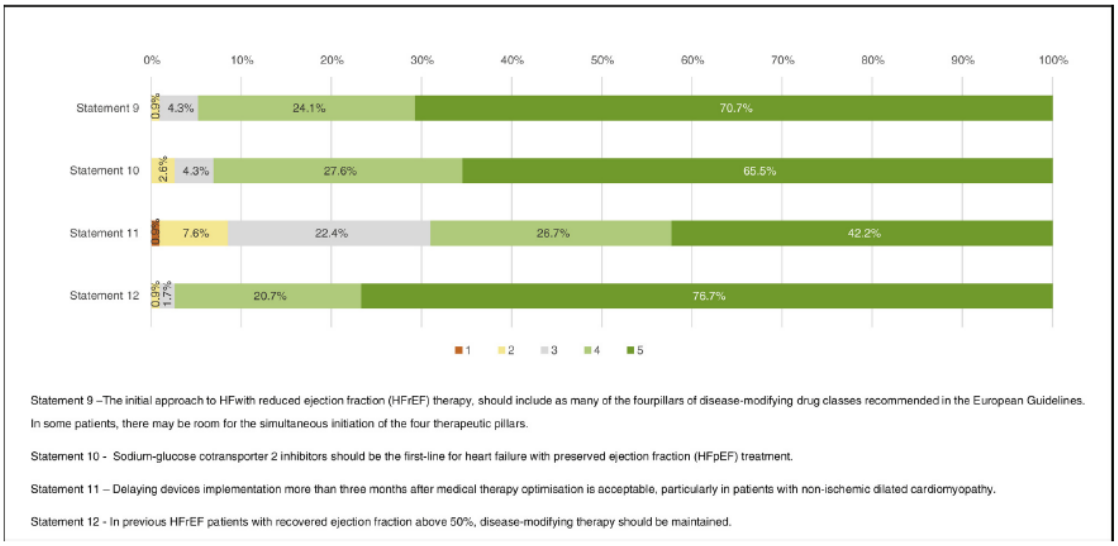


Figure 4 Level of agreement with heart failure treatment statements.



Figure 5 Level of agreement with healthcare organization statements.

with primary healthcare (including general practitioners and nurses). Their role includes timely determination of HF etiology, therapeutic reconciliation, patient education and elaboration of treatment plan (outpatient and inpatient settings). Finally, the interaction with other medical and non-medical specialties (nutrition, social services, pharmacists, etc.) should be guaranteed.'' (84.9%) and 16 – ''A single, integrated, shared patient electronic record significantly improves HF patient care.'' (88.2%). ''Agreement'' was obtained in Statements 13 – ''HF healthcare organization should include the articulation of three care levels with different roles: A. Primary healthcare; B. Regional hospitals; C. Central hospitals.'' (96.7%) and 15 – ''HF care contractualisation, either at primary or hospital care levels, should

include quality indicators. They should be accessible to HF team coordinators.'' (88.1%).

A well-defined integrated healthcare system including the various HF care levels and using shared electronic medical records and information was considered crucial. Critical points in providing appropriate care to HF patients included the establishment of multidisciplinary integrated teams and the creation of easy communication pathways. Health professionals' education was highlighted as being fundamental. Cardiac rehabilitation is also a central part of HF care. Finally, the contribution of psychologists was referred as of most importance.

Although contractualisation was accepted, some respondents questioned HF quality indicators utility in clinical practice. They argued that it does not ensure care improvement, stressing the need for defining the correct quality of care indicators to successfully implement contractualisation.

Discussion

Patient education and awareness in heart failure

The respondents (HCPs) identified HF literacy as an important unmet need among Portuguese HF patients. This is also true when considering the general population and political decision-makers. Indeed, community awareness of HF is low, and strategies to educate the public are needed.[13,14] In a 2005 survey conducted in nine European countries, 86% of respondents affirmed having already heard of HF; however, only 3% could correctly identify HF from a description of typical symptoms and signs. Additionally, 34% believed HF was a normal consequence of ageing, and 67% thought that HF patients live longer than cancer patients.[14]

The 2021 European Society of Cardiolgy (ESC) Guidelines recommend self-management strategies to reduce the risk of HF hospitalization and mortality.[3] Patient education is particularly important to achieve this. The TOGETHER-PT participants recognized the need to promote patient/caregiver education and empowerment. ESC recommends the use of online platforms (e.g., HF matters) to promote HF patient self-education.[3] In Portugal, patient associations and scientific societies promote HF patient education and support.

Policymakers should designate HF as a health policy and management priority.[13] HF should be classified as a chronic disabling status, like other diseases such as diabetes or cancer. This would ensure simplified access to healthcare facilities and allow patient care optimization with a potential impact on HF hospitalizations and quality of life.

Heart failure diagnosis

According to the ESC Guidelines, HF diagnosis is based on typical symptoms and signs, in addition to the information provided by ECG, NP and echocardiography.[3]

The lack of access to complementary diagnostic tests, such as NP and echocardiography at the primary healthcare level, has been described in Portugal.[13,15] This is particularly relevant since registry data showed that, although 40% of patients present symptoms that should result in an earlier diagnosis at the primary healthcare level, 80% of HF diagnoses are made at the hospital[16].

The participants reinforced the central role of NPs, equitably accessed, as a diagnosis tool, if proper training is given to ensure their adequate use and interpretation. However, as previously stated, in Portugal, BNP/NT-ProBNP measurements are not reimbursed in primary healthcare. This situation should be revised as their use enables the optimization of echocardiography use, resulting in cost-reduction for the Portuguese public health system.[13,17,18]

The participants agreed with the relevance of the availability of high-quality echocardiograms, including Doppler assessment. They are central to HF diagnosis and treatment prioritization and should be equitably accessible. Echocardiograms should have a standardized report and be performed timely, in accordance with the literature, such as the Portuguese Society of Cardiology recommendations.[13,19,20]

Patients at risk of developing HF (patients with cardiovascular risk factors, such as diabetes, hypertension, smoking habits and/or obesity) should be screened early by actively looking for HF signs and symptoms. There is no specific mention to dyslipidemia because abnormal lipid concentrations, by themselves, are recognized as an important independent risk factor for CV diseases, but mainly for atherosclerotic events. On the other hand, the use of NP for screening was not consensual among the consulted panel of health professionals. In the recently published HF classification update,[21] subjects without signs or symptoms of HF, without evidence of structural heart disease or abnormal cardiac function but with elevated NPs or cardiac troponin levels could be classified as pre-HF patients, formerly stage B. In the primary healthcare setting, in the non-acute setting, the diagnostic value of NPs, in addition to the presence of signs and symptoms of HF, relies on their high negative predictive value, helping physicians to rule out HF.[3]

Heart failure treatment

The main goals of HF treatment include the control of symptoms and signs, improvement of functional capacity and quality of life, and decrease of hospitalizations and mortality.[3] In recent years new therapies emerged with unprecedented results that contributed to these goals.[22–29]

The PARADIGM-HF,[23] DAPA-HF[24] and EMPEROR-REDUCED studies[25] led to the updated HFrEF treatment algorithm of the 2021 ESC HF Guidelines. It proposes a four-pillar strategy involving the association of an angiotensin-converting enzyme inhibitor (ACEi), an angiotensin receptor-neprilysin inhibitor (ARNI), an angiotensin II receptor blocker (ARB), a beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA) and an SGLT2i.[3]

These four pillars of therapy are recognized as first-line HFrEF treatment by the Portuguese health care professionals gathered in the TOGETHER-PT project.

This is particularly important because, according to registry data, guideline-directed medical therapies (GDMT) are not being implemented consistently in clinical practice.[30–33] The CHAMP-HF registry[30] showed that the use of GDMT was under 75% in stable outpatients with HFrEF, both regarding the prescription of disease-modifying drugs and

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the achievement of target dosage. Only 1% of patients were treated simultaneously with target doses of ACEi/ARB/ARNI, BB, and MRA therapy, and less than 25% simultaneously received any dose of all three medications.[30] Additionally, data from the ESC Long-Term Registry[32] regarding patients with chronic HFrEF showed that, with respect to the target dosages of GDMT, far fewer than one-third of the patients were on the target dosages suggested by the current Guidelines: 29.3% for ACEi, 24.1% for ARB,17.5% for BB, and 30.5% for MRA. Data from ESC HFA EORP 2011–2016[31] showed GDMT use rates of 85.7% for ACEi/ARB/, 88.7% for BB and 58.8% for MRAs. Additionally, the EVOLUTION-HF observational study[34] showed that the initiation of dapagliflozin and sacubitril/valsartan was delayed compared with other GDMT. In this study, only a few patients were on target doses. The above registries reveal the unmet need of initiating treatment early with ensuing rapid dose up-titration in order to improve HFrEF patients' prognosis.[34]

In TOGETHER-PT, the participants considered SGLT2i as the first-line option for HFpEF management.

SGLT2i are the only treatment reducing morbidity and mortality in HFpEF.[22,26,27] The 2022 AHA/ACC/HFSA Guidelines for the management of HF[35] give a class II-A recommendation for using SGLT2i in HFpEF to reduce mortality and HF hospitalizations, based mainly on EMPEROR-preserved trial results.[26,27,36] DELIVER[22] trial, published in 2022, after the release of the 2022 AHA/ACC/HFSA Guidelines, reinforced the evidence of SGLT2i for the reduction of CV death and worsening of HF in subacute and chronic outpatient setting with LVEF >40%. Additionally, a pre-specified pooled analysis of DAPA-HF and DELIVER[29] showed a significant CV death reduction across the HF spectrum. All these compelling data on SGLT2i reinforces their role on HF patients regardless of LVEF.

Participants also globally agreed on the importance of maintaining GDMT in HF patients with improved ejection fraction. This is particularly important because, following resolution of symptoms and recovery in cardiac function, patients frequently ask to stop medications. According to ESC Guidelines,[3] these patients should continue on their medication, as it is challenging to be certain of a complete and sustained recovery. This is in accordance with the TRED-HF trial[37] that showed that withdrawal from treatment was associated with relapse. In addition, the DELIVER trial[38] included HF patients with improved ejection fraction. Of 6263 patients, 18% had improved ejection fraction, and their benefit with dapagliflozin regarding both primary and secondary endpoints was consistent with the overall population.[38] This data suggest that patients with improved ejection fraction should continue treatment with disease-modifying therapies and initiate dapagliflozin if it was not initiated before.

Finally, despite Statement 11 (''Delaying devices implementation more than three months after medical therapy optimization is acceptable, particularly in patients with non-ischemic dilated cardiomyopathy.'') not scoring enough for ''Agreement'', we acknowledge significant limitations to interpreting the results. In a closer analysis of the results according to medical specialty, there was an agreement of 89.7% if we consider only the answers from the cardiologists. Although this analysis was not previously specified, it is particularly relevant since the device implementation is usually a decision of cardiologists and/or the heart team. Thus, we believe the inclusion of general practitioners significantly biased the results.

Healthcare organization

A high level of agreement was observed regarding the healthcare organization statements. Strategies to coordinate the different healthcare levels, develop optimized care and effective prevention programs are needed to decrease the economic and social impact of HF.[3]

The recent ESC, the National Institute for Health and Care Excellence and AHA/ACC/HFSA Guidelines recommend multidisciplinary HF management programs (HF-MPs).[3,35,39] Multidisciplinary teams (MDTs) are decisive in providing care to HF patients along their vital journey, including onset, hospital admissions and outpatient journey during apparent stability. Medical, devices and surgical therapies should be provided as well as rehabilitation, advanced, palliative and terminal care.[3] The MDT should be led by an HF specialist, usually a cardiologist or internal medicine specialist, and include nurses with HF training, who are central players in these teams.[40] Care needs should be coordinated carefully with the general practitioners, and permanent communication is essential to succeed.[40,41] Pharmacists, physiotherapists, nutritionists, palliative care teams, psychologists, social workers, occupational therapists, and administrators should also integrate the multidisciplinary teams providing holistic and patient-centric care to HF patients.[40]

Several implemented HF-MPs have shown positive results in HF readmissions. A recent meta-analysis including 38 randomized clinical trials (RCTs), concluded that multidisciplinary interventions significantly reduced readmissions up to six months post the index HF hospitalisation.[42] A previous network meta-analysis including 53 RCTs showed a reduction of all-cause mortality after hospitalization for HF due to disease-management clinics and home visits by nurses compared to usual care.[43] In Spain, the STOP-HF-Clinic intervention resulted in a 50% significant reduction in all-cause 30-day readmission, mainly driven by reduced HF-related readmissions.[44]

Models of care may vary in their components and should be adapted to healthcare systems, local conditions and patients' needs.

Strengths and limitations

This project has several strengths that need to be emphasized. To our knowledge, TOGETHER-PT is the largest HF questionnaire ever conducted in Portugal, including the participation of 152 HCPs highly interested in HF. This work is a glimpse into the views of Portuguese physicians and nurses on the issues related to HF awareness, diagnosis, treatment, and organization of care. TOGETHER-PT questionnaire included a sizeable number of participants not only from different medical specialties but also nurses.

Finally, TOGETHER-PT was designed by a joint effort of the three main national study groups related to HF – GEIC-SPC, NEIC-SPMI and GEsdCard-APMGF.

There are some limitations to this study. The first is the selection bias. The HCP invited into TOGETHER-PT were selected by GEIC-SPC, NEIC-SPMI and GEsdCard-APMGF. The authors cannot rule out that this bias influenced the results. However, the primary goal was not to have a representative sample of the Portuguese HF treating community. In contrast, we wanted to obtain the opinion of a sample of the most recognizable Portuguese HF experts. We believe the sample of 152 participants from diversified geographies and care contexts confers a varied perspective on Portuguese HF-related issues.

Thus, we consider that TOGETHER-PT can contribute to the improvement of HF care in Portugal.

Conclusions

TOGETHER-PT is the largest project conducted in Portugal aiming to obtain the perspectives of a broad group of HF experts on HF awareness, diagnosis, treatment, and organization of care in Portugal. There was significant consensus expressed by the participants regarding the four HF dimensions addressed.

This project, endorsed by GEIC, NEIC and GEsdCard, aims at being a promoter of change on HF landscape in Portugal to improve Portuguese HF patients' quality of life and prognosis.

This joint effort may inspire further cooperative actions among scientific societies and other relevant stakeholders to promote change in this field in our country.

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Conflict of interest

Aurora Andrade has received speaker or advisory boards fees from Novartis, AstraZeneca, Servier, Orion, Boehringer Ingelheim and Bayer.

Brenda Moura has received advisory and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Servier, Novartis, and Vifor Pharma.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2023.05.012.

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5.10. Beyond clinical trials - The cost saving associated with dapagliflozin use in Portugal hospital clinical practice

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ORIGINAL ARTICLE

Beyond clinical trials – The cost saving associated with dapagliflozin use in Portugal hospital clinical practice

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KEYWORDS
Heart failure;
SGLT2i;

Abstract
Introduction and objectives: Heart failure (HF) is a clinical syndrome associated with substantial morbidity, mortality, and healthcare costs. Dapagliflozin has proven efficacy in reducing the

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Dapagliflozin;
Healthcare costs;
Economic burden;
HF hospitalization

risk of death and hospitalization in HF patients, regardless of left ventricular ejection fraction (LVEF). This paper aimed to project the potential impact of dapagliflozin on healthcare costs related to HF subsequent hospitalizations (HFHs) in Portuguese hospitals.
Methods: The total number of HF-related hospitalizations (hHF), HFHs, and the average length of stay for patients with a primary diagnosis of HF from six Portuguese hospitals, between January 2019 and December 2021, were collected and aggregated by hospital classification. Costs associated with HFHs were calculated according to Portuguese legislation and considering conservative, average, and complex approaches. Cost-saving projections were based on extrapolations from hHF risk reductions reported in dapagliflozin clinical trials.
Results: Considering a 26% risk reduction in hHF reported on pooled-analysis of DAPA-HF and DELIVER as the expected reduction in HFHs, the use of dapagliflozin would be associated with cost savings ranging from EUR 1 612 851.54 up to EUR 6 587 360.09, when considering all hospitals and the different approaches, between 2019 and 2021. A similar projection is observed based on 24% RRR derived by weighting DAPA-HF and DELIVER sub-analyses and PORTHOS epidemiological data.
Conclusions: In this projection, dapagliflozin use in all eligible hHF patients is associated with a significant reduction in direct costs. Our data support that, in addition to the improvements in HF-related outcomes, dapagliflozin may have a significant economic impact on healthcare costs in Portuguese hospitals.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
iSGLT2;
Dapagliflozina;
Custos de saúde;
Encargos económicos;
Hospitalização por IC

Além dos ensaios clínicos – A redução de custos associada à utilização de dapagliflozina na prática clínica hospitalar em Portugal

Resumo
Introdução e objetivos: A insuficiência cardíaca (IC) é uma síndrome clínica associada a uma elevada morbidade, mortalidade e despesa com custos de saúde. A dapagliflozina demonstrou ser eficaz na redução do risco de morte e hospitalização em doentes com IC, independentemente da fração de ejeção do ventrículo esquerdo. Este artigo visa projetar o potencial impacto da dapagliflozina na redução dos custos relacionados com hospitalizações subsequentes por IC em hospitais portugueses.
Métodos: Foi recolhido, e posteriormente analisado de forma agregada em *clusters*, o número total de hospitalizações por IC, hospitalizações subsequentes por IC e duração média de internamento dos doentes com diagnóstico primário de IC em seis hospitais portugueses, entre janeiro de 2019 e dezembro de 2021. Os custos relacionados com hospitalizações subsequentes por IC foram calculados de acordo com a legislação portuguesa e tendo em consideração três abordagens – conservadora, média e complexa. A projeção da redução de custos teve por base as reduções do risco relativo (RRR) de hospitalizações por IC (hIC) reportadas nos ensaios clínicos com dapagliflozina.
Resultados: Considerando uma RRR de 26% do risco de hospitalização subsequente por IC, com base no valor reportado na análise agregada dos estudos DAPA-HF e DELIVER relativa à RRR de hIC, a nossa projeção indica que a utilização da dapagliflozina resulta numa redução de custos. De acordo com a nossa projeção a redução de custos oscila entre €1,612,851.54 e €6,587,360.09, entre 2019 e 2021, ao considerar todos os hospitais envolvidos e as diferentes abordagens metodológicas. A projeção aponta para um resultado similar tendo por base uma RRR de 24%, resultante da ponderação das subanálises de DAPA-HF e DELIVER, juntamente com dados epidemiológicos do estudo PORTHOS.
Conclusões: Nesta projeção, a utilização de dapagliflozina, em todos os doentes hospitalizados por IC que sejam elegíveis, está associada a uma redução direta significativa nos custos hospitalares. Estes dados reforçam a ideia de que, para além da melhoria nos resultados de saúde relacionados com a IC, a dapagliflozina pode ter um impacto significativo nos hospitais portugueses ao nível dos custos de saúde.
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Introduction

Heart failure (HF) stands as a pressing public health issue, exerting a substantial negative impact on healthcare costs and quality of life for those affected.[1–3] HF affects more than 64 million people worldwide, including 15 million in Europe.[1,4,5] The Heart Failure Association Atlas 2019 report showed a median HF incidence in Europe of three per 1000 person-years for all ages and a median prevalence of 17 cases per 1000 people, while data from the EPICA study, published in 2002, reported a prevalence of 43.6 cases per 1000 people.[2,6] Prevalence is expected to increase with an aging population, in addition to the extended survival observed in patients following guideline-directed medical therapy (GDMT).[7–9] Recently, in Portugal, data from the PORTHOS observational study were presented showing an HF prevalence of 16.54% in the population aged 50 years or more, according to an updated and guideline-based diagnosis approach (Rui Baptista and Cristina Gavina, personal communication, December 12, 2023).

Heart failure has a major economic impact and implies high direct and indirect costs.[10] Hospital care, due to the high rate of hospitalizations, is the major driver of HF costs.[10] Not only does HF represent a significant economic burden to the healthcare systems, accounting for 1–3% of global health expenses, but the costs associated with in-hospital treatment are estimated to represent 39–75% of the total HF costs.[3,11] More than one million hospitalizations deriving from HF have been reported in Europe and America per year, as well as readmission rates of 30% and multiple readmissions.[1,12] Following an HF diagnosis, patients are hospitalized, on average, once per year.[13] Globally, the number of hospitalizations may be expected to increase by up to 50% in the next 25 years, due to the aging population and the increased prevalence of comorbidities.[14,15] In Portugal, 39% of the costs associated with HF derive from hospitalizations.[3] As HF prevalence in Portugal is expected to increase by 30% by 2035, the total costs are also predicted to rise to EUR 503 million during the next decade.[3] Simultaneously, a rise in the in-hospital mortality can be expected.[16] Effective treatments that allow a reduction in HF-related hospitalizations (hHF) can play a significant role in the reduction of long-term HF costs.[3]

Several successful HF therapies have been developed in recent years. Among them, SGLT2 inhibitors (SGLT2i), including dapagliflozin, and empagliflozin, have been shown to reduce the risk of cardiovascular death and hospitalization in HF patients.[17,18] First, SGLT2i have proven their efficacy in patients with HF and reduced ejection fraction (HFrEF).[19,20] In 2021, the results of the SOLOIST-WHF trial showed the benefits of sotagliflozin, a dual SGLT2 and SGLT1 inhibitor, in reducing deaths from cardiovascular causes, hospitalizations, and urgent visits for HF in patients with diabetes and recent worsening HF, regardless of EF.[21] Then, the EMPEROR-Preserved trial and DELIVER showed the benefit of SGLT2i in HF patients with mildly reduced (HfmrEF) and preserved ejection fraction (HfpEF), regardless of type 2 diabetes.[22,23] Additionally, the DELIVER study showed benefits for patients who were hospitalized or had been recently hospitalized with HF, and for those with HF with improved LVEF.[23,24]

Both the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines recommend SGLT2i use in the treatment of patients with HFrEF, regardless of diabetes status (class of recommendation I, level of evidence A) due to the beneficial role in decreasing hHF and mortality.[25,26] SGLT2i are also recommended for the treatment of patients with both HfmrEF and HfpEF (class of recommendation I, level of evidence A and class of recommendation II, level of evidence B, according to the ESC and AHA/ACC/HFSA guidelines, respectively).[25,27]

The benefit of SGLT2i across all HF patients, regardless of LVEF, represents a significant breakthrough, particularly for patients with HfpEF who had no previously effective therapeutic options except for control of comorbidities and symptomatic relief.[22,23] Given the high prevalence of HfpEF, the opportunity SGLT2i bring is considerable. Therefore, considering the economic burden of HF and the robust evidence that consolidates the unique role of SGLT2i, we aimed to gather insights on the impact dapagliflozin might have on cost outcomes had it been used in a hospital setting. For this purpose, we hypothesized that the use of in-hospital dapagliflozin to all eligible patients will be associated with a decrease in healthcare costs associated with HF subsequent hospitalizations (HFHs) in six Portuguese hospitals.

Objectives

Using a modeling approach that was informed by clinical study results, epidemiological data, and real-world evidence data, the aim of this paper was to project the economic impact of dapagliflozin on HFHs when started on patients who were hospitalized for HF.

Methods

Population

For this economic projection, we gathered information from six Portuguese hospitals and included patients hospitalized with a primary HF diagnosis between the years of 2019 and 2021 retrospectively. The HF diagnosis was coded in accordance with the International Classification of Diseases (ICD) ninth and tenth revisions (Tables S1 and S2). Considering the renal restrictions associated with dapagliflozin use (estimated glomerular filtration rate [eGFR] must be >25 mL/kg/1.73 m^2 for treatment initiation), we adjusted the population eligible for dapagliflozin in this projection by considering data from renal function characterizations documented in an available Portuguese HF cohort.[28] Specifically, to be conservative, we excluded 19% of coded HF patients due to a eGFR <30 mL/kg/1.73 m^2, according to published data.[28] For an additional projection, we excluded a further 44.7% of patients corresponding to HF patients with diabetes, as reported in the literature.[29] The data collected were then aggregated and analyzed based on hospital clusters: university hospitals (2), non-university hospitals (2) and HF clinics (2).[30] Additionally, we performed an independent

analysis of dapagliflozin-associated cost reduction by using previously published HF Portuguese data.[31]

Assumptions for heart failure cost projection

The estimated cost per day of HFHs was determined by calculating the mean in-patient daily cost (overnight costs) and hospitalization prices (maximum costs of hospitalization, influenced by other factors, such as comorbidities) in accordance with Portuguese legislation (Table S3).[32] The cost projection was conducted using three approaches (conservative, average and complex), taking into consideration the costs associated with the four levels of HF severity (minor, moderate, major, or extreme)[32] (Table S3). In the conservative approach, the cost associated with the lower level of severity for all HF patients was used, resulting in a HFHs cost per day of EUR 876.07. The average approach was estimated by calculating the average of the cost values associated with the four levels of severity, amounting to EUR 1859.98 per day. Finally, the complex approach used the cost value associated with the highest level of severity (extreme), totaling EUR 3568.44 per day (Table S4).[32]

Concerning medication costs, only dapagliflozin treatment was considered, excluding other interventions (drugs or devices). Based on the assumptions that other treatments were used equally independently of dapagliflozin, excluding costs of other treatment would not impact the cost reduction associated with dapagliflozin.

Clinical inputs regarding HFHs cost-saving projection

For the projection of HFHs-related savings associated with dapagliflozin use in hHF patients, we utilized the collected aggregated data by clusters of hospitals and the dapagliflozin reported outcomes in clinical trials as inputs to our projection model. We projected two scenarios on HFHs cost reduction by extrapolating expected risk reductions on HFHs based on the hHF relative risk reductions obtained in the DAPA-HF and DELIVER clinical trials.[19,23] Scenario A considered a 26% expected reduction on HFHs. In the DAPA-HF and DELIVER pooled-analysis the reported relative risk associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls >29%. The scenario B considered an expected HFHs extrapolated from the 36% hHF relative risk reduction in HFrEF patients with a previous hospitalization in less than one year, and a 24% risk reduction in both HfmrEF and HfpEF patients that were recently hospitalized.[33,34] Since the data collected from the Portuguese hospitals did not differentiate among the HF phenotypes, we used the recent data from PORTHOS study to weight the values extrapolated from the literature according to PORTHOS HF phenotype reported prevalence. Thus, since PORTHOS reported a prevalence of 0.35%, 0.97% and 15.22% for HFrEF, HfmrEF and HfpEF in mainland Portugal (Rui Baptista and Cristina Gavina, personal communication, December 12, 2023), we considered a reduction of 24% of hHF risk, according with the formula: % risk reduction=(0.36×0.02)+(0.24×0.98), where the 2% and 98% are the proportion of Portuguese HF patients with either HFrEF or HfmrEF and HfpEF, respectively.

For projections, we used the collected data and calculated the costs associated with patient subsequent hospitalizations using the values described above. The details of projections are illustrated in Table S5.

Results

Hospitalization and patient characteristics

Between January 2019 until December 2021, a total of 4813 hHF were registered in the enrolled hospitals. Among these, 81.5% corresponded to first-time hospitalizations, and 18.5% to HFHs. The average length of stay for readmissions was 10 days. Out of the total of hHF, 58.6% were registered at university hospitals, 38.0% in non-university hospitals, and only 3.4% in HF clinics. However, data from HF clinics were only collected for the year 2019 due to COVID-19 constraints.

Regarding patient's characteristics, 49.2% were female. The mean age of hHF patients was 78 years. Detailed information on the number of hospitalizations, average number of hospitalization days and patient's characteristics are expressed in Table 1.

Cost saving associated with dapagliflozin use

The detailed costs associated with HFHs in the different hospital clusters, years, and approaches, as well as the savings associated with dapagliflozin using the two scenarios, are presented in Table 2. In scenario A we projected HFHs cost savings associated with dapagliflozin use, considering a 26% reduction in HFHs. At university hospitals, 2019 and 2021, dapagliflozin initiation was associated with a reduction of EUR 820 968.79, EUR 1 746 316.23, and EUR 3 353 078.00 in the conservative, average and complex approaches, respectively (Table 2). Similarly, projections applied to the non-university hospitals showed reductions in HFHs costs of EUR 758 896.63, for the conservative approach; EUR 1 614 280.02 in the average approach; and EUR 3 099 557.07 for the complex approach, in the same years (Table 2). In 2019, the implementation of dapagliflozin in HF clinics was associated with reductions of EUR 32 986.12, EUR 70 166.12, and EUR 134 725.02 considering the conservative, average and complex approaches, respectively (Table 2). According to our model, cost savings associated with the implementation of dapagliflozin for all eligible hHF patients could range from EUR 1 612 852 in the conservative approach, to EUR 6 587 360 in the complex approach.

In scenario B, in the conservative approach, we observed cost reductions of EUR 765 125.30 for the university hospitals between 2019 and 2021. In the average approach, the cost savings were EUR 1 627 833.84 for the same years. In the complex approach, we observed a cost reduction of EUR 3 125 830.19 (Table 2). Applying this second projection to data from non-university hospitals, we observed a reduction

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Table 1 Characteristics of heart failure admissions in study hospitals.

Variable	University hospitals (n=2)						Non-university hospitals (n=2)						HF clinics (n=2)	
	2019		2020		2021		2019		2020		2021		2019	
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD
Total hospitalizations, mean	1242	318.20	844	147.08	737	229.81	586	172.53	584	214.25	660	253.85	161	115.26
First-time hospitalizations, mean	1053 (85%)	275.06	729 (86%)	121.62	627 (85%)	167.58	430 (73%)	71.42	449 (77%)	136.47	495 (75%)	154.86	139 (86%)	122.33
Subsequent hospitalizations, mean	189 (15%)	43.13	115 (14%)	25.46	110 (15%)	62.23	157 (27%)	101.12	135 (23%)	77.78	165 (25%)	98.99	22 (14%)	7.07
Length of stay in days, mean	10	0.42	11	0.76	12	2.03	9	1.14	8	0.17	10	1.51	8	0.31
Female patients, mean	521 (42%)		354 (42%)		310 (42%)		353 (60%)		356 (61%)		393 (60%)		79 (49%)	
Age in years, mean	75	4.07	75	4.08	75	3.63	81	0.15	81	0.36	82	0.56	77	0.28

HF: heart failure; SD: standard deviation.

Table 2 Cost-saving projections for hospital readmissions associated with dapagliflozin use.

		Total cost of annual subsequent hospitalization*	Scenario A (26% expected RRR on HFHs[a])			Scenario B (24% RRR derived by weighting DAPA-HF, DELIVER with PORTHOS study[b])		
			Conservative	Average	Complex	Conservative	Average	Complex
University hospitals	2019	Without dapagliflozin	€ 1 314 428.27	€ 2 790 662.33	€ 5 353 976.75	€ 1 314 428.27	€ 2 790 662.33	€ 5 353 976.75
		With dapagliflozin	€ 973 902.18	€ 2 066 315.39	€ 3 963 168.06	€ 997 065.26	€ 2 115 460.19	€ 4 057 427.20
		Savings	€ 340 526.09	€ 724 346.94	€ 1 390 808.69	€ 317 363.01	€ 675 202.14	€ 1 296 549.56
	2020	Without dapagliflozin	€ 917 776.68	€ 1 948 531.44	€ 3 738 321.15	€ 917 776.68	€ 1 948 531.44	€ 3 738 321.15
		With dapagliflozin	€ 680 010.26	€ 1 442 768.79	€ 2 767 213.17	€ 696 183.48	€ 1 477 083.29	€ 2 833 027.97
		Savings	€ 237 766.42	€ 505 762.65	€ 971 107.98	€ 221 593.20	€ 471 448.15	€ 905 293.18
	2021	Without dapagliflozin	€ 936 728.74	€ 1 988 768.55	€ 3 815 517.36	€ 936 728.74	€ 1 988 768.55	€ 3 815 517.36
		With dapagliflozin	€ 694 052.45	€ 1 472 561.91	€ 2 824 356.03	€ 710 559.64	€ 1 507 585.01	€ 2 891 529.90
		Savings	€ 242 676.28	€ 516 206.64	€ 991 161.33	€ 226 169.09	€ 481 183.54	€ 923 987.45
Non-university hospitals	2019	Without dapagliflozin	€ 1 005 489.96	€ 2 134 755.49	€ 4 095 598.08	€ 1 005 489.96	€ 2 134 755.49	€ 4 095 598.08
		With dapagliflozin	€ 744 999.86	€ 1 580 656.35	€ 3 031 679.86	€ 762 718.77	€ 1 618 250.34	€ 3 103 784.68
		Savings	€ 260 490.11	€ 554 099.14	€ 1 063 918.22	€ 242 771.19	€ 516 505.16	€ 991 813.40
	2020	Without dapagliflozin	€ 758 760.16	€ 1 610 923.51	€ 3 090 609.33	€ 758 760.16	€ 1 610 923.51	€ 3 090 609.33
		With dapagliflozin	€ 562 189.81	€ 1 192 790.69	€ 2 287 758.19	€ 575 560.81	€ 1 221 159.77	€ 2 342 169.74
		Savings	€ 196 570.35	€ 418 132.82	€ 802 851.13	€ 183 199.35	€ 389 763.75	€ 748 439.59
	2021	Without dapagliflozin	€ 1 165 085.49	€ 2 473 592.72	€ 4 745 668.36	€ 1 165 085.49	€ 2 473 592.72	€ 4 745 668.36
		With dapagliflozin	€ 863 249.32	€ 1 831 544.67	€ 3 512 880.64	€ 883 780.65	€ 1 875 105.73	€ 3 596 430.23
		Savings	€ 301 836.18	€ 642 048.05	€ 1 232 787.72	€ 281 304.84	€ 598 486.99	€ 1 149 238.13
HF clinics	2019	Without dapagliflozin	€ 127 326.19	€ 270 326.21	€ 518 629.65	€ 127 326.19	€ 270 326.21	€ 518 629.65
		With dapagliflozin	€ 94 340.07	€ 200 160.08	€ 383 904.63	€ 96 583.83	€ 204 920.65	€ 393 035.33
		Savings	€ 32 986.12	€ 70 166.12	€ 134 725.02	€ 30 742.36	€ 65 405.56	€ 125 594.31

HF: heart failure; HFHs: heat failure subsequent hospitalizations; RRR: relative risk reduction.

* Total cost of annual subsequent hospitalizations in patients that could have initiated dapagliflozin during the index-hospitalization due to heart failure.

[a] The scenario A considered a 26% expected RRR on HFHs. In the DAPA-HF and DELIVER pooled-analysis the reported RR associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls above 29%.

[b] The scenario B considered a 24% RRR as expected RRR on HFHs derived by weighting DAPA-HF and DELIVER RRRs with PORTHOS epidemiological data.

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in HFHs costs of EUR 707 275.38, EUR 1 504 755.90, and 2 889 491.11 in the same years, considering the conservative, average and complex approaches, respectively (Table 2). Finally, in HF clinics, the cost savings associated with dapagliflozin considering a 24% reduction of HFHs risk were EUR 30 742.36 in the conservative approach, EUR 65 405.56 in the average approach, and EUR 125 594.31 in the complex approach (Table 2). Overall, in scenario B the use of dapagliflozin, and taking into account all years in the study this projection indicates a cost reduction up to EUR 6 140 916.

SGLT2i were already widely used in HF diabetic patients, therefore, a significant proportion of patients in our analysis could have previously taken or started an SGLT2i, which has a proven impact on HFHs. To address this limitation, we performed an independent analysis excluding 44.7% of patients corresponding to the reported diabetes incidence among HF patients.[29] Even excluding these patients, cost savings associated with dapagliflozin implementation can reach EUR 718 501.50, EUR 1 528 353.89, and EUR 2 934 571.47 in the conservative, average and complex approaches, respectively, when considering the 26% HFHs risk reduction for all the years and hospitals in the study (Table S6). Taking into account the 24% HFHs risk reduction, cost savings range between EUR 669 627.99, EUR 1 424 659.60 and EUR 2 735 687.07 in the conservative, average, and complex approaches for all hospitals and years analyzed (Table S6).

Cost saving associated with dapagliflozin use in previous published Portuguese heart failure cohorts

According to the literature, between 2012 and 2014, 51 310 patients with a primary diagnosis of HF were hospitalized in Portuguese hospitals.[31] From these, 22.1% were considered heavy users, meaning that they had two or more HF admissions within a 365-day period.[31] According to the same study, the length of hospital stay for frequent users was at least 20 days.[31] Taking into consideration these data, according to scenario A, dapagliflozin could have saved EUR 41 486 961.55, EUR 88 248 610 or EUR 169 444 954 considering the conservative, average, and complex approaches, respectively between 2012 and 2014. If we consider scenario B cost savings reach the EUR 38 664 958.16, EUR 82 261 202.84, and EUR 157 961 178.47 in each approach.

Discussion

Heart failure is related to significant morbidity and mortality, representing an important social and economic burden.[35] The increasing aging of the population, and the improvement in healthcare including innovative secondary prevention therapy and rehabilitation programs, are factors that highly contribute to the rising incidence and prevalence of this condition.[3] According to the literature, HF costs represent 2.6% of total Portuguese public health expenditure.[3] Furthermore, costs related to HF admissions represent 1.6% of Portuguese hospitals' budgets, and over 41% of these costs are attributed to patients that are re-hospitalized at least once within one year after previous discharge.[31] Given this approach, the approval of therapies that significantly reduce hHF risk can have an important impact on healthcare costs.

Dapagliflozin was associated with a reduction in the number of HF hospitalizations and subsequent hospitalizations.[33,34,36] In this paper, we projected the impact of in-hospital dapagliflozin use on healthcare costs related to HF readmissions by analyzing aggregated data collected from different Portuguese hospitals. The complexity of HF management in an hHF setting varies significantly, influenced by factors such as whether it is the first or a repeated event, comorbidities, the severity of the condition, the type of hospitalization and medical specialty. Therefore, for simplification, in this projection, the data were aggregated into three different approaches. Although the data used for the projection may not be representative of the national reality, this approach aimed to create a simple and comprehensive approach that reflects the economic impact of dapagliflozin use in all eligible patients in the different healthcare infrastructures (in terms of size) where an HF patient can be managed. Categorization of the data collected by the hospital sources provides a snapshot of these savings in these three different realities. We also evaluated data from HF clinics. Although these clinics can be placed in university and non-university hospitals, we also aimed to evaluate the impact of dapagliflozin in this setting since it is an increasing practice for patient management in our country. Our findings demonstrate that the use of in-hospital dapagliflozin for all eligible HF patients is associated with a significant decrease in costs in all considered approaches. Our projection model is based on the reported reduction of hHF risk associated with dapagliflozin use. Specifically, we project the HFHs cost savings associated with dapagliflozin use based on extrapolations for expected HFHs relative reductions based on data available from DAPA-HF and DELIVER clinical trials.[33,34] Both DAPA-HF and DELIVER studies were multinational, double-blinded, placebo-controlled randomized clinical trials in patients with HFrEF and with mildly reduced, preserved, or improved LVEF, respectively. These studies evaluated the efficacy and safety of 10 mg dapagliflozin, daily, in comparison with placebo over a follow-up of 18.2 months (DAPA-HF) and 2.3 years (DELIVER).[19,23]

In scenario A, dapagliflozin was associated with HFHs cost savings ranging from EUR 32 986.12, when applied to HF clinics in 2019, considering a conservative approach, to EUR 1 390 808.69, when considering the complex approach with data collected from 2019 in university hospitals. Similarly, if we consider the scenario B, cost savings can reach EUR 1 296 549.56 in the case of university hospitals in 2019. For these projections, we specifically focused on the medication expenses attributed to dapagliflozin only. This decision stemmed from our assumption that the utilization of other HF medications would likely maintain a similar rate, irrespective of dapagliflozin use. Moreover, our analysis presumed that the benefits associated with dapagliflozin remain constant regardless of variations in other patterns of HF treatment, as previously reported in the literature.[37,38]

In the university hospitals cluster, the use of dapagliflozin in the represented years could involve savings of EUR 813 916.92 per hospital in an average approach. Considering that Portugal has seven university hospitals, savings could

reach EUR 5 697 418.43 in these years.[39] Additionally, for non-university hospitals, extrapolation we only considered hospitals equipped a cardiology unit. We estimate an average cost reduction of EUR 752 377.95 per hospital resulting in a potential total cost reduction of EUR 22 571 338.43 for all the 30 Portuguese non-university hospitals with a structured cardiology unit.[39] Notwithstanding, it is relevant to highlight that many HF patients are managed by internal medicine, and the role of internal medicine is paramount in the management of patients with acute HF. For simplification purposes, we took into account only these 30 hospitals, however even hospitals without a structured cardiology unit might benefit from cost savings associated with dapagliflozin use. Moreover, non-university hospitals vary in size, resources, and population served, and thus this value may be biased; the projection indicates the economic impact that dapagliflozin can have among Portuguese hospitals.

Regarding the HF clinics, although they have grown significantly internationally and even nationally in recent years, there is no information available on the exact number of HF clinics in our country. Therefore, we are unable to estimate the total savings that the use of dapagliflozin can generate in this context. Nevertheless, from the independent projection, our model pointed to potential significant savings. Overall, according to scenario B, Portuguese healthcare costs could be reduced in EUR 28 268 756.86 through the treatment with dapagliflozin to all eligible patients. It is also important to notice that even after excluding a significant percentage of patients corresponding to the HF diabetic population already treated with SGLT2i, our projections still indicate a significant cost saving associated with dapagliflozin use.

Although we did not intend it to be a cost-effectiveness study, the results from our projections are aligned with previous cost-effectiveness studies, in which dapagliflozin was a cost-effective treatment for HFrEF relative to GDMT when evaluated in various healthcare systems, including the US,[40] UK, German, and Spain.[41] A similar conclusion is indicated by recent cost-effectiveness studies of dapagliflozin in HfmrEF and HfpEF patients.[42,43]

In this projection, we considered data from HF readmissions coded as the main diagnosis, opting for conservative yet more accurate projection. Nevertheless, the cost savings could potentially be higher in clinical practice, when considering all hHF, given that hHF is often recorded as a secondary cause of readmission. Additionally, we focused only on the direct cost of patients' readmissions to estimate cost savings. However, HF also represents a burden on patients' quality of life, impacting the daily living activities of patients and their caregivers.[10] Given the impact of dapagliflozin in improving HF-related outcomes, its implementation can also contribute to improvements in patients' quality of life.

We also applied our methodology to calculate the savings associated with hHF according to the Portuguese published data. Between 2012 and 2014, 51 310 patients with a main diagnosis of HF have been hospitalized in Portuguese hospitals,[31] leading to 68 565 admissions and 665 000 bed-days. The inpatient hospital services cost associated with these hospitalizations amounted to EUR 193 million, which corresponds to nearly 1.6% of the total costs from the national healthcare service.[31] From the 51 310 admitted patients, 22.1% had an average of 2.5 inpatient admissions per year, while 21.8% of these patients were re-hospitalized within 30 days, and 54.9% within 90 days of discharge.[31] Considering this data and an average approach, the national health service could have saved up to EUR 82 261 202.84 if dapagliflozin had been available and implemented at that time.

On average, 19% of our sample HF patients were re-hospitalized at least once after a previous HF hospitalization. This aligns with published national results showing a subsequent hospitalizations rate of 22.10%.[31] Our data are also consistent with the literature regarding the average age of patients (78 years for both) and gender distribution (51% female patients in our sample compared with 56% in published data).[31] According to our data, the average length of stay for acute HF subsequent hospitalizations was approximately 10 days, which is lower than that reported in previous studies.[31]

Limitations

This projection has several limitations that should be acknowledged. The clusters have only two sources which is not sufficient for a comprehensive representation of the entire cluster. Moreover, a broad standard deviation demonstrates the variability between the two sources. The data collected spanned three years, including the period of the coronavirus pandemic (COVID-19), which significantly affected access to healthcare and patient willingness to seek medical help. In Portugal, the first patient with COVID-19 was diagnosed in March 2020, so the 2019 data was not influenced by the pandemic. If HF hospitalization rates in 2020 and 2021 were similar to 2019, the cost savings would increase up to EUR 19 762 080.26 and EUR 18 422 746.86 considering 26% and 24% RRR on HFHs, respectively, in a complex scenario and for all considered hospitals. At the same time, we cannot rule out the worsening of HF COVID-19-related conditions.[44] Therefore, our projection would benefit from the inclusion of data collected in recent years either before or after the pandemic. Additionally, data regarding the use of out-patient services were not assessed, and for simplicity, other not expected costs have a significant impact on the projections performed were also not included. Similarly, costs related with dapagliflozin side effects were not considered.

Another limitation concerns the public nature of the hospitals from which our data were collected, as the costs associated with patients' follow-up in the private sector cannot be included, which could impact the reduction of health expenditure in the projections. Moreover, and as shown by previous studies focusing on the QoL of HF patients,[36,45] dapagliflozin may help further reducing indirect costs associated to absenteeism related to consultations, emergency visits and hospitalizations. However, the evaluation of these costs falls outside the scope of this projection.

For this projection, we considered the recently presented data regarding HfrEF, HfmrEF and HfpEF incidence in Portugal (Rui Baptista and Cristina Gavina, personal communication, 12 December 2023). However, the characteristics of the inpatient population may not reflect this incidence

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since a higher number of hospitalizations due to HFrEF is expected when compared with the other forms of HF. For projection purposes, we assumed that all eligible HF patients initiated dapagliflozin treatment during their first hHF event each year (index hHF). However, it is plausible that some of these eligible patients might have been already receiving dapagliflozin treatment. To strengthen our conclusions, we performed a separate analysis excluding the percentage of reported HF diabetic patients. Furthermore, it is worth noting that dapagliflozin had received approval in Europe for HFrEF treatment, in addition to type 2 diabetes, by the end of 2020, and for HF treatment irrespective of LVEF in 2022. Considering the update of ESC HF guidelines occurred only in 2021, it is anticipated that the adoption rate of dapagliflozin treatment among non-diabetic HF patients from 2019 to 2021 remained relatively low.

Aside from the assumption mentioned above, our model has other important assumptions to be taken in to consideration in the discussion of the results. Firstly, we considered only HF readmissions occurring within the same year to calculate the subsequent hospitalizations rate; secondly, the mean length of hospital stays was used instead of the median (which would be less impacted by possible outliers); thirdly, the calculated costs used were based on the Portuguese legislation and not in data specifically gathered from each hospital. Additionally, our data sources comprised only two hospitals for each group, contributing to increased standard deviation. However, despite these limitations, the results consistently indicate substantial cost reductions across all approaches tested within hospital settings.

Conclusions

Heart failure has a significant economic impact on healthcare costs, and this economic impact is expected to increase in the coming years. A considerable proportion of HF costs are attributed to hospitalizations, which are frequently recurrent. We had no intention of developing a comprehensive cost-effectiveness model, but this simplified projection based on real-world data acts as a significant addition to the translation of clinical trial data into clinical practice. This paper underscores the vital importance of implementing scientific knowledge to everyday medical practice. Our projections point to a significant cost reduction in all tested approaches, highlighting the importance of dapagliflozin use in an economic context. In addition to the reported value of dapagliflozin in improving HF outcomes, our projection clearly indicates a substantial cost reduction associated with subsequent HF hospitalizations when dapagliflozin is started during a HF hospitalization in all HF eligible patients.

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Conflict of interests

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.repc.2024.04.012.

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5.11. A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment

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REVIEW ARTICLE

A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction – Part I: Pathophysiology, diagnosis and treatment

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KEYWORDS
Heart failure;
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Abstract Heart failure (HF) with preserved ejection fraction (HFpEF) affects more than 50% of HF patients worldwide, and more than 70% of HF patients aged over 65. This is a complex syndrome with a clinically heterogeneous presentation and a multifactorial pathophysiology, both of which make its diagnosis and treatment challenging.

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HFpEF;
Pathophysiology;
Diagnosis;
Treatment

A Portuguese HF expert panel convened to address HFpEF pathophysiology and therapy, as well as appropriate management within the Portuguese context. This initiative resulted in two position papers that examine the most recently published literature in the field.

The present Part I includes a review of the HFpEF literature covering pathophysiology, clinical presentation, diagnosis and treatment, including pharmacological and non-pharmacological strategies.

Part II, the second paper, addresses the development of a holistic and integrated HFPEF clinical care system within the Portuguese context that is capable of reducing morbidity and mortality and improving patients' functional capacity and quality of life.

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PALAVRAS-CHAVE
Insuficiência cardíaca;
Insuficiência cardíaca com fração de ejeção preservada;
ICEp;
Fisiopatologia;
Diagnóstico;
Tratamento

Artigo de posicionamento de peritos portugueses sobre a gestão da ICFEp – Parte I: Fisiopatologia, Diagnóstico e Tratamento

Resumo A insuficiência cardíaca com fração de ejeção preservada (ICFEp) afeta mais de 50% dos doentes com IC em todo o mundo e mais de 70% dos doentes com IC com mais de 65 anos. É uma síndrome complexa, com uma apresentação clinicamente heterógena, e com uma fisiopatologia multifatorial, o que torna o seu diagnóstico e tratamento desafiantes.

Um painel de peritos portugueses em IC reuniu-se para abordar fisiopatologia e terapêutica da ICFEp, bem como a sua gestão adequada no contexto português. Este trabalho resultou em dois artigos de posicionamento, considerando a literatura da área publicada mais recentemente.

A presente Parte I inclui uma revisão da literatura sobre ICFEp abrangendo a fisiopatologia, apresentação clínica, diagnóstico e tratamento, incluindo estratégias farmacológicas e não farmacológicas.

A Parte II, num segundo artigo, integra o desenvolvimento de um sistema de cuidados clínicos de ICFEp holístico e integrado no contexto português, capaz de reduzir a morbi-mortalidade e melhorar a capacidade funcional e a qualidade de vida dos doentes.

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Introduction

According to the European Society of Cardiology (ESC), the diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF) is made when patients with established HF have left ventricular ejection fraction (LVEF) ≥50%.[1] In the presence of supranormal LVEF (>65–70%), diseases like hypertrophic cardiomyopathy or cardiac amyloidosis should be investigated, since supranormal LVEF may be due to reduced end-diastolic volume.[1] The American College of Cardiology defines HFpEF as a clinical diagnosis of HF and LVEF ≥50% not due to infiltrative or hypertrophic cardiomyopathy, valvular or pericardial disease, or a high output state.[2]

HFpEF affects more than 50% of HF patients worldwide,[3,4] and its prevalence increases sharply with age, affecting 70% of HF patients aged over 65 years.[5]

The recent PORTuguese Heart failure prevalence Observational Study (PORTHOS), a population-based cross-sectional study, screened over 6000 participants aged ≥50 years.[6] HF prevalence was 16.5%, higher in older people (odds ratio [OR] 10.6 in ≥70 vs. 50–59 years) and in women (OR 2.3 vs. men).[7] Most HF patients presented with HFpEF (15.2% vs. 1.3% of HF with reduced/mildly reduced ejection fraction [HFrEF/HFmrEF]). Three quarters of HFpEF patients were women and the same proportion were aged ≥70 years.[7]

The prevalence of HFpEF is expected to increase further in the near future due to aging of the population and the growing burden of comorbidities, particularly obesity, metabolic syndrome, diabetes, hypertension, atrial fibrillation (AF), and coronary artery disease.[4,8]

In addition to its increasing prevalence, HFpEF is a complex syndrome, clinically heterogeneous and with a multifactorial pathophysiology, which makes its diagnosis and treatment challenging. Considering the importance of HFpEF and the most recently published literature in the field, a panel of Portuguese heart failure experts convened to address HFpEF management within the Portuguese context. This position paper consists of two articles (Part I and Part II). The present Part I includes a review of the HFpEF literature covering pathophysiology, clinical presentation, and clinical management. Part II addresses the current status of HFpEF care in Portugal, identifies unmet needs, proposes a pragmatic approach to HFpEF management, and presents a diagnosis and referral roadmap, along with a strategy for treatment implementation.

Pathophysiology of heart failure with preserved ejection fraction

HFpEF is particularly common in older, overweight women with multiple comorbidities and elevated inflammatory plasma biomarkers.[9–11] Unlike HFrEF, in which neurohormonal activation plays a central role, chronic low-grade systemic inflammation is key in HFpEF.[12,13] Inflammation may be induced or aggravated by comorbidities such as obesity, metabolic syndrome and chronic kidney disease (CKD), together with the natural process of aging.[14] Chronic systemic inflammatory disorders such as rheumatoid arthritis also increase the occurrence of HFpEF.[15,16]

Obesity, age-related metabolic changes and systemic inflammatory disorders at the inception of heart failure with preserved ejection fraction

During the 1970s and 1980s HFpEF was most frequently associated with hypertension, but obesity is currently the most common associated comorbidity.[17–19] Obesity is an independent risk factor for HFpEF, more markedly in females than in males, while older women with central obesity are at the highest risk.[18,19]

Central obesity is defined as increased visceral (intra-abdominal) adipose tissue (VAT).[20] Intra-abdominal fat is highly metabolically active, and produces a chronic inflammatory state, as well as hemodynamic imbalance, both of which damage the heart and blood vessels.[21]

Intra-abdominal adipocytes produce leptin, neprilysin and aldosterone, and promote beta-2 adrenegic receptor and renal sympathetic nerve activation.[22] Neprylisin degrades natriuretic peptides, while aldosterone promotes sodium retention, resulting in plasma volume expansion and hence congestion.[22] Additionally, neprilysin and aldosterone, as well as adipokines (leptin and others), induce a low-grade chronic inflammatory state, promoting myocardial and vascular fibrosis.[23,24] Sodium retention is further amplified by the direct action of beta-2 adrenergic activation, which stimulates mineralocorticoid receptors, leading to cardiac and vascular fibrosis, sodium retention, and consequent plasma volume expansion.[22]

In sum, adiposity-driven plasma volume expansion is coupled with reduced ventricular and vascular distensibility due to fibrosis, induced by the overstimulation of cardiac and vascular mineralocorticoid receptors. This leads to a marked increase in end-diastolic pressure (hemodynamic congestion), resulting in dyspnea and peripheral edema (clinical congestion).[25]

Epicardial tissue expansion and inflammation

The above-mentioned persistent systemic inflammatory state results, in turn, in expansion and inflammation of epicardial adipose tissue. The latter creates a substrate for AF and induces coronary microvascular endothelial inflammation, contributing to myocardial dysfunction and remodeling.[12,26,27] Cardiac fibroblasts are activated, leading to interstitial myocardial fibrosis.[28]

This chain of events leads to myocardial diastolic dysfunction and left ventricular (LV) concentric remodeling, both resulting, again, in a marked increase in end-diastolic pressure.[14]

Atrial fibrillation and left ventricular diastolic dysfunction

As the sequence of events described above involves the left atrium, it can lead to AF and, by involving the left ventricle, promotes diastolic dysfunction, both of which are associated with HFpEF.[12]

The emergence of AF is very common and important in HFpEF patients, since in a small ventricle with diminished distensibility, the contribution of atrial kick is extremely important to maintain LV filling and cardiac output. Thus, the presence of AF reduces LV filling, leading to diminished output. Additionally, a stiff ventricle is more dependent on diastolic time for adequate filling. Rapid AF dramatically reduces LV diastolic time and thus may lead to flash pulmonary edema.[29]

Accordingly, the H_2FPEF score attributes the greatest weight to the presence of AF among all variables considered when predicting the likelihood that HFpEF is present in an individual patient.[30]

Furthermore, ventricular fibrosis also occurs in HFpEF and may lead to an increased risk of ventricular arrhythmias and sudden cardiac death.[31,32]

Hypertension and heart failure with preserved ejection fraction

Between 55% and 90% of HFpEF patients have arterial hypertension, which is the most prevalent comorbidity in HFpEF.[33,34]

Important mechanisms linking hypertension and HFpEF include LV hypertrophy, myocardial fibrosis, and subsequent diastolic dysfunction.

Myocardial fibrosis and reduced capillary density, in the presence of LV hypertrophy, result in myocardial ischemia, thus worsening LV diastolic function.[33–35]

Additionally, aortic stiffness consequent to hypertension is responsible for increased arterial wave reflection velocity, inducing late systolic load, thus contributing to LV diastolic dysfunction.

Vascular fibrosis and stiffening

Vascular fibrosis and stiffening also play an important role in HFpEF, since they reduce arterial compliance, increasing LV diastolic dysfunction and producing left and right ventricular-arterial uncoupling.[36,37]

Diabetes and heart failure with preserved ejection fraction

The association between diabetes and HFpEF may be mediated by hyperinsulinemia, which can suppress autophagy and promote mitochondrial dysfunction. Increased sympathetic activation and cardiac hypertrophy are important conse-

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quences of hyperinsulinemia.[27] It can also activate Na-H exchangers in renal tubules and cardiomyocytes, and cause expansion of epicardial fat, which is associated with microcirculatory dysfunction and myocardial fibrosis.[12]

Additionally, the myocardium can become insulin-resistant with obesity, and gender and obesity interact in predicting myocardial glucose uptake and insulin sensitivity.[38]

Chronic kidney disease and the cardiovascular-kidney-metabolic syndrome

Chronic kidney disease is present in about half of patients with HFpEF. Pathophysiological mechanisms implicated in HFpEF are linked to the association of CKD with hypertension and metabolic abnormalities, which activate a systemic inflammatory reaction, endothelial dysfunction, and myocardial fibrosis, including increased central venous and intra-abdominal pressures, renin-angiotensin system activation, oxidative stress, and chronic inflammation.[33,34]

Considering the overlap between the cardiorenal and cardiometabolic syndromes, it has been suggested that a wider concept of a cardiovascular-kidney-metabolic (CKM) syndrome should be adopted.[39] The molecular mechanisms of CKM syndrome include a variety of interconnected factors; however, what links risk factors for CKM to cardiovascular disease and CKD remains unclear.[39]

Other pathophysiological mechanisms in heart failure with preserved ejection fraction

Impaired cellular calcium regulation, loss of muscle mass and decline in muscle strength, among many other factors, may play a role in the pathogenesis of HFpEF.[40,41]

Chronotropic incompetence, defined as a significantly lower peak heart rate during exercise compared to that of normal individuals of the same age group, has also been consistently associated with exercise intolerance in HFpEF, by limiting these patients' ability to increase cardiac output.[42]

The particular case of women

It is still unclear why HFpEF is more prevalent in women. Women, particularly when older and obese, tend to have greater epicardial and intramyocardial fat volume and higher levels of adipocyte-associated proinflammatory mediators than men.[18] Additionally, women with increased visceral adipose tissue (VAT) present 33% greater exercise pulmonary capillary wedge pressure than those without, whereas this was not observed in men.[17] Moreover, women tend to show greater arterial stiffness, and a smaller, thicker and stiffer left ventricle than men.[43]

Clinical presentation and diagnosis of heart failure with preserved ejection fraction

Diagnosing HFpEF requires the investigation of specific etiologies that may present with or without HF signs and symptoms and preserved LVEF, but require specific diagnostic assessment and therapeutic management.[2] These include conditions such as amyloid, hypertrophic or other restrictive/infiltrative cardiomyopathies, and valvular or pericardial diseases.[2]

Additionally, in patients with dyspnea and other signs and symptoms associated with HF, diagnosing HFpEF is not straightforward, since the presence of preserved LVEF requires differential diagnosis with non-cardiac causes of dyspnea. In some cases, advanced imaging or invasive cardiopulmonary exercise testing may be required in patients who only develop physical manifestations of congestion during exercise.[5,44]

Two tools have been developed to help in the diagnosis of HFpEF: the H_2FPEF score and the HFA-PEFF algorithm.[30,44]

The H_2FPEF score was created using an invasively diagnosed HFpEF cohort, and was subsequently tested in a validation cohort. It is based on six clinical variables, most of which are readily assessed in clinical practice, and an online calculator is available.[30]

The HFA-PEFF algorithm was created by an expert consensus panel and is more complex than the H_2FPEF score. An initial probability of HFpEF is established, based on clinical assessment complemented by a diagnostic work-up including natriuretic peptides, electrocardiography, chest X-ray, and advanced echocardiography.[44] If this probability is low, HFpEF is excluded, while if it is high, HFpEF is confirmed.[44] When the probability of HFpEF is intermediate, a diastolic stress test should be performed.[44] This uses exercise right heart catheterization to directly measure HFpEF-defining parameters, and is therefore the diagnostic gold standard. However, this is an invasive technique, requires operator expertise and has high associated costs, making it unsuitable as an universal diagnostic tool.[5] The HFA-PEFF algorithm incorporates diastolic stress testing only on a case-by-case basis.

Treatment of heart failure with preserved ejection fraction

Addressing etiology and comorbidities

Both the 2021 ESC and the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) heart failure guidelines recommend the identification and treatment of HFpEF etiology and comorbidities with a class I indication[1,33,45,46] and consider them core elements of HFpEF management.[1,33,45,46] They also recommend increased physical activity and reduction of body weight in overweight and obese patients.[1,45]

Physical activity

Exercise intolerance is a major feature of HFpEF, affecting quality of life. Impaired exercise capacity in HFpEF is due to various pathophysiological mechanisms involving the heart, lungs, vessels, and skeletal muscles. Regular exercise has demonstrated a pleiotropic array of positive effects that can ameliorate these cardiac and extracardiac abnormalities.[47] Current guidelines strongly advocate exercise training for HF patients, assigning it a class I recommendation (level of evidence A).[47] Several trials have consistently shown improvements in

exercise capacity in HFpEF patients through various exercise modalities, including facility-based and home-based interventions.[47,48]

Reduction of body weight

Weight loss via caloric restriction or aerobic exercise reduced LV mass and inflammatory markers and improved exercise capacity and quality of life in a seminal clinical trial in older obese patients with HFpEF, with the combination of the two interventions being additive.[49] Weight loss can be achieved through a combination of lifestyle interventions including diet and exercise training, pharmacotherapy, and bariatric surgery.

In the recently published STEP-HFpEF trial, the glucagon-like peptide-1 (GLP-1) agonist semaglutide led to reductions in symptoms and physical limitations and greater exercise capacity and weight loss, compared with placebo in non-diabetic obese HFpEF patients, across obesity categories.[50,51] The magnitude of benefit was directly related to the extent of weight reduction, supporting the drug as a key treatment strategy in the obese HFpEF phenotype. The recent STEP-HFpEF DM trial showed similar results with semaglutide in patients with obesity-related HFpEF and type 2 diabetes.[52] Recently released data from the SUMMIT trial with tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 agonist, showed a 38% relative risk reduction in the co-primary endpoint of time to first cardiovascular death, HF urgent visit/hospitalization, or oral diuretic intensification with tirzepatide vs. placebo over a median follow-up of 104 weeks in 731 patients with obesity (body mass index $\geq$30 kg/m^2) and New York Heart Association (NYHA) class II–IV HFpEF (LVEF $\geq$50%), with N-terminal pro-brain natriuretic peptide (NT-proBNP) >200 pg/ml (>600 pg/ml with AF) and estimated glomerular filtration rate (GFR) between 15 and 70 ml/min/1.73 m^2, and without glycated hemoglobin $\geq$9.5%, uncontrolled diabetes, or a major cardiovascular event in the last 90 days of screening.[53] Additionally, mean body weight reduction from baseline to week 52 was observed with tirzepatide, with an approximate 15.7% body weight reduction vs. 2.2% in the placebo arm.[53,54]

Although bariatric surgery is associated with significant and sustained weight reduction, there are no data on HFpEF patients or randomized trials assessing its effect on cardiovascular outcomes; however, observational data support its association with a reduced incidence of HF.[55]

Diuretics: congestion control

Congestion is central in HFpEF, and thus loop diuretics are a crucial part of therapy.[1,45] Elevated LV filling pressures, as measured by LV end-diastolic pressure (LVEDP), are needed to ensure appropriate diastolic filling, which is essential to maintain cardiac output. However, increased LVEDP, if above a certain level, leads to pulmonary congestion. On the one hand, diuretics are key to reducing congestion and dyspnea in HFpEF by lowering LVEDP. On the other hand, in the context of a stiff ventricle, this may compromise LV filling, impairing cardiac output and causing hypotension.[56,57] This is why in HFpEF the window between volume overload and hypovolemia is very narrow; thus, diuretics must be managed with caution. Additionally, considering the preload dependence of HFpEF, congestion correction requires smaller doses of diuretics than in HFrEF.[57] Despite the paucity of evidence from randomized controlled trials, diuretics have a class I indication for HFpEF treatment in both the European and American guidelines.[1,45]

Sodium-glucose co-transporter-2 inhibitors: the first prognosis-modifying drugs for heart failure with preserved ejection fraction

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) were initially shown to reduce HF hospitalizations in patients with type 2 diabetes, and subsequently demonstrated a reduction in HF hospitalizations and cardiovascular and all-cause mortality in HFrEF patients.[58,59]

In patients with HFpEF, the EMPEROR-Preserved[60] and DELIVER[61] studies showed that SGLT2is, regardless of the presence of diabetes, reduced the combined risk of cardiovascular death/HF hospitalization (EMPEROR-Preserved) and the risk of cardiovascular death/worsening HF (DELIVER). The combined results of these two studies met the criteria for a class I indication, level of evidence A, from the ESC[1] and a II-A recommendation from the AHA/ACC/HFSA guidelines.[45] Currently, SGLT2is are the only class of drugs with this level of indication in HFpEF. All patients with HFpEF should be under an SGLT2i (empagliflozin or dapagliflozin), unless not tolerated or contraindicated.

Several hypothetical mechanisms of action for SGLT2is in HFpEF have been advanced to explain their cardioprotective role. These include a modest direct decrease in blood pressure and an increase in diuresis/natriuresis. The latter results in a more selective reduction in extravascular rather than intravascular congestion. Additional possibilities include decreased epicardial fat mass, inflammation prevention, reduction of neurohormonal activation, increase in autophagy and lysosomal degradation, decreased oxidative stress, and the prevention of ischemia/reperfusion injury, among others.[62–65] Although the blood pressure-lowering effects of SGLT2is were initially thought to be secondary to diuresis and natriuresis, they have been shown to persist even after a decline in GFR. This suggests that additional mechanisms of action (possibly involving reduced arterial stiffness, changes in sympathetic nervous system activity or improved endothelial function) may play a role as well.[63] One of the most recent hypotheses to explain the effects of SGLT2is on cardiac function involves the possible modification of cardiomyocyte metabolic pathways induced by these agents (specifically, the use of ketogenic metabolism rather than fatty acid and glucose metabolism), resulting in improved cardiac efficiency.[63,66] It has been proposed that SGLT2 acts as a nutrient surplus sensor, and so its inhibition enhances nutrient deprivation signaling and activates an autophagic flux that reduces cellular stress and promotes cellular survival.[67] Another hypothesis involves SGLT2i-induced improvement in myocardial ionic homeostasis.[63,66]

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Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system inhibitors (RAASis) include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), angiotensin receptor/neprilysin inhibitors (ARNIs) and mineralocorticoid receptor antagonists (MRAs). None of the large trials involving RAASis in HFpEF met the composite endpoint of reducing cardiovascular mortality/HF hospitalizations. These include PEP-CHF (with perindopril), CHARM-Preserved[68] (with candesartan), PARAGON-HF[69] (with sacubitril/valsartan) and TOPCAT[70] (with spironolactone). Nevertheless, although cardiovascular mortality was not reduced in the active arm in any of the above studies, candesartan and spironolactone reduced HF hospitalizations and sacubitril/valsartan showed a trend with no statistical significance.

The TOPCAT study deserves some additional comments. A pre-specified subgroup analysis suggested that the primary outcome was significantly reduced by spironolactone in patients with elevated natriuretic peptide levels at baseline. A subsequent subanalysis restricted to patients enrolled in North and South America showed a significant reduction in the primary composite endpoint (time to cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure) in the intervention arm compared to placebo, whereas this was not observed in the European cohort.[71,72] It is noteworthy that among the Russian cohort, a higher percentage of participants showed undetectable levels of canrenone (an active metabolite of spironolactone) compared to American and Canadian subjects.[73]

Considering the importance of vascular and cardiac fibrosis in HFpEF, it is plausible that antagonizing the mineralocorticoid receptor may have a positive impact on prognosis.[74]

ARNIs, ARBs and MRAs received a class II-B indication in the AHA/ACC/HFSA guidelines for HFpEF patients, with the disclaimer of higher benefit demonstrated in patients with LVEF closer to 50%.[1,45]

Additionally, following the FIDELIO-DKD and FIGARO-DKD trials, finerenone, a non-steroidal MRA with high binding affinity, has a class I level A recommendation for the prevention of HF hospitalizations in patients with albuminuric CKD and type 2 diabetes.[75] Pre-specified subgroup analyses of these two studies suggested a potential beneficial effect of finerenone in HF patients without symptomatic HFrEF.[76,77] This effect was recently confirmed in the FINEARTS-HF study, which included 6016 NYHA class II–IV HFmrEF/HFpEF (LVEF $\geq$40%; LVEF $\geq$60% capped at 20%) patients with structural cardiac abnormalities, NT-proBNP $\geq$300 pg/ml ($\geq$900 pg/ml if AF), K+ $\leq$5.0 mmol/l, estimated GFR $\geq$25 ml/min/1.73 m^2, and on diuretic treatment for $\geq$30 days. This study met the primary endpoint with a statistically significant and clinically meaningful reduction in the composite of cardiovascular death and total HF events vs. placebo.[78,79]

Beta-blockers

There is no prospective evidence of a positive impact of beta-blockers on HFpEF. Some studies suggest a deleterious effect, with a higher risk of hospitalizations.[80]

Treatment of heart failure with preserved ejection fraction: future avenues

Ferric carboxymaltose

Iron supplementation with IV administration of ferric carboxymaltose (FCM) has a clear beneficial effect on HFrEF patients.[81,82] However, there are scarce data on the potential of iron supplementation in patients with HFpEF. Small-sample randomized clinical trials and retrospective studies have shown that supplementation with FCM significantly improves cardiac performance of HFpEF patients.[83,84] Results from the ongoing PREFER-HF and FAIR-HFpEF trials may add evidence on this subject.[85,86]

Glucagon-like peptide-1 receptor agonists

Although they reduce epicardial fat and inflammation, GLP-1 receptor agonists pose challenges with sodium retention in HFpEF.[87] As stated above, in the STEP-HFpEF trial, the GLP-1 agonist semaglutide demonstrated significant benefits in non-diabetic obese HFpEF patients, including reduced symptoms, enhanced exercise capacity, and greater weight loss compared to placebo across obesity categories.[50,51] Notably, the degree of benefit correlated directly with weight reduction, emphasizing its pivotal role as a treatment strategy in the obesity phenotype of HFpEF.

Metformin

Metformin reduces epicardial tissue expansion and inflammation, as well as myocardial fibrosis.[87] In observational studies, it appeared to reduce the incidence of AF and HFpEF.[87]

Thiazolidinediones and dipeptidyl peptidase-4 inhibitors

Thiazolidinediones and dipeptidyl peptidase-4 inhibitors reduce epicardial adipose tissue dysfunction and could potentially reduce the risk of AF and HFpEF.[87] However, although thiazolidinediones have favorable effects on experimental HFpEF and AF, their antinatriuretic properties make them inappropriate for use in HFpEF patients.[87]

Targeting visceral adipose tissue

VAT is a highly active endocrine organ that secretes cytokines and other mediators. As pointed out above, increased VAT seen in central obesity leads to epicardial fat expansion and inflammation, a major step in the genesis of HFpEF. Thus, targeting VAT may be a future approach to HFpEF through dietary, drug and/or surgical weight loss strategies.[88]

Anti-inflammatory agents

Epicardial adipose tissue expansion and associated inflammatory activity may be reduced by statins and anticytokine

agents.[87] These agents could, in theory, thereby reduce the incidence of AF and HFpEF.[87]

Ongoing clinical trials

The ongoing EMPA-PRED and ENRICH-PEF clinical trials are expected to provide further evidence on HFpEF management. The EMPA-PRED study aims to assess the safety and efficacy of empagliflozin in patients with end-stage renal disease and HFpEF.[89] The effects of enavogliflozin on exercise performance, diastolic dysfunction, and quality of life in HFpEF patients will be investigated in the ENRICH-PEF trial.[90] Additionally, trials with aldosterone synthase inhibitors, such as baxdrostat, for treatment-resistant hypertension are ongoing.[91]

Non-pharmacological alternatives under study

Atrial pacing, atrial shunting and AF ablation are three non-pharmacological alternatives that are being studied in HFpEF, although the evidence is not consistent. In the RAPID-HF trial, atrial pacing increased early and peak exercise heart rate, but no improvement in exercise performance or quality of life was observed.[92] The CABA-HFPEF trial will assess whether catheter-based AF ablation can improve cardiovascular outcomes compared to conventional treatment in these patients.[93] Lastly, the first large trial of an atrial shunt device, designed to lower left atrial pressure, presented neutral overall results. Ongoing trials are expected to add evidence in this field.[94]

Conclusion

Worldwide population aging, changes in lifestyle and the resulting diabesity epidemic are leading to a steep increase in the prevalence of HFpEF, which is becoming the dominant HF phenotype. The epidemiology, pathophysiology, diagnostic work-up and treatment of HFpEF differ from HFrEF.

The clinical management of HFpEF requires the involvement of multidisciplinary teams, covering hospital and outpatient settings. It is essential to address its multiple dimensions, from diagnosis to follow-up and therapy, in order to reduce morbidity and mortality and improve patients' functional capacity and quality of life.

A better understanding of this condition can help develop an effective, holistic and integrated clinical management of HFpEF. This will be the subject of Part II of this expert panel position paper, which will address the burden of HFpEF and organization of care, while proposing a pragmatic approach to its management.

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5.12. A Portuguese Expert Panel Position Paper on HFpEF Management - Part II: Unmet needs and Organization of Care in Portugal

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GUIDELINES

A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction – Part II: Unmet needs and organization of care in Portugal

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KEYWORDS
Heart failure;
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Abstract In Portugal, a 15.2% prevalence of heart failure with preserved ejection fraction (HFpEF) was recently identified among those aged ≥50 years. HFpEF represents 90% of Portuguese heart failure patients.

HFpEF management in Portugal is challenging due to patient heterogeneity, diagnostic and therapeutic complexity, and organizational constraints on the healthcare system.

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HFpEF;
Organization of care;
Roadmap;
Screening;
Diagnosis;
Referral;
Follow-up;
Treatment

Considering the above, a panel of Portuguese experts convened to address HFpEF management within the national context. This was done in a two-paper set.

This, the second paper, identifies unmet needs and suggests a set of measures to improve the current organization of HFpEF management in Portugal. Our purpose is to create a multidisciplinary integrated care system, ensuring a seamless connection between hospitals and primary care. Additionally, we propose a practical approach to the management of HFpEF, including a roadmap for screening, diagnosis, referral and treatment. The aim is to help clinicians improve HFpEF management throughout the disease trajectory.
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PALAVRAS-CHAVE
Insuficiência cardíaca;
Insuficiência cardíaca com fração de ejeção preservada;
ICEp;
Organização de cuidados;
Roadmap;
Rastreio;
Diagnóstico;
Referenciação;
Seguimento;
Tratamento

Gestão da ICFEp: um artigo de posicionamento de peritos portugueses – Parte II: Lacunas e Proposta de Organização dos Cuidados em Portugal

Resumo Em Portugal, foi recentemente identificada uma prevalência de 15,2% de insuficiência cardíaca com fração de ejeção preservada (ICFEp) em indivíduos ≥50 anos. A ICFEp representa 90% dos doentes portugueses com insuficiência cardíaca (IC).

A gestão da ICFEP em Portugal é um desafio devido à heterogeneidade dos doentes, à complexidade diagnóstica e terapêutica e às restrições organizacionais do sistema de saúde.

Considerando o acima exposto, reuniu-se um painel de peritos portugueses para abordar a gestão da ICFEP no contexto nacional. Este foi feito num conjunto de dois artigos.

Este segundo artigo identifica as necessidades não satisfeitas e sugere um conjunto de medidas de melhoria para a atual organização da gestão da ICFEp em Portugal. O objetivo é criar um sistema de cuidados integrados multidisciplinares, garantindo uma ligação perfeita entre os hospitais e os cuidados de saúde primários. Além disso, propomos uma abordagem prática para a gestão da ICFEp, incluindo um guião de rastreio, diagnóstico, encaminhamento e tratamento. O objetivo é ajudar os médicos a melhorar a gestão da ICFEP ao longo da trajetória da doença.
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Introduction

It is commonly accepted that heart failure with preserved ejection fraction (HFpEF) affects approximately 50% of patients with heart failure (HF).[1] The incidence of HFpEF increases sharply with age, and 70% of HFpEF patients are aged >65 years.[2] The prevalence of HFpEF is expected to rise in the near future due to aging of the population and the increasing prevalence of obesity, hypertension, metabolic syndrome, coronary artery disease and diabetes.[3]

The management of HFpEF can be challenging due to the heterogeneity of patient profiles and diagnostic and therapeutic issues. This position paper consists of two articles (Part I and Part II). Part I includes a review of the HFpEF literature covering pathophysiology, clinical presentation, and clinical management. In the present Part II, we address the current status of HFpEF management in Portugal, identifying unmet needs, proposing a pragmatic approach to HFpEF management, and presenting a roadmap for diagnosis and referral, along with a strategy for treatment implementation.

The prevalence of heart failure with preserved ejection fraction and associated burden in Portugal

In 2002, the EPICA study[4] established an HF prevalence of 4.36% among the mainland Portuguese population, amounting to 400 000 patients, of whom approximately 40% had preserved systolic function.[4] The recent Portuguese Heart Failure Observational Study (PORTHOS), a population-based, nationwide, three-stage screening study in people ≥50 years of age that recruited over 6000 participants in mainland Portugal, updated these figures.[5] According to this study, HF prevalence underwent a major increase in Portugal, reaching 16.5%, higher in older people (10.6 times higher in those aged ≥70 vs. 50–59 years) and in women (2.3 times higher). This was mainly due to a disproportionate increase in HFpEF,

with a prevalence of 15.2%, about three quarters of whom were women and aged ≥70 years.[6]

Profile of patients with heart failure with preserved ejection fraction

The typical HFpEF patient profile is an elderly obese woman with multiple comorbidities (such as diabetes, hypertension, atrial fibrillation and chronic kidney disease), frequently living alone.[7–11] These patient characteristics were also found in the PORTHOS HFpEF population.[6]

Portugal has one of the highest rates of elderly people in the world (23.8% of the Portuguese population in 2022).[12] In 2021, nearly 450 000 Portuguese people aged ≥65 years lived alone.[13] Nearly 31% of PORTHOS participants aged 70 or older had HFpEF.[6]

Additionally, PORTHOS found a prevalence of 30.5% for obesity, 25.4% for type 2 diabetes (T2D), and 76.0% for hypertension in HFpEF patients aged ≥50 years.[6]

Overall, these data confirm a high burden of HFpEF in Portugal and many unmet needs regarding its management in the national context.

Heart failure with preserved ejection fraction in Portugal: unmet needs

Access to primary care

Comprehensive primary healthcare coverage is essential to diagnose and monitor health conditions such as HFpEF. However, 16% of the Portuguese population do not have a primary care physician under the National Health Service and, in many cases, even those who do, report limited access.[14] Such limited access to primary care may compromise early HFpEF diagnosis, and constitutes a major unmet need in our national context.

Establishing the diagnosis of heart failure with preserved ejection fraction

Diagnosing HFpEF can be challenging since numerous clinical conditions manifest with similar symptoms and signs. These include chronic respiratory diseases, obesity, venous pathology, and anemia. The presence of preserved left ventricular ejection fraction (LVEF) necessitates differential diagnosis with non-cardiac dyspnea, which occasionally requires advanced imaging or invasive cardiopulmonary exercise testing, particularly in patients who only develop physical manifestations of congestion during exercise.[2,15,16]

In recent years, integrated diagnostic approaches have been proposed based on composite scores derived from medical history, laboratory results, and electrocardiographic and imaging data.[17–19] The European Society of Cardiology (ESC) heart failure guidelines state that a diagnosis of HFpEF should be based on the presence of typical symptoms and signs of HF, with additional information from natriuretic peptides, electrocardiography and echocardiography, to ensure efficient, early and accurate diagnosis.[18]

Natriuretic peptides

Natriuretic peptides are particularly important for diagnosing HFpEF, both as a rule-out test and as a marker of congestion, and for prognosis.[18] However, in Portugal, access to this diagnostic test at the primary healthcare level remains limited due to a lack of reimbursement in this context.[20–22]

Interpretation of natriuretic peptide levels in HFpEF may not be straightforward, which underlines the need to train clinicians appropriately in the correct use and interpretation of the test. This is particularly important in patients with obesity, atrial fibrillation, advanced age or chronic kidney disease, conditions that carry a high risk of developing HFpEF and significantly impact natriuretic peptide levels.[23]

Echocardiography

The situation throughout Portugal, in both primary healthcare and hospital settings, is of inequitable access to echocardiography, with long waiting lists in several hospitals.

There is considerable heterogeneity in the content of echocardiographic reports, with frequent omission of essential functional and structural parameters, which makes the inclusion of echocardiographic criteria in HFpEF diagnosis more challenging.

Additionally, in Portugal there is no reimbursement of Doppler modalities in primary care, so the great majority of patients in this context only have access to two-dimensional echocardiography.

Other cardiac structural and functional tests

There is limited access nationwide to comprehensive diagnostic work-up tests, such as cardiac magnetic resonance imaging and exercise stress tests with echocardiographic or invasive hemodynamic monitoring, that may be required to better identify etiology or to diagnose more challenging HFpEF patients.

Treating heart failure with preserved ejection fraction

Non-pharmacological management

Regular exercise has been shown to offer a pleiotropic array of positive effects that can ameliorate cardiac and extracardiac abnormalities in HFpEF.[24] Current guidelines strongly advocate for exercise training in HF patients, assigning it a class I recommendation (level of evidence A).[24]

Despite the potential of exercise to improve outcomes in HFpEF,[24–26] and the growing number of cardiac rehabilitation centers in Portugal, there is still a shortage of cardiac rehabilitation programs and they are unevenly distributed throughout the country. In a 2019 survey, only 14.5% of referrals to phase II and 19.8% of referrals to phase III cardiac rehabilitation programs were due to HF, although the former percentage was higher than in previous surveys.[27] There was a 37% decrease in patients undergoing phase III programs overall. These data reflect the need to increase the national coverage of cardiac rehabilitation programs and to overcome obstacles in the referral, enrollment, and adherence of HF patients. Additionally, other alternatives, such as cardiac telerehabilitation programs, should be adopted

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in view of their positive impact on functional measures and patients' quality of life.[28–31]

Pharmacological therapy

As previously discussed,[26] following the publication of the EMPEROR-Preserved and DELIVER trials, sodium-glucose cotransporter-2 (SGLT2) inhibitors have become a fundamental HFpEF therapeutic pillar with a class I indication, level of evidence A, in the ESC guidelines, alongside diuretics in patients with congestion.[3]

No data are available to date concerning the uptake of these medications in Portuguese HFpEF cohorts.

Managing comorbidities

The presence of multiple comorbidities in HFpEF patients is the rule, not the exception, adding to the complexity of their management and leading to an increased risk of pharmacological interactions.

The obesity phenotype is common in HFpEF.[32] Weight loss can be achieved through lifestyle interventions including diet and exercise training, pharmacotherapy, and bariatric surgery.[26]

In Portugal, where 17% of the population is obese, there is asymmetry in access to obesity treatment, with most of the centers offering bariatric surgery concentrated in a few geographical areas, with different access to nutritional counseling and follow-up.[33]

Portugal does not have a pharmacological coverage strategy for obesity. A recent government directive sets out the implementation of an integrated care model for the prevention and treatment of obesity.[34] However, this document deals with general principles and intentions, but lacks specific regulation and strategic operationalization.

Considering the available therapeutics, among glucagon-like peptide-1 agonists there are specific doses and formulations of both semaglutide and liraglutide approved in the EU for treating obesity, independent of T2D status, although they are not covered by the Portuguese National Health Service reimbursement system or by most health insurance plans.[35] Accordingly, treatment costs may be a significant barrier to their use by obese patients in Portugal.

Hypertension, the most prevalent comorbidity in HFpEF, also constitutes a challenge in the Portuguese context. The INSEF study found that more than 30% of individuals aged between 25 and 74 years with hypertension were not aware of their condition, and 30% were not on medical treatment.[3,36]

There is still a considerable number of patients with unidentified atrial fibrillation. The SAFIRA study showed a 9% prevalence of atrial fibrillation in individuals aged ≥65 years, 36% of whom were unaware of their condition. Additionally, there are nationwide disparities in access to ablation therapy.

It is essential to implement strategies that identify and monitor high-risk patients, given the mechanisms that have been described underlying HFpEF and these conditions.[26]

Healthcare organization

The PORTHOS study showed that HFpEF is more prevalent in women and in older individuals.[6] Typical age-associated factors such as cognitive impairment, depression, reduced social support, frailty, and economic deprivation add a level of complexity to patient management. All these factors constitute serious barriers to access to appropriate therapy and to its adherence and optimization, and underline the need for a comprehensive approach.

Multidisciplinary teams are key structures for improving HF management, and may help overcome these barriers by providing patient-centered care to HFpEF patients.[20] In Portugal, there are few examples of such integrated management, which is endorsed by international HF guidelines.[18,19,37–40]

Palliative care is another important component of HF management. Advanced age and a greater burden of comorbidities, compared to HF in patients with reduced ejection fraction, mean that HFpEF patients are particularly in need of this level of care. Palliative care units have been created in multiple hospital and primary healthcare centers all over Portugal. Nevertheless, few HF patients have access to palliative consultations in Portugal, typically only when approaching the end-of-life stage, probably due to many factors, including lack of awareness on the part of patients and providers and resource constraints.[41–43] As is increasingly recognized, a palliative approach should begin early in the disease trajectory of HF patients, although not necessarily relying on formal palliative care teams.

Additionally, in order to improve HF care, there is a recognized need for health professionals to undergo specific training in HF, for HF care quality indicators to be defined, and for a national registry to be established.[44]

In conclusion, there is a large unmet need concerning planning and organization of HFpEF care across institutions of the Portuguese healthcare system, from individual primary healthcare and hospital centers to local, regional and national care networks.

Proposal for improving management of heart failure with preserved ejection fraction

Stakeholders

Considering the aforementioned unmet needs, a national strategy aiming at improving HFpEF care should focus on the organization of a multidisciplinary integrated care system that is able to ensure a seamless connection between hospital and outpatient care.[20] Additionally, support from social workers is paramount in reinforcing the connection between the health system and the patient's household.

In short, three levels of support of the National Health System should be considered: hospital services, outpatient health services, and community social support.[20]

In addition to the above-mentioned caregivers, this plan requires the active involvement of other stakeholders acting at different levels, including regulatory and political bodies (such as the Parliamentary Health Committee, the Ministry of Health, and the head of the Program for Cerebral and Cardiovascular Diseases).

Undoubtedly, a strong HF patients' association, such as the Portuguese Association to Support Patients with Heart Failure (AADIC), is of paramount importance in creating the

political leverage needed to implement this comprehensive HF care network.

The Portuguese Societies of Cardiology, Cardiothoracic and Vascular Surgery, Internal Medicine, General and Family Medicine, and Intensive Care, as well as the Portuguese Medical Pharmaceutical and Nursing Associations, should also be involved in this effort. The participation of the media is also essential to promote the public's and patients' HF literacy, to enhance the visibility of HF and to leverage the efforts of the various HF stakeholders to improve HF care in Portugal. Finally, the pharmaceutical and medical devices industries can be important partners in supporting this effort.

This plan should follow the recommendations in the ESC HF guidelines and should include training programs for all caregivers involved.[18]

General strategy

Organization of care for HFpEF patients should consist in a unified system in which the patient, when stable, is managed in an outpatient context by primary care physicians and nurses, and when unstable, is managed by cardiologists and internal medicine specialists with the assistance of nurses in a hospital setting (Figure 1).[20] Along this life journey, the patient and his/her informal caregiver should be viewed as a single entity, stressing the paramount role of informal caregivers in providing physical, emotional, and spiritual support.[20]

Multidisciplinary teams

Primary care physicians should have a major role in establishing the HFpEF diagnosis, initiating non-pharmacological and pharmacological HFpEF therapy, promoting management of comorbidities, assuring patient follow-up, and referring HFpEF patients to hospital care when appropriate. Hospital specialists (cardiologists and internists) should be responsible for treatment of worsening HF and acute HF events, management of complex comorbidities and advanced diagnostic and etiological investigation, as well as assessment of patients' eligibility for advanced therapies (Figure 1). Cardiology subspecialties may be needed to perform atrial fibrillation ablation (electrophysiologists) or to address coronary artery or valvular disease (interventional cardiologists and cardiac surgeons). Other medical specialists, such as endocrinologists, nephrologists and pulmonologists, may be needed to address relevant comorbidities.[45] Additionally, psychiatrists and psychologists, palliative care practitioners, physiatrists and physiotherapists, and other professionals such as pharmacists, nutritionists, and social workers, may also be involved.

Settings of care

Primary healthcare and hospital settings should be integrated within a seamless communication system.[20] Importantly, to strengthen this system, coordinated HF day clinic and HF transition care teams should be implemented to safely bridge the problematic patient transition from the outpatient setting to the hospital and vice versa (Figure 1).[20]

In cases of severe clinical instability, most patients are currently attended in the emergency department, with further admission to an intensive care unit or a cardiology or internal medicine ward. To reduce the hospital burden associated with frequent HF decompensations and to promote a more patient-centered approach, these decompensated patients should be attended at a HF day clinic and referred back to the outpatient setting after short-term administration of appropriate intravenous medication. This strategy enables more streamlined patient management, preferably within the local HF team network. A hospital-at-home strategy is suitable for some patients, particularly those with advanced HF and/or severe comorbidities and requiring intravenous diuretics, or after a short hospital stay.[46,47] Following a Ministry of Health policy, Portugal has implemented several hospital-at-home units, generally led by internal medicine specialists, that provide substantial national coverage. HF is a common cause of admission, mirroring conventional hospitalization.[48]

An HF day clinic can provide short-term reassessment of early post-discharge patients, contributing to a safer and more efficacious transition strategy, enabling same-day blood analysis and more straightforward management of medical therapy, to replicate the successful STRONG-HF trial strategy.[49]

Thus, a circular system should be established, integrating the outpatient setting, HF day clinics, hospital admission, the transition care team and back to the outpatient setting, as a unified continuum of care (Figure 1).

Communication and networking

Importantly, this system should be based on a unified team approach. It should be built on ease of communication and sharing of information grounded in a common electronic record system. This should be reinforced by using a dedicated email address and/or telephone number and frequent teleconferences involving all the above in-hospital and out-of-hospital healthcare professionals, as well as members of transition care and HF day clinic teams.

These teleconferences should serve as a forum for discussing specific patient problems, as well as for sharing scientific knowledge. Other professionals should be encouraged to participate in these online meetings, so that they can also act as members of the multidisciplinary team.

Finally, this expanded multidisciplinary integrated care team should coordinate with other teams at a national level in order to create a 'hub and spoke' system.[50] This will allow flexible communication between the periphery and more specialized centers, culminating in the few centers dedicated to advanced HF, in accordance with the ESC guidelines.[50]

An effective palliative care network should also be implemented,[18] enhancing both the accessibility and the quality of palliative care for HF patients across the entire disease trajectory and not exclusively restricted to end-of-life care, by integrating palliative care into HF management earlier.[51] General palliative care should be provided by HF specialists at different levels, with specialized input from the palliative care physician or specialist teams, as required.[51]

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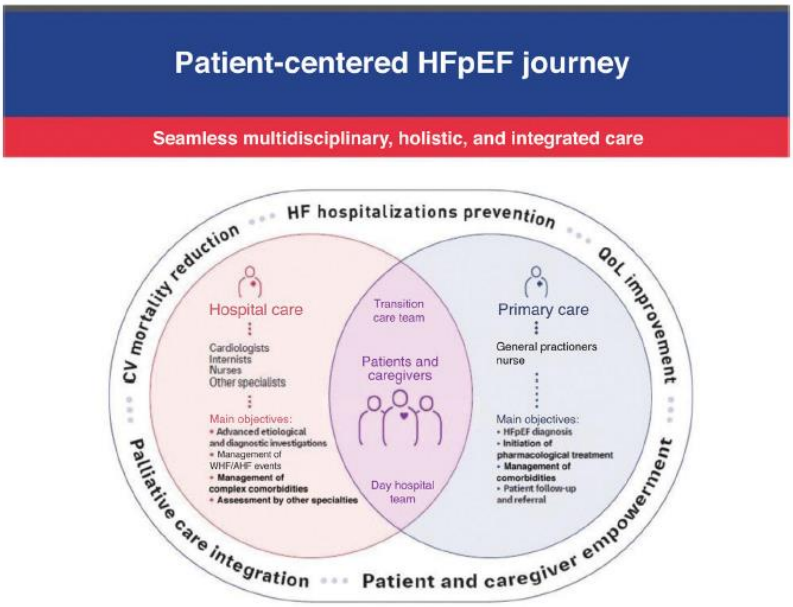


Figure 1 The patient-centered life journey of heart failure with preserved ejection fraction. AHF: acute heart failure; CV: cardiovascular; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; QoL: quality of life; WHF: worsening heart failure.

Quality monitoring

Performance indicators should be developed that assess outpatient and inpatient care to help improve quality.[44]

The development of a single, integrated, shared electronic health record dedicated to HF, combined with quality of care indicators, has been proposed to facilitate the capture of demographic, clinical, management and outcome data.[44] An electronic platform is critical for launching a high-quality continuous clinical registry to determine compliance with guidelines and to develop programs for continuous quality improvement.[52]

Raising awareness

HF awareness campaigns, specifically addressing HFpEF, should be carried out targeting healthcare professionals, patients, and the general population.

The need for a pathway for heart failure with preserved ejection fraction in Portugal

The current fragmented and heterogeneous care delivered to HF patients in Portugal requires an effort to organize a streamlined structured pathway for the management of the syndrome. This need is particularly striking with regard to HFpEF, a condition with multiple diagnostic and therapeutic issues and uncertainties affecting a challenging patient profile.

A Ministry of Health policy on HF management has long been awaited and deemed extremely important. Nevertheless, medical societies should also have an active role in proposing measures to achieve the much-needed step forward in quality. Thus, we propose a pragmatic approach to the management of HFpEF patients in Portugal, including a roadmap for diagnosis, referral and treatment, based on international guidelines and adapted to the specific characteristics of the Portuguese situation.[18,38] This is addressed to all healthcare professionals involved in the management of HFpEF patients.

A pragmatic approach to management of heart failure with preserved ejection fraction in Portugal: a roadmap for screening, diagnosis, referral and treatment

Diagnosis

Suspicion of heart failure with preserved ejection fraction

Suspicion of HFpEF may arise in patients presenting with dyspnea and/or fatigue and/or peripheral edema. The concomitant presence of age ≥70 years, atrial fibrillation, obesity/overweight (body mass index ≥25 kg/m^2), high blood pressure, chronic kidney disease, diabetes and/or metabolic syndrome, and electrocardiogram (ECG) changes increases the probability of HFpEF.

At this point, an ECG should be performed. If it identifies atrial fibrillation, left atrial enlargement and/or left ventricular (LV) hypertrophy, or myocardial infarction patterns, suspicion of HFpEF increases further.

In order to recall the above checklist, we propose ordering these seven characteristics according to the abbreviation A_2B_2CDE (Figure 2).

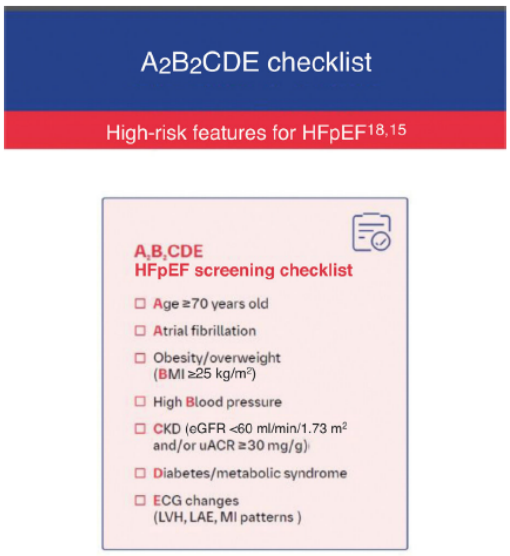


Figure 2 A_2B_2CDE checklist. BMI: body mass index; CKD: chronic kidney disease; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HFpEF: heart failure with preserved ejection fraction; LAE: left atrial enlargement; LVH: left ventricular hypertrophy; MI: myocardial infarction; uACR: urine albumin–creatinine ratio. H_2FPEF score available at: https://www.mdcalc.com/calc/10105/h2fpef-score-for-heart-failure-with-preserved-ejection-fraction.

HFpEF mimics such as thyroid, liver, pulmonary or advanced kidney disease, and anemia, should be excluded.

Natriuretic peptides

Quantification of natriuretic peptides (NPs) follows in the HFpEF diagnostic pathway. B-type natriuretic peptide (BNP) <35 pg/ml or N-terminal proBNP <125 pg/ml, in patients not treated with diuretics, renders HFpEF unlikely.[53]

If NP quantification is not available, echocardiographic assessment should follow directly (Figure 3a).

Echocardiography

Echocardiographic examination, preferably including tissue Doppler, is central to the diagnosis of HFpEF. Quantification of LVEF is mandatory, as well as LV mass index, relative wall thickness, and left atrial volume index; these parameters can be readily obtained via two-dimensional echocardiography, which is widely available and reimbursed within the Portuguese primary healthcare system.

Doppler-derived variables that can be used to estimate LV filling pressures, including E/e′ ratio and pulmonary artery systolic pressure, are highly recommended. Alongside calculation of the H_2FPEF score, we refer clinicians to pragmatic HFpEF diagnosis criteria derived from the 2021 ESC HF guidelines, in which Table 9 includes key echocardiographic variables, in combination with NPs, thus offering a consistent, yet simplified approach to the HFA-PEFF algorithm (Figure 3).[53] Ideally, integration of all these parameters would improve HFpEF diagnosis in patients with LVEF >50%, as their combination increases the likelihood of HFpEF. However, echocardiographic reports often omit some of these variables. Thus, the specific inclusion of these parameters in echocardiographic requests is suggested.

Calculating the probability of heart failure with reduced ejection fraction

As there is no single non-invasive test to unequivocally diagnose HFpEF, diagnostic scores are clinically useful. Two clinical and echocardiographic scores have been developed for HFpEF diagnosis: the HFA-PEFF algorithm and the H_2FPEF score.[15,17] The HFA-PEFF algorithm is more complex than the H_2FPEF score and includes more echocardiography-derived measurements.

Due to the high prevalence of HFpEF, most of these patients are attended at the primary care level. In this setting, the H_2FPEF score appears to be more suitable than the HFA-PEFF algorithm, since it includes significantly fewer echocardiographic variables and has been hemodynamically validated.[52] In a patient with suspected HFpEF, a score $\geq$6 is highly suggestive of the diagnosis.[17,44] Additionally, there are several versions of the H_2FPEF score calculators, both online and in smartphone apps, which may further support its dissemination in clinical practice (Figure 3a).

In addition to being more complex, the HFA-PEFF algorithm may in certain cases require invasive hemodynamic parameters, which are available in very few centers in Portugal.

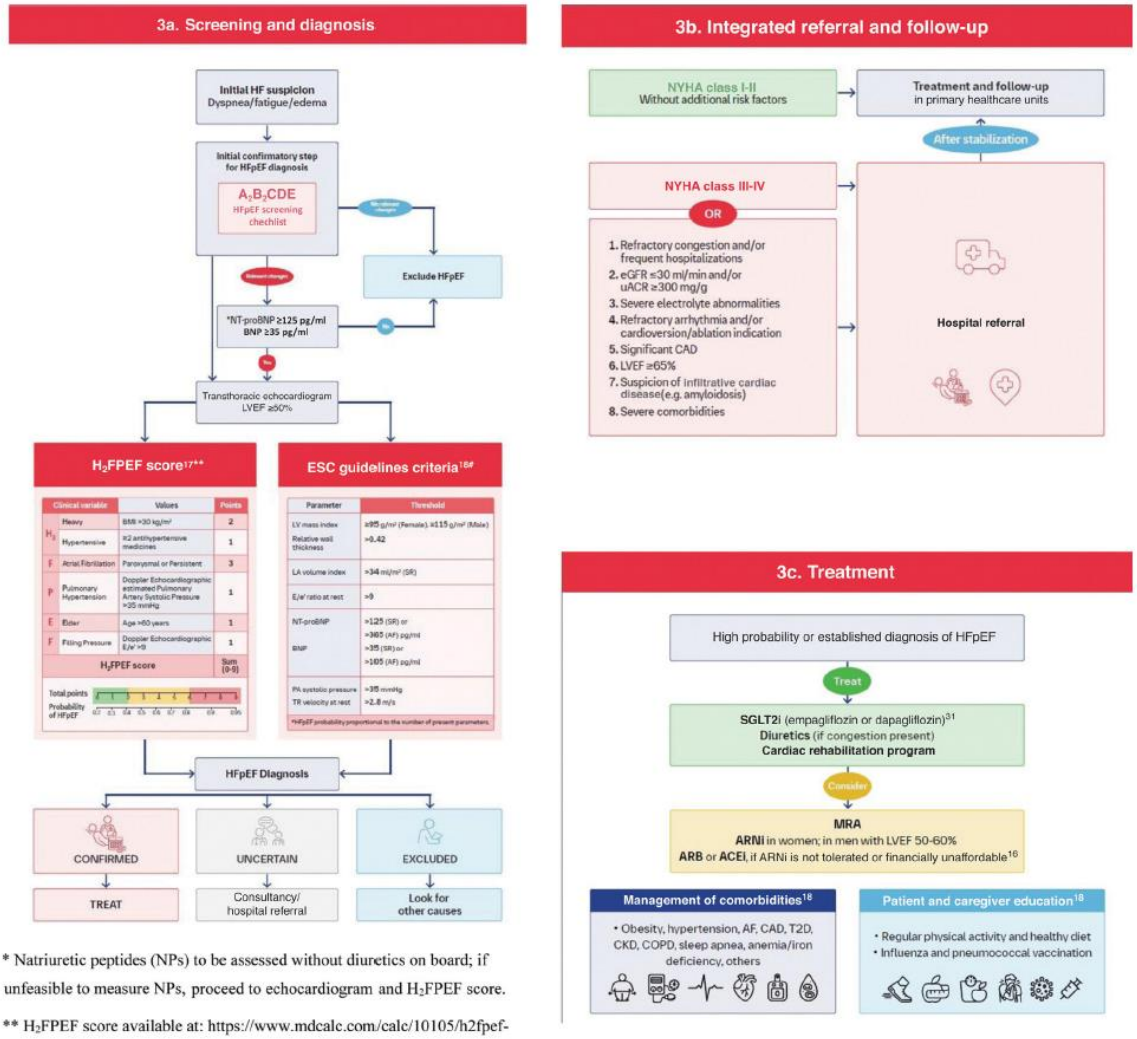
Considering specific etiologies of heart failure with reduced ejection fraction

Establishing a HFpEF diagnosis requires investigation of specific etiologies that may present with HF signs and symptoms and preserved LVEF, but warrant distinct diagnostic and therapeutic management. Conditions like amyloid heart disease, hypertrophic or other restrictive/infiltrative cardiomyopathies, and valvular or pericardial disease should be considered during the diagnostic work-up, as established in step F2 of the HFA-PEFF algorithm.[15,45] Although valvular disease is readily detected on a routine echocardiogram, other etiologies generally require more specific tests like cardiac magnetic resonance, invasive hemodynamic studies or cardiac biopsy that are only available in specialized hospital settings. Nevertheless, it is crucial for primary care physicians to suspect these conditions, integrating clinical assessment with clues from diagnostic testing (such as red flags for amyloid cardiomyopathy or LVEF $\geq$65%), to identify patients in need of hospital referral for etiological work-up and treatment.

Management strategy for heart failure with reduced ejection fraction

Whenever an HFpEF diagnosis is confirmed (Figure 3c), an SGLT2 inhibitor should be prescribed.[18,38] In cases of congestion, a loop diuretic should be added and subsequently titrated to the lowest dose to maintain euvolemia. Adding an MRA, particularly finerenone, may be considered, in light of the recent FINEARTS-HF topline results.[54] For obese patients, semaglutide or tirzepatide may also be considered given the STEP-HFpEF and SUMMIT trials. It is expected that

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* Natriuretic peptides (NPs) to be assessed without diuretics on board; if unfeasible to measure NPs, proceed to echocardiogram and H_2FPEF score.

** H_2FPEF score available at: https://www.mdcalc.com/calc/10105/h2fpef-score-for-heart-failure-with-preserved-ejection-fraction.

Figure 3 A roadmap for management of heart failure with preserved ejection fraction. (a) Screening and diagnosis; (b) integrated referral and follow-up; (c) treatment. ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; AF: atrial fibrillation; AMI: acute myocardial infarction; BMI: body mass index; BNP: B-type natriuretic peptide; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LA: left atrium; LV: left ventricular; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; PA: pulmonary artery; PASP: pulmonary artery systolic pressure; SGLT2i: sodium-glucose cotransporter-2 inhibitors; SR: sinus rhythm; T2D: type 2 diabetes; TR: tricuspid regurgitation; TTE: transthoracic echocardiography; uACR: urine albumin–creatinine ratio.

the increasing evidence and pharmacological therapeutic options will be reflected in future international guideline updates.

Patients in New York Heart Association (NYHA) class I-II without additional risk factors should generally be managed in the primary healthcare setting (Figure 3b). Patients remaining in NYHA class III–IV despite HFpEF treatment, and/or with complex management characteristics, including refractory congestion and/or frequent hospitalizations, severe renal disease (estimated glomerular filtration rate ≤30 ml/min and/or urine albumin–creatinine ratio ≥300 mg/g), severe electrolyte disturbances, significant coronary artery disease, refractory cardiac arrhythmias and/or indication for ablation/cardioversion, severe comorbidities,

uncertain etiologies (e.g. amyloidosis) and/or LVEF ≥65%, should be referred to a hospital setting for advanced investigation and/or treatment.

An angiotensin receptor/neprilysin inhibitor (ARNi) may also be considered in women across the LVEF range, and in men with LVEF between 50 and 60%, or alternatively an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACEi), for patients who cannot take ARNis due to intolerance or financial barriers (Figure 3c).[16,38]

In both primary healthcare and hospital settings, comprehensive HFpEF treatment always includes management of comorbidities, as well as education in disease awareness and self-care for patients and informal caregivers, exercise, and vaccination promotion. Patients may be referred to a cardiac rehabilitation program if one is available. Referral for palliative care should be considered when deemed appropriate. Social needs should be assessed and addressed.

Patient-centered multidisciplinary care for heart failure with preserved ejection fraction in Portugal

The organization of HFpEF care should be patient-centered and should include multidisciplinary integrated care teams involving cardiologists, internists, primary care physicians, nurses, and other health professionals, linked together in a seamless care system. These teams should ultimately work together to reduce morbidity and mortality and to improve patients' functional capacity and quality of life. The contribution of social workers and informal caregivers is essential. The creation of Local Health Units (*Unidades Locais de Saúde*) all over Portugal as an organizational model of care should help to disseminate this integrative and collaborative patient-centered approach to the country's HFpEF patients.

Conclusions

HFpEF is highly prevalent in Portugal, as shown by the PORTHOS study, particularly in older patients.

This represents an extraordinary challenge to organize a national system of HFpEF diagnosis and treatment. Primary care physicians are central to identifying these patients, initiating therapy and referring them to hospital when necessary. To do so, measurement of NPs is desirable and high-quality echocardiograms are crucial to providing the most accurate assessments. Additionally, a comprehensive approach, consisting of multidisciplinary teams and a systematic, pragmatic vision, are key to improving HFpEF management, helping to address all the patient's needs and providing patient-centered care.

In this paper, we propose a holistic roadmap intended to guide clinicians from all specialties in the pragmatic management of HFpEF patients throughout the disease trajectory, from diagnosis to treatment, and to promote appropriate coordination between primary and hospital care, built on the most recent international HF guidelines and on the position of a multidisciplinary and representative HF national expert panel.

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5.13. Quality of Life Scores Association with other Patient Reported Outcomes: Validating Minnesota Living with Heart Failure Questionnaire to Portuguese

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ORIGINAL ARTICLE

Quality of life score association with other patient-reported outcomes: Validating *Minnesota Living with Heart Failure Questionnaire* to Portuguese

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KEYWORDS
Quality of life;
Heart failure;
Patient reported outcome measures

Abstract
Introduction and objectives: Pragmatic validated instruments are needed to assess quality of life (QoL) in the real-world care of heart failure (HF) patients. This study aimed to validate the Minnesota Living with Heart Failure Questionnaire (MLHFQ) in European Portuguese and to search for associations with other patient-reported outcomes (PROs).
Methods: This is a single-center prospective study with two samples of HF patients, used for MLHFQ translation, cultural adaptation and validation. Validation sample included patients managed in a multidisciplinary HF clinic between February 29, 2016, and February 29, 2020.
Results: The validation sample included 294 HF patients, with a median age of 78 years, 53.1% female sex, 45.2% with reduced left ventricle ejection fraction (LVEF) and 43.9% with preserved LVEF. The principal component analysis identified three components, representing three groups of questions from the MLHFQ, each related to one domain and subscore: physical, emotional and

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social. The validated version showed a reliable general factor and good internal consistency. MLHFQ total score was associated with all the other variables studied. All the scores were strongly associated with NYHA functional class. Associations were found between the physical score and both the Borg fatigue score and the six-minute walking distance. Emotional score was associated with both anxiety and depression scores from Hospital Anxiety and Depression Scale.

Conclusions: This study validated the MLHFQ in Portuguese and revealed the existence of three subscores. It enables the pragmatic assessment of the QoL of Portuguese HF patients, particularly of those with preserved LVEF, and future research concerning PROs.

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PALAVRAS-CHAVE
Qualidade de vida;
Insuficiência cardíaca;
Resultados reportados pelos doentes

Avaliação da qualidade de vida e a sua associação a outros resultados reportados pelo doente: validação para português do *Minnesota Living with Heart Failure Questionnaire*

Resumo

Introdução e objetivos: Na prática clínica são necessários instrumentos validados e pragmáticos para avaliar a qualidade de vida (QdV) dos doentes com insuficiência cardíaca (IC). Este estudo tem como objetivo validar o *Minnesota Living with Heart Failure Questionnaire* (MLHFQ) para português e procurar associações com outros resultados reportados pelos doentes (PROs).

Métodos: Este é um estudo prospetivo e observacional de um só centro, com duas amostras de doentes com IC, utilizadas para a tradução, adaptação cultural e validação do MLHFQ. A amostra de validação incluiu doentes integrados numa clínica multidisciplinar de IC entre 29/02/2016 e 29/02/2020.

Resultados: A amostra de validação incluiu 294 doentes, com uma mediana de idades de 78 anos, 53,1% do sexo feminino, 45,2% com fração de ejeção do ventrículo esquerdo (FEVE) reduzida e 43,9% com FEVE preservada. A análise do componente principal identificou 3 componentes, representando 3 grupos de questões do MLHFQ, cada um relacionado com um domínio e uma pontuação parcial: físico, emocional e social. A versão validada mostrou um fator geral fiável e boa consistência interna. A pontuação total do MLHFQ associou-se a todas as outras variáveis estudadas. Todas as pontuações se associaram fortemente à classe funcional de NYHA. Adicionalmente, foram encontradas associações entre a pontuação do domínio físico e a pontuação de cansaço na escala de Borg, assim como com a distância percorrida em 6 minutos. A pontuação do domínio emocional revelou associações com as pontuações de ansiedade e de depressão da *Hospital Anxiety and Depression Scale*.

Conclusões: Este estudo validou o MLHFQ em português e revelou a existência de 3 pontuações parciais. Torna assim possível a avaliação pragmática da QdV em doentes portugueses com IC, particularmente daqueles com FEVE preservada, e a investigação futura no âmbito dos PROs.

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Introduction

Quality of life (QoL) is a distinctive human aim only recently introduced as an important outcome and quality indicator for the management of patients with heart failure (HF).[1,2] The World Health Organization defines QoL as ''an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.''[3] This view reinforces the contemporary concept of QoL having a broad and multilayered scope, which should be considered when assessing it in the context of underlying diseases, such as chronic HF.[4]

HF is the leading cause of hospitalization in people over 65 years of age in developed countries.[5] In Portugal, it affects approximately 770 000 patients, with a prevalence of 16.54% in people aged ≥50 years.[6,7]

Traditionally, the primary endpoints of HF trials consisted of all-cause or cardiovascular mortality and/or HF hospitalizations. QoL and patient-reported health outcomes (PROs) have been viewed as ''soft'' endpoints, although they provide insight into treatment effects from the patient's perspective.[8] In 2013, a clinical outcome endpoints consensus document in HF trials was published by the European Society of Cardiology (ESC), reporting symptoms and PROs as independent endpoints for HF trials. The document stated

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the need for development of validated and simpler instruments sensitive to changes in health status over time.[1]

There are several validated instruments to assess QoL in patients with HF. The two most used questionnaires are the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[9] and the Kansas City Cardiomyopathy Questionnaire (KCCQ).[10] The use of these instruments, however, remains largely limited to clinical trials.[11] They are both time-intensive, and their current use in real-world care is very limited.[2,12] Other authors identified the MLHFQ as the most appropriate instrument for QoL assessment in HF patients, because it has a simple structure and is easy to administer.[13]

Multidisciplinary HF clinics reduce mortality and hospitalizations and are a class I recommendation in European and American HF guidelines. QoL improvement is a major goal of HF clinics and treatment algorithms for all HF patients.[14–16] PROs represent excellent tools to promote patient-centered care and a real opportunity to integrate patients' voices in healthcare quality assessment.[12]

Objectives

The aim of this study was to validate a translated version of the original MLHFQ in a sample of Portuguese HF patients managed in a multidisciplinary HF clinic. In addition, this study aimed to identify associations of MLHFQ scores with other PROs measures.

Methods

Study design

This single-center, prospective study enrolled two samples of HF patients. Pre-test sample was used for the MLHFQ translation and cultural adaptation to Portuguese. Validation sample was used to identify significant associations between the MLHFQ total and partial scores with five variables: (1) the New York Heart Association (NYHA) functional class,[17] (2) the six-minute walking distance (6MWD),[18] (3) the Borg fatigue score at the end of the six-minute walking test (6MWT),[19] (4) anxiety score and (5) depression score assessed by the Hospital Anxiety and Depression Scale (HADS).[20]

A full license agreement from the University of Minnesota was obtained for validating the MLHFQ in the Portuguese language. The study adhered to the recommendations of the Declaration of Helsinki and the study protocol was approved by the local ethics committee and institutional review boards, reference number 2017.040 (040-DEFI/040-CES).

Translation and cultural adaptation

The translation process followed the steps described by Boateng et al.[21] The translation into Portuguese was performed by two nonmedical independent professionals, both Portuguese native speakers and fluent English speakers. Both were aware of the aim of the study and were asked to prioritize conceptual translation. The aim of translation was to obtain a version that maintained the integrity of the instrument, preserving the meaning of the items between the two languages. To verify the content, clarity and understanding of the translation, a panel of experts composed of two cardiologists and a psychiatrist analyzed the first version. The review of equivalences included the following domains: conceptual, equivalence between items, and semantics. Changes were made when considered relevant for the cultural adaptation of the instrument, resulting in a consensus version (version 1.0). Version 1.0 was then translated into English by a native English speaker who was fluent in Portuguese, had no training in healthcare, was unaware of the original version and had not participated in the previous stages of the study. The grammatical and semantic discrepancies related to the original scale were presented

Table 1 Baseline characteristics of the validation sample.

Characteristics	Value	n
Age (years), median (P25; P75)	78 (69; 83)	294
Female, n (%)	156 (53.1)	294
Comorbidities		
Hypertension, n (%)	251 (85.4)	294
Iron deficiency, n (%)	128 (61.5)	208
Kidney dysfunction,[a] n (%)	162 (55.1)	294
Diabetes mellitus, n (%)	153 (52.6)	291
Atrial flutter/fibrillation, n (%)	149 (50.7)	294
Anemia, n (%)	143 (48.8)	293
Chronic pulmonary condition, n (%)	104 (35.4)	294
Depression, n (%)	75 (25.5)	294
Cerebrovascular disease, n (%)	64 (21.5)	294
Peripheral arterial disease, n (%)	36 (12.2)	294
Anxiety, n (%)	15 (5.1)	294
HF etiology, n (%)		294
Hypertensive	122 (41.5)	
Ischemic	115 (39.1)	
Valvular	97 (33.0)	
Others	54 (18.4)	
NYHA functional class, n (%)		287
I	44 (15.3)	
II	190 (66.2)	
III	52 (18.1)	
IV	1 (0.3)	
LVEF, n (%)		294
≤40%	133 (45.2)	
41–49%	32 (10.9)	
≥50%	129 (43.9)	
NT-proBNP (pg/mL), median (P25; P75)	2135 (727.5; 4805)	294

HF: heart failure; LVEF: left ventricle ejection fraction; NT-proBNP: N-terminal-pro-B type natriuretic peptide; NYHA: New York Heart Association.

[a] Kidney dysfunction defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Table 2 Response frequency, item statistics and reliability.

	Response frequency							Corr item-total	Alpha drop item
	0 (%)	1 (%)	2 (%)	3 (%)	4(%)	5(%)	Miss (%)		
Physical domain									
Q1	69.73	10.54	9.18	4.08	3.40	3.06	0	0.45	0.88
Q2	47.96	9.18	15.31	13.27	9.52	4.76	0	0.71	0.86
Q3	35.03	14.29	17.69	11.22	12.24	9.52	0	0.75	0.85
Q4	55.78	11.56	9.86	6.80	10.20	5.78	0	0.69	0.86
Q5	57.48	9.18	7.82	12.59	8.50	4.42	0	0.67	0.86
Q6	69.73	12.24	6.80	6.80	3.40	1.02	0	0.51	0.88
Q12	59.52	12.93	10.20	6.80	5.78	4.76	0	0.60	0.87
Q13	35.37	14.29	19.05	10.54	15.31	5.44	0	0.74	0.85
Total									0.88
Social domain									
Q8	81.38	8.28	4.14	1.72	1.72	2.76	1.36	0.53	0.64
Q9	68.71	8.50	8.50	4.76	4.08	5.44	0.00	0.56	0.61
Q10	81.44	4.12	2.41	3.78	3.09	5.15	1.02	0.53	0.62
Q11	54.42	13.61	11.22	9.52	5.78	5.44	0.00	0.46	0.66
Q16	84.35	5.78	5.78	1.36	1.70	1.02	0.00	0.24	0.73
Total									0.70
Emotional domain									
Q7	69.39	9.86	10.20	4.42	4.08	2.04	0	0.63	0.83
Q14	88.10	3.40	2.38	2.04	1.70	2.38	0	0.26	0.87
Q15	71.43	6.12	7.82	8.16	4.08	2.38	0	0.45	0.85
Q17	66.67	8.50	8.84	6.80	6.46	2.72	0	0.70	0.82
Q18	66.67	8.50	7.48	8.84	4.42	4.08	0	0.73	0.82
Q19	40.48	15.99	14.63	12.24	7.14	9.52	0	0.68	0.82
Q20	57.48	12.59	13.61	8.16	5.10	3.06	0	0.56	0.84
Q21	51.02	12.59	12.59	8.50	9.52	5.78	0	0.72	0.82
Total									0.85

Q: question.

to a panel of experts, and a revised version (version 2.0) was assembled. Version 2.0 was then applied to the pre-test sample. The relevance of the form of administration and response in Portuguese culture, understanding of the meaning and content of the questions, and concepts presented were assessed. The final version (version 3.0; see supplementary Table S1) incorporated all these issues.

Study samples

Pre-test sample included 13 patients consecutively referred to an outpatient cardiac rehabilitation program, diagnosed with HF in accordance with the criteria of the ESC guidelines.[22] Eligible patients were 18 years or older, clinically stable for the last 3 months, with no comorbidities that could impose physical limitations or inability to express themselves. All patients signed an informed consent before study participation. The MLHFQ was administered at the baseline assessment of each patient.

The validation sample included patients managed in a multidisciplinary HF clinic between February 29, 2016, and February 29, 2020, before the first coronavirus disease (COVID-19) patient was diagnosed in Portugal, in March 2020. To be admitted to the HF clinic patients had to be 18 years of age or older and either were recently hospitalized for HF, had a history of previous HF hospitalization or had frequent urgent HF visits. In the study period, a total of 321 patients were referred to the HF clinic but only 294 were eligible to MLHFQ administration. The remaining patients had at least one of the following exclusion criteria: functional dependence, unable to express themselves or to understand written questionnaires. The MLHFQ was prospectively administrated, in average 4 months after HF clinic admission, to prevent that the answers to the questionnaire reported to the period of a HF hospitalization. HF diagnosis and classification followed the Universal definition and classification of the HF consensus statement.[23] The follow-up and management program was based on an outpatient ambulatory setting.[24,25] The NYHA functional class was evaluated at every visit and HADS and 6MWT were regularly performed, every six to twelve months as part of the program. Only the evaluations of NYHA functional class, HADS and 6MWT performed at the same date as when the MLHFQ was administered were considered to assess the correlation between them and the MLHFQ scores. The total score of MLHFQ and results of the other tests were immediately available to the health care professionals. The following data were collected retrospectively from clinical records, at the time of HF clinic admission: age, sex, HF etiology, comorbidities, N-terminal-pro-B type natriuretic peptide (NT-proBNP)

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Table 3 Standardized factor loadings from principal component analysis with three components and oblimin rotation.

	PC1	PC2	PC3
Q1	−0.02	0.62	−0.05
Q2	0.16	0.80	−0.22
Q3	0.21	0.69	−0.02
Q4	0.22	0.53	0.24
Q5	0.40	0.50	−0.04
Q6	−0.04	0.48	0.36
Q7	0.67	0.05	0.18
Q8	0.16	0.09	0.62
Q9	0.35	0.14	0.48
Q10	0.04	−0.08	0.83
Q11	−0.07	0.42	0.46
Q12	−0.26	0.81	0.17
Q13	0.15	0.71	0.09
Q14	*0.29*	0.12	−0.07
Q15	0.61	−0.09	0.06
Q16	0.04	−0.04	0.45
Q17	0.83	0.01	−0.09
Q18	0.84	−0.07	0.12
Q19	0.51	0.32	0.09
Q20	0.63	0.10	−0.03
Q21	0.63	0.23	0.03
SS loadings	4.41	4.39	2.35
Proportion Var	0.21	0.21	0.11
Cumulative Var	0.21	0.42	0.53
With component correlations of			
PC1	1	0.49	0.27
PC2	0.49	1	0.33
PC3	0.27	0.33	1

Q: question.
The numbers in bold represent the statistically significant values.
The only value in italics, ''0.29'', is the only one that exhibits special behaviour in the analysis.

levels, estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, and left ventricle ejection fraction (LVEF) values.

Questionnaires

The MLHFQ consists of 21 questions specific to HF and appraises QoL over the previous month. Questions are answered using a Likert scale ranging from 0 to 5; 0 indicates that the question has no impact on the patient or is not applicable, and 5 indicates the greatest adverse impact. The original questionnaire can be divided into three domains: the overall QoL domain (score range 0–105), the physical domain consisting of eight questions (score range 0–40), and the emotional domain consisting of five questions (score range 0–25). A higher score represents a poorer QoL.[26]

Borg is a scale for rating perceived exertion and uses a Likert scale ranging from 0 to 10, which links verbal expressions to a specific score; 0 indicates ''nothing at all'', and 10 indicates ''very, very strong''.[19]

The HADS is a 14-item scale, in which all items are rated on a 4-point Likert scale, and scores are computed by summing the scores of each subscale, for anxiety or depression. Scores range from 0 to 21, where higher scores indicate more anxiety or depression symptoms.[20]

Statistical analysis

The categorical variables were presented as frequencies and percentages. The normality of the data was assessed through visual graphic verification and the Shapiro–Wilk test. Nonskewed continuous variables were described using means and standard deviations (SD), and variables with skewed distributions were described using medians and the respective interquartile ranges.

A significance level of 5% was assumed. Statistical analysis was performed using software R version 4.3.0. The detailed statistical methods are reported in the supplementary file.

Results

Validation sample

The validation sample enrolled 294 patients whose baseline characteristics at HF clinic admission included the follow-

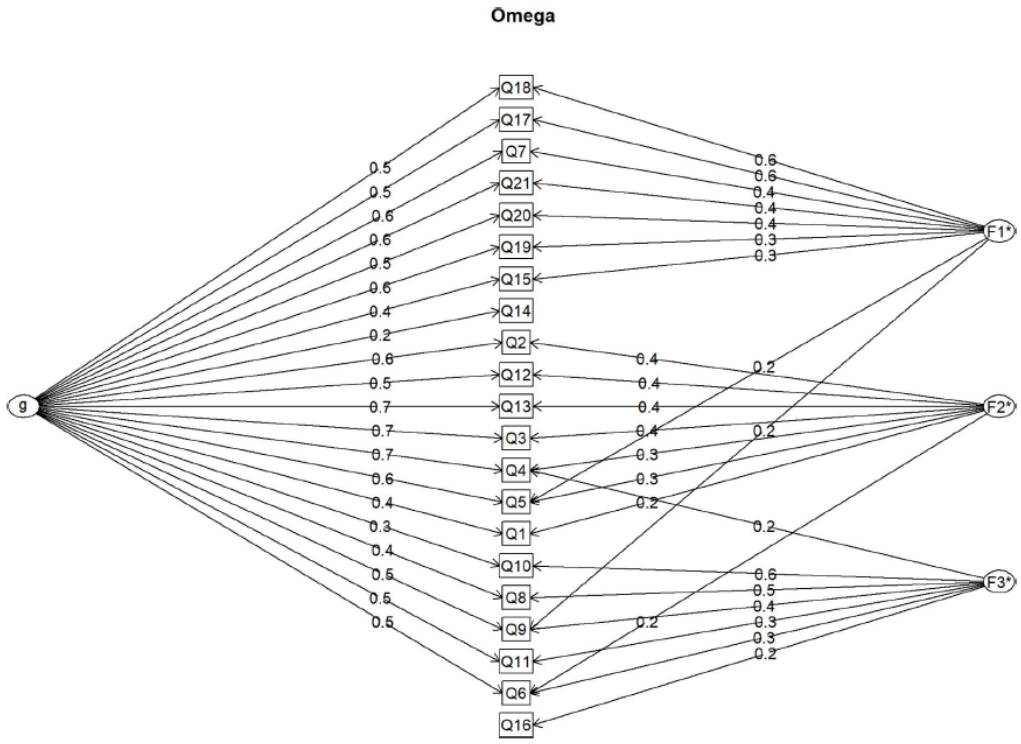


Figure 1 Schmid-Leiman transformation applied to principal components analysis with three components with oblique rotation.

ing: median age of 78 years, 53.1% female sex, a high number of comorbidities, namely, hypertension, iron deficiency, kidney dysfunction and diabetes, which were present in 85.4%, 61.5%, 55.1% and 52.6% of them, respectively. Depression and/or anxiety were present in 25.5% and 5.1% of the patients, respectively. Hypertensive heart disease was the main HF etiology (41.5%) and HF with reduced (≤40%) and preserved (≥50%) LVEF were almost equally represented (45.2% and 43.9%, respectively). Most patients were in NYHA functional class II, and the median NT-proBNP level was 2135 pg/mL (Table 1).

MLHFQ

The percentage of missing values per item from the MLHFQ ranged from 0% to 1.36% (item 8). The most frequent response was ''No/0'', ranging from 35.03% for item 3 to 88.10% for item 14 (Table 2).

Content validity

The visual inspection of the scree plot values from the principal component analysis identified three components as the final solution (Table 3). The second component included items (factor loadings higher than 0.4) related to the physical domain: 1, 2, 3, 4, 5, 6, 12 and 13. The first component included items related to the emotional domain: 7, 15, 17, 18, 19, 20 and 21. The third component included items related to the social domain: 8, 9, 10, 11 and 16. The only item with moderated standardized factor loading was item 14, which showed a correlation of 0.29 with component 1. All three components had moderate correlations with each other ranging from 0.27 to 0.49. This last result suggests the existence of a general factor.

Domain and subdomain reliability and internal consistency

The Schmid-Leiman transformation was applied to the principal component analysis of the original dataset, and the components were rotated obliquely (Figure 1). This allowed us to identify McDonald's omega hierarchical and total as estimates of the general factor saturation of the scale. The omega hierarchical and total values were 0.70 and 0.93, respectively. Therefore, the MLHFQ has a reliable high-order factor (general factor) and good internal consistency for the scale without considering the hierarchical structure.

When the internal consistency of the three main subdomains was analyzed, the physical domain had a Cronbach's alpha of 0.88, the emotional domain had a Cronbach's alpha of 0.85, and the social domain had a Cronbach's alpha of 0.70. The internal consistency analysis revealed that the only items that slightly increased the Cronbach's alpha if dropped were items 14 and 16. Nevertheless, all the items presented item-total correlations greater than 0.4, except for items 14 and 16, which represented correlations of approximately 0.25 (Table 2).

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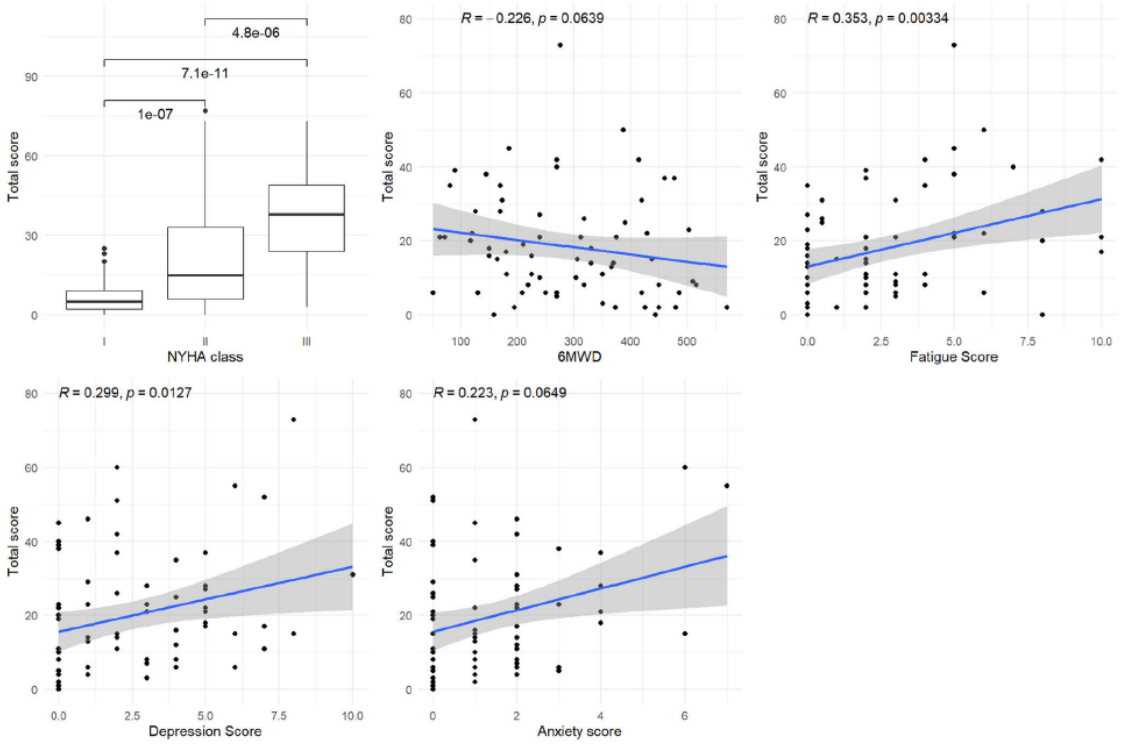


Figure 2 MLHFQ total score associations with NYHA class, 6MWD, Borg fatigue, and HADS depression and anxiety scores. HADS: Hospital Anxiety and Depression Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; 6MWD: six-minute walking distance.

Floor and ceiling effects

The percentages of patients with a score of 0 (floor effect) were 6.1%, 14.2%, 20.7% and 40.4% for the general factor, physical, emotional, and social domains, respectively. The percentage of patients with the maximum score was 0% for all domains. The median scores (P25–P75) were 15 (6–33), 7 (2–15), 4.5 (1–7.4) and 2 (0–5) for general factor, physical, emotional and social domains, respectively.

Construct validation

Figures 2–5 show the associations of each domain and subdomain with the NYHA functional class, the 6MWD, the Borg fatigue score at the end of the 6MWT, and the HADS depression and anxiety scores.

Figure 2 shows that the general factor was statistically significantly or marginally significantly associated with all the variables: NYHA functional class (I vs II and I vs III, $p<0.001$ and $p<0.001$, respectively), 6MWD ($p=0.064$), Borg fatigue score ($p=0.003$), HADS depression score ($p=0.013$) and HADS anxiety score ($p=0.065$).

Figure 3 shows a significant or marginally significant association between the physical domain score and the 6MWD and Borg fatigue score ($p=0.068$ and $p<0.001$, respectively). Figure 4 shows a significant association between the emotional domain score and both HADS scores ($p<0.001$ for depression and $p=0.008$ for anxiety scores, respectively). Figure 5 shows a significant association between the social domain score and HADS depression score ($p=0.011$). Figures 2–5 demonstrate that the main domain and subdomains are strongly related to the NYHA functional class. The above findings are graphically summarized in Figure 6.

Discussion

This study aimed to validate the MLHFQ and to identify associations of MLHFQ scores with other clinical evaluations and PROs measures. Here we present the validation of the MLHFQ to European Portuguese and report the existence of three subscores: physical, emotional and social. All the scores were strongly associated with the NYHA functional class, and the MLHFQ total score was associated with all the studied variables. Additionally, to the best of our knowledge, this is the first study reporting associations between: (1) the physical score and both the Borg fatigue score and the 6MWD and (2) the emotional score and anxiety and depression HADS scores.

Recently, a working group of the ESC defined quality indicators for the care and outcomes of adults with HF, including a domain for the assessment of patients' QoL and the recommendation of the use of a ''validated tool''. The experts considered that QoL assessment by itself constitutes an accomplishment of that quality indicator, without set-

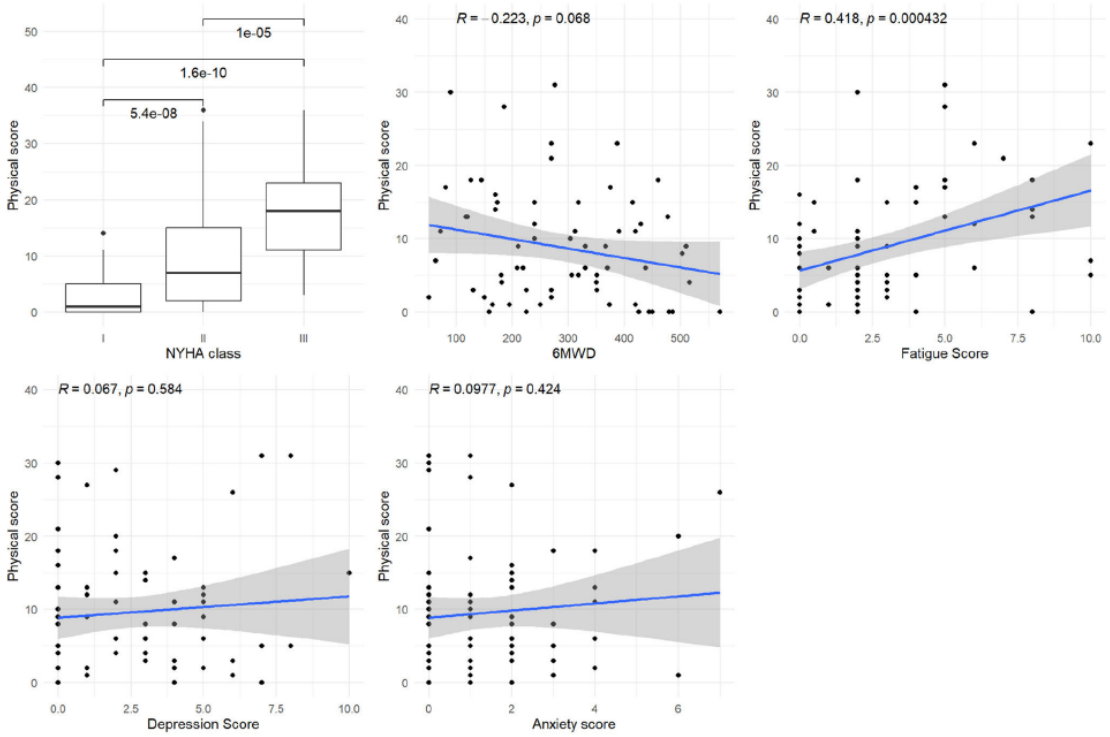


Figure 3 MLHFQ physical score associations with NYHA class, 6MWD, Borg fatigue, and HADS depression and anxiety scores. HADS: Hospital Anxiety and Depression Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; 6MWD: six-minute walking distance.

ting any target score, given concerns about the feasibility of capturing QoL in clinical practice.[2] The position of the ESC highlights the unmet need for a very pragmatic instrument in the assessment of HF-specific QoL. The MLHFQ is easy to administer, has a simple structure with 21 questions, answers displayed on a Likert scale, fits to one page only and takes approximately 5 minutes to complete.[9] Gallagher et al. studied the acceptability and feasibility of implementing validated QoL instruments in HF clinics, reporting that the MLHFQ had a higher completion rate than the KCCQ, with all the questions answered by 85% vs 49% of patients, respectively.[11]

The validation sample in our study represented elderly patients of both sexes with many comorbidities, several HF etiologies, symptomatic HF, and similar proportion of reduced and preserved LVEF. This representation of HF patients from real world clinical practice is one of the strengths of this study. The analysis of the answers to the 21 questions of the MLHFQ revealed that there were only a few missing values. Noteworthy, 88.10% of the patients answered ''No'' to question 14 concerning HF hospitalization in the previous month. This may be because patients had optimized care and a low hospitalization rate.[25]

The Portuguese version of the MLHFQ validated in this study has a reliable total score and good internal consistency. The median total score (P25–P75) of the MLHFQ was 15 (6–33), indicating relatively good HF-related QoL, considering the range of possible total scores from 0 (zero) to 105. Gallagher et al reported an MLHFQ mean total score of 40.9±25.6 in 152 outpatients from two specialist cardiology outpatient clinics.[11] It is well established that one-quarter to one-third of participants in HF trials show significant improvement in QoL when receiving placebo.[27] This may reflect exposure to the beneficial environment trial, where patients are often followed more closely than in routine clinical care and healthcare providers pay particular attention to patient-reported symptoms.[28] Likely, the same happens with patients under optimized care in the setting of multidisciplinary HF clinics, justifying the relatively low total score reported in this study. In fact, all the patients received education and optimized care through a HF management program, which was delivered by a multidisciplinary team of trained professionals.

This study reports the existence of three MLHFQ subscores: physical, emotional and social. This is in accordance with reports from several other authors that identified a social score.[29] Bilbao et al. compared several authors' proposals for social factors[29] and recommended the use of Munyombwe et al. social factor[30] because it has the best psychometric properties. When comparing the questions that compose the social score in our study and those proposed by Munyombwe et al., there is a match in questions 8, 9,

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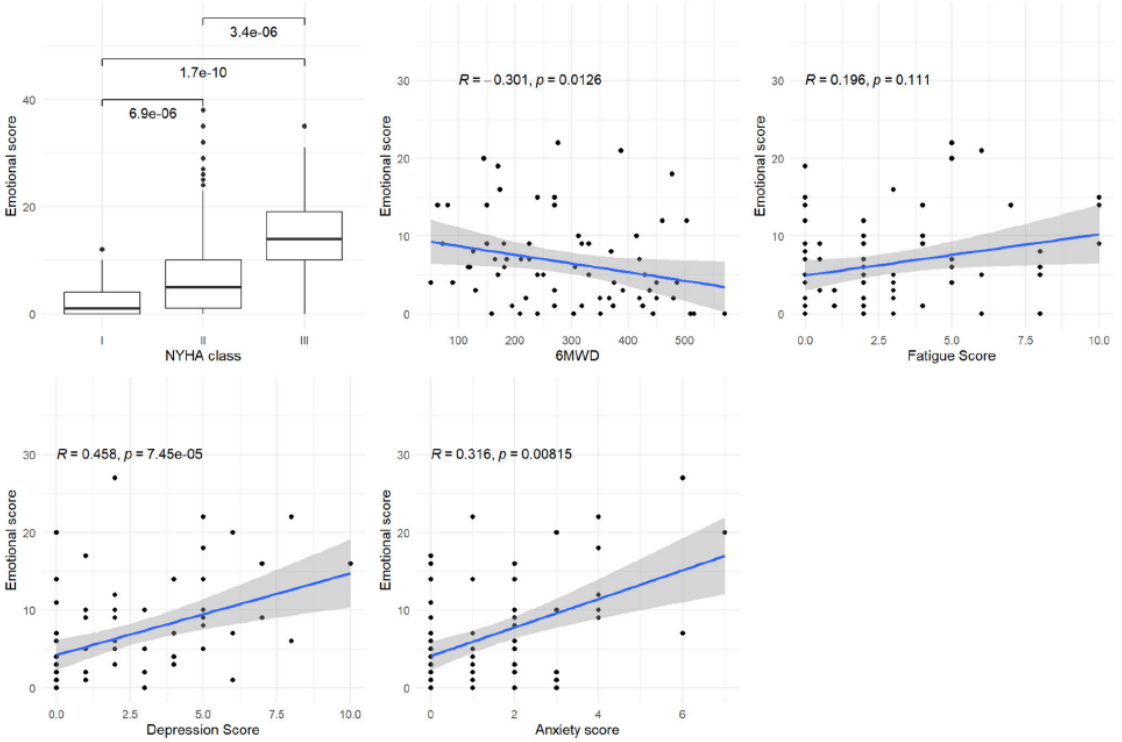


Figure 4 MLHFQ emotional score associations with NYHA class, 6MWD, Borg fatigue, and HADS depression and anxiety scores. HADS: Hospital Anxiety and Depression Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; 6MWD: six-minute walking distance.

10 and 16. However, our study included question 11 but not questions 14 and 15.

Our validated version of the MLHFQ includes 20 of the 21 questions in one of the three subscores. Thus, considering subscores for the three-domain structure could be an alternative to the total score of the MLHFQ.[29]

The impact of HF has traditionally been measured using clinical tools, such as the NYHA classification or the 6MWT.[31] The limitations of the NYHA classification include its subjective assessment and high interobserver variability, previously reported at 54%.[32] In this study, the total and subdomains scores of the MLHFQ were strongly associated with the NYHA functional class. Other authors reported a significant association of HF-specific QoL scores with the NYHA functional class,[11,33] highlighting the need for routine measurement of QoL in HF clinics. While QoL scores report the patient perspective, the NYHA functional class is typically rated from the clinician's perspective. Additionally, recent clinical trials have shown that the beneficial effects of HF medications in terms of symptoms, mortality and hospitalization, may not be related to improvements in QoL.[28]

This study revealed that the MLHFQ total score was associated with all the studied variables, namely: (1) 6MWD, (2) Borg fatigue score at the end of the 6MWT, (3) HADS depression and (4) HADS anxiety scores. These findings support the validity and reliability of the Portuguese version. The physical score was associated with fatigue and the 6MWD, the latter being an objective measure of exercise tolerance. The emotional score was significantly associated with both anxiety and depression HADS scores. However, the negative impact of anxiety and depression symptoms on the QoL of HF patients is well established in the literature.[34,35]

Notably, this study validated the MLHFQ in a sample with a balanced representation of HF patients with reduced and preserved LVEF. Currently, HF guidelines report interventions aimed at improving QoL only in patients with reduced LVEF.[14] However, Chandra et al. reported that HF patients with preserved LVEF generally have more impaired QoL than patients with reduced LVEF. Additionally, they reported regional differences in QoL among patients with preserved LVEF.[33] Thus, this study's version of the MLHFQ has potential high value, opening a door to research in the field of QoL in patients with preserved LVEF followed in Portuguese HF clinics. Nowadays, it is estimated that 650 000 people live in Portugal with HF and preserved LVEF.[7]

Our study has some limitations that we must acknowledge. This was a single-center study conducted at an HF clinic and was not designed to include a nationally representative sample. The responsiveness of this version of the MLHFQ was not tested, although we plan to do so in the future. Nevertheless, our findings are a step forward to a better QoL assessment of Portuguese HF patients.

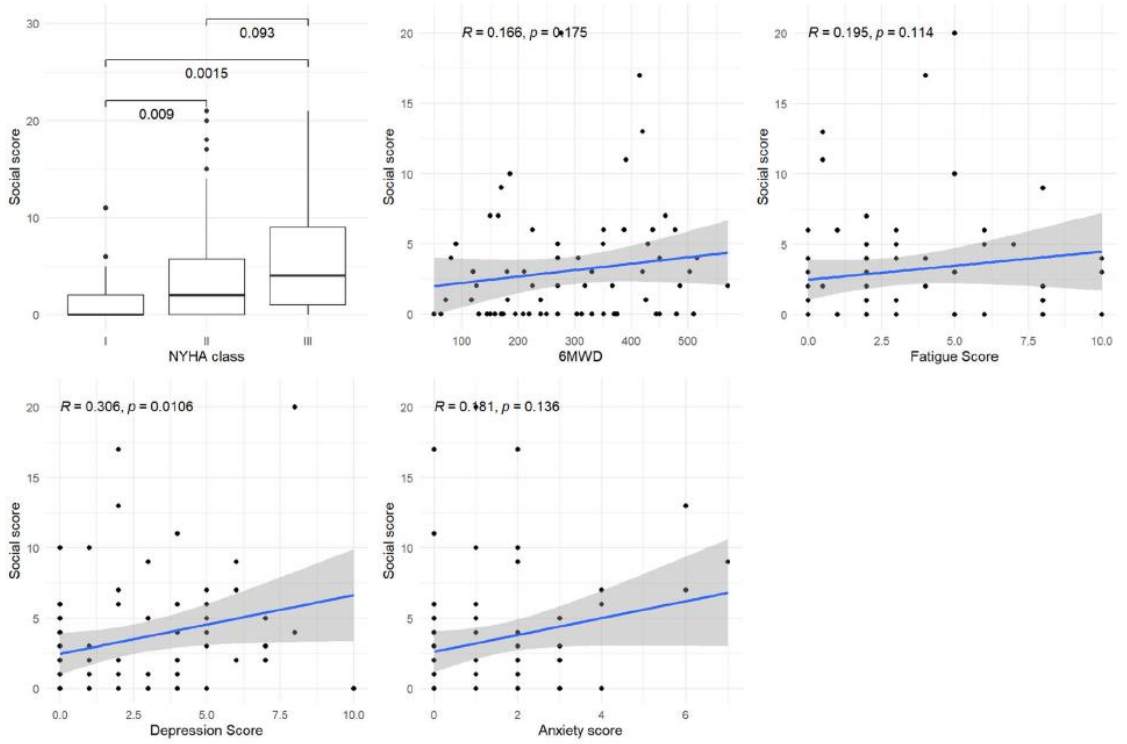


Figure 5 MLHFQ social score association with NYHA class, 6MWD, Borg fatigue, and HADS depression and anxiety scores. HADS: Hospital Anxiety and Depression Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; 6MWD: six-minute walking distance.

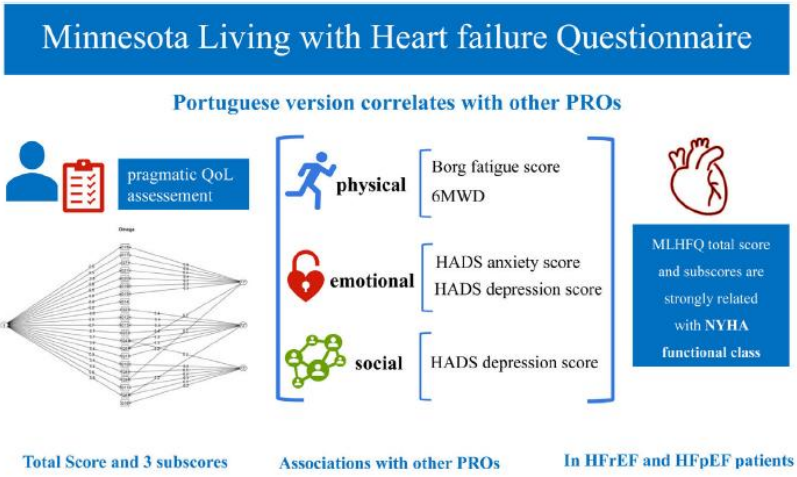


Figure 6 Association of MLHFQ scores with other PROs. HADS: Hospital Anxiety and Depression Scale; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; PROs: patient-reported health outcomes; QoL: quality of life; 6MWD: six-minute walking distance.

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Conclusions

This study supports the validity and reliability of the Portuguese MLHFQ version, recognizing the existence of a total score and three subscores: physical, emotional and social scores. All the scores were associated with the NYHA functional class. In addition, we report new and convincing evidence that the physical score is associated with the 6MWD and Borg fatigue score at the end of the 6MWT, and that the emotional score is associated with HADS anxiety and depression scores.

We believe that this MLHFQ validated version can help to overcome the challenge of QoL assessment in everyday clinical practice in Portuguese HF clinics using a pragmatic approach. Further research is needed to assess the responsiveness of the scale and the impact of routine QoL assessment in clinical practice.

CRediT authorship contribution statement

IM and SV designed the study. IM, SV and AGM collected the data. IM, AGP and MS analyzed and interpreted the data. IM and MS performed the statistical analysis and prepared the manuscript. All authors vouch for the accuracy and completeness of the data and analysis. All the authors contributed to the article and read and approved the final manuscript.

Ethical approval

Health Ethics Commission (CES) of the Porto Hospital Center. Reference number 2017.040 (040-DEFI/040-CES).

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This research received no funding.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2025.03.005.

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Supplementary Table S1

Minnesota Living with Heart Failure Questionnaire validated in Portuguese (final version, v3.0)

As seguintes questões procuram avaliar em que medida a sua insuficiência cardíaca (problema cardíaco) afetou a sua vida no último mês (4 semanas). Em cada questão, assinale com um círculo o número que melhor reflete o modo como a sua vida foi afetada (0, 1, 2, 3, 4 ou 5). Se alguma questão não se aplicar a si, assinale o número 0 (zero).

No último mês (4 semanas), a sua insuficiência cardíaca impediu-o(a) de viver como queria porque…	**Não**					**Muito**
		Muito Pouco				
1. lhe provocou inchaço nos tornozelos ou pernas?	0	1	2	3	4	5
2. o(a) obrigou a sentar-se ou deitar-se para descansar durante o dia?	0	1	2	3	4	5
3. lhe causou dificuldade em caminhar ou subir escadas?	0	1	2	3	4	5
4. lhe dificultou a realização das tarefas domésticas ou no quintal?	0	1	2	3	4	5
5. dificultou as suas saídas de casa?	0	1	2	3	4	5
6. o impediu de dormir bem de noite?	0	1	2	3	4	5
7. dificultou o seu relacionamento e as atividades com amigos ou familiares?	0	1	2	3	4	5
8. dificultou a realização das suas atividades profissionais?	0	1	2	3	4	5
9. dificultou as suas atividades de lazer, desportivas ou os seus passatempos?	0	1	2	3	4	5
10. dificultou a sua atividade sexual?	0	1	2	3	4	5
11. o(a) fez comer menos quantidade das comidas de que gosta?	0	1	2	3	4	5
12. lhe causou falta de ar?	0	1	2	3	4	5
13. o(a) fez sentir-se cansado(a), fatigado(a) ou com pouca energia?	0	1	2	3	4	5
14. o(a) obrigou a internamento hospitalar?	0	1	2	3	4	5
15. lhe criou despesas com cuidados médicos?	0	1	2	3	4	5
16. fê-lo(a) sentir efeitos secundários provocados pela medicação?	0	1	2	3	4	5
17. fê-lo(a) sentir-se um fardo para a família e amigos?	0	1	2	3	4	5
18. fê-lo(a) sentir perda de autocontrole na sua vida?	0	1	2	3	4	5
19. fê-lo(a) sentir-se preocupado(a)?	0	1	2	3	4	5
20. lhe dificultou a concentração ou a memória?	0	1	2	3	4	5
21. fê-lo(a) sentir-se deprimido(a)?	0	1	2	3	4	5

Supplementary File: Detailed statistical methods

Statistical methods

Content validity

Principal components with oblimin rotation were applied to identify the subdomains of the scale. The scree plot and, more specifically, the elbow rule and the Kaiser criterion were used to identify the number of domains/components that were retained. An item was considered to be in a component if the standardized factor loading was equal to or greater than 0.4.

The Schmid-Leiman transformation was applied to the principal component analysis of the original dataset, and the components were rotated obliquely to identify the existence of a general factor. This allowed us to identify McDonald's omega hierarchical and total as estimates of the general factor saturation of the scale.

Floor and ceiling effects

For each domain and subdomain of the MLHFQ, the maximum possible score (ceiling effect) and minimum possible score (floor effect) were assessed. A percentage lower than 15% was considered acceptable.

Reliability

Reliability was assessed by calculating the internal consistency (an indirect indicator of reliability), which was estimated via the Cronbach's alpha coefficient and the Cronbach's alpha if the item was deleted.

Construct validity

Version 3.0 was applied prospectively to a group of 294 HF patients. Among these patients, 30 (10.2%), 225 (76.5%), and 226 (76.9%) had missing information on the NYHA functional class, HADS, and 6MWT, respectively (**Figure**).

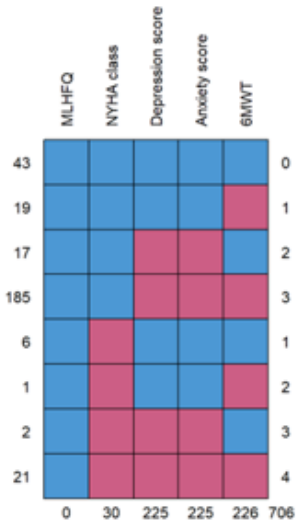


Figure. Frequency of different evaluations: MLHFQ, NYHA functional class, HADS depression and anxiety, and 6MWT

6MWT, six-minute walking test; HADS, Hospital Anxiety and Depression Scale; MLHFQ, Minnesota Living with Heart Failure Questionnaire, NYHA: New York Heart Association.

Rows: on the left is the number of patients who performed all the tests in blue; on the right is the number of tests not performed, marked in pink. Columns: bottom, is the number of patients with missing results in the test mentioned at the top.

Only the evaluations performed at the same visit where the MLHFQ was administered were considered to assess the correlation between the related domains. The MLHFQ and HADS were self-administered under supervision, and the 6MWT was always performed by the same investigators, in the same way, to preserve the pattern of application and maximize accuracy.

It was expected that all variables would be related to the general factor (main domain or total score), the physical domain with the 6MWD and the fatigue score, and the emotional domain would be strongly related to HADS scores. All domains and subdomains would be related to the NYHA functional class.

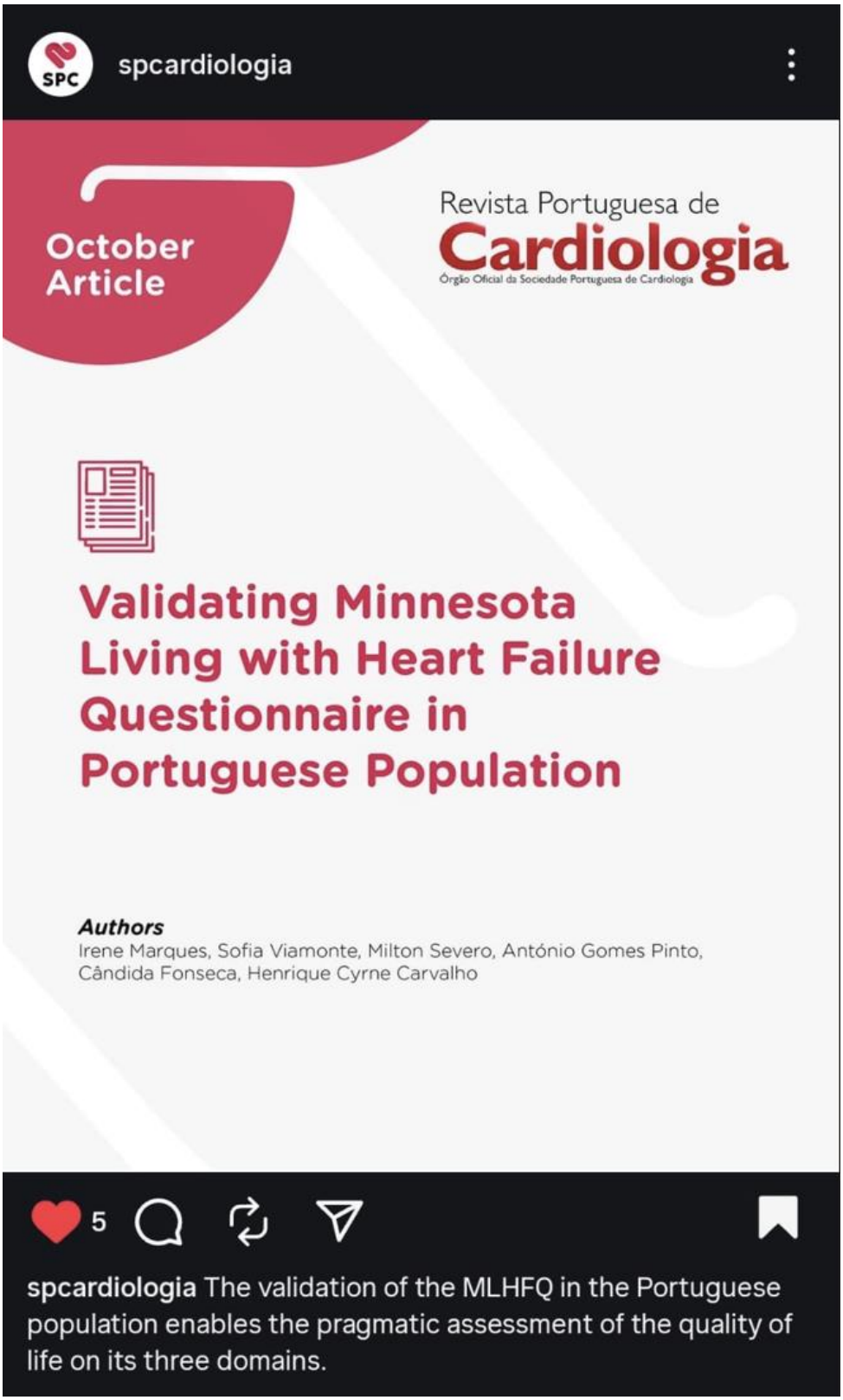
Three hypotheses were defined to analyze the construct validity of the scale:

Hypothesis 1: The shorter the distance walked and the higher the fatigue score at the end of the 6MWT are, the greater the impact of HF on patients' physical QoL.

Hypothesis 2: The higher the HADS depression and anxiety scores are, the greater the impact of HF on patients' emotional and social QoL.

Hypothesis 3: The greater the NYHA functional class is, the greater the impact of HF on patients' QoL.

Spearman correlation was used to measure the associations between the general factor and the subdomains with the 6MWD, the fatigue score at the end of the 6MWT, and the depression and anxiety HADS scores. The Mann-Whitney test was performed to compare the medians of all domains between the NYHA functional class groups.



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5.14 Factors Associated with Clinically Important Changes in Quality of Life of Heart Failure Patients: The QUALIFIER Prospective Cohort Study

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My contribution to this work was as follows: I designed the study; collected, analyzed, and interpreted the data; performed part of the statistical analysis; and prepared and submitted the manuscript. This article has not been included in any other thesis. This is an open access publication, with no financial, legal or technical barriers to accessing it.

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Article

Factors Associated with Clinically Important Changes in Quality of Life of Heart Failure Patients: The QUALIFIER Prospective Cohort Study

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Abstract

Background/Objectives: We aimed to identify the factors associated with clinically important changes in quality of life (QoL) of real-world heart failure (HF) patients. **Methods**: This is a single-centre, prospective cohort study including 419 patients at an HF clinic between January 2013 and February 2020. QoL was assessed regularly using Minnesota Living with Heart Failure Questionnaire (MLHFQ). We used five nested linear mixed-effects models to account for QoL measurements between patients and within-patient. Models were adjusted for time, sociodemographic factors, comorbidities, self-care adherence, and HF severity factors. **Results**: Median age was 78 years, 54.4% of patients were female, and 49.6% had left ventricle ejection fraction $\geq$ 50%. At baseline, 62.5% of patients were New York Heart Association (NYHA) class II. Median N-terminal-pro-B type natriuretic peptide level was 1454 pg/mL. Mean MLHFQ total score at baseline was 25 points (95%CI: 22.97–27.60). Having an implanted cardiac resynchronization therapy-pacemaker (CRT-P) was associated with moderate to large improvement in QoL (−13.55 points, 95%CI: −22.45–−4.65). NYHA class II and estimated glomerular filtration rate < 30 mL/min/1.73 m^2 were associated with small to moderate QoL deterioration (9.74 points, 95%CI: 6.74–12.75 and 5.82 points, 95%CI: 1.17–10.47, respectively). NYHA classes III or IV and a recent HF hospitalization were associated with large to very large QoL deterioration (28.39 points, 95%CI: 23.82–32.96; 60.59 points, 95%CI: 34.46–86.72; and 26.91 points, 95%CI: 21.80–32.03, respectively). **Conclusions**: CRT-P implantation, NYHA class and HF hospitalization are associated with the most clinically important QoL changes.

Keywords: quality of life; heart failure; real-world

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1. Introduction

Heart failure (HF) is a multifaceted and life-threatening syndrome characterized by significant morbidity and mortality and poor functional capacity [1]. HF affects multiple aspects of a patient's life (e.g., physical, mental/emotional, and social), resulting in a reduction in quality of life (QoL) [2]. For patients with such chronic and progressive disease, QoL is just as important as prolonging survival, especially considering that HF primarily affects older adults. Worldwide, Portugal is one of the countries with the highest proportions of elderly people, reported to be 24.11% in 2023, according to the World Bank [3]. In Portugal, one in three individuals aged 70 years or older has HF [4]. Therefore, it is urgent to better understand patients' perspectives to move toward patient-centred HF management [2].

QoL has been used as a relevant patient-reported outcome and independent endpoint in HF trials [5–7]. Additionally, QoL assessment using a validated questionnaire was defined as a quality indicator for the management of HF patients [8]. The magnitude of within-patient changes in QoL scores that are clinically meaningful to HF patients has been studied [9]. Clinically important changes in QoL have been proposed, to identify patients who experience improvement or deterioration. In March 2025, the European Society of Cardiology reported a position statement on QoL in HF that aims to foster the systematic integration of the patient's standpoint in HF care [10].

The QUALIFIER (QUALIty oF lIfe in hEart failuRe) study aims to assess QoL using a validated HF-specific questionnaire in a real-world cohort of patients admitted to an HF multidisciplinary clinic, and to identify the factors associated with clinically important changes in QoL.

2. Materials and Methods

2.1. Study Design and Clinical Setting

This single-centre, prospective, open cohort study included all patients admitted to a multidisciplinary HF outpatient clinic between January 2013 and February 2020, with at least one QoL assessment by the Minnesota Living with Heart Failure Questionnaire (MLHFQ). HF diagnosis and classification followed the universal definition and classification of HF [11]. The HF clinic inclusion and exclusion criteria, and management program, have been described previously [12,13]. Briefly, at every visit, the patient was observed by a nurse and an internist. The nurse conducted motivational interviews, assessing and promoting HF literacy and self-care behaviour through a prespecified checklist. New York Heart Association (NYHA) functional class was assessed by the physician. The Six-Minute Walking Test was performed, and the Hospital Anxiety and Depression Scale was administered regularly to assess functional capacity, as well as anxiety and depression. Polysomnography was requested for most patients. Patients were invited to participate in a cardiac rehabilitation program.

A holistic approach was used, concerning the diagnosis, management and treatment of patient comorbidities, targeted alongside HF care. Nurse and physician evaluations were documented in the electronic medical records immediately after patient consultation using prespecified structured records. The MLHFQ total score was made available to the professionals immediately. The HF multidisciplinary team meet weekly to decide investigation and/or treatment plans, namely cardiac device implantation.

The study adhered to the recommendations of the Declaration of Helsinki. The study protocol was approved by the local ethics committee and institutional review boards, with reference number 2017.040 (040-DEFI/040-CES).

2.2. QoL Evaluation and Data Collection

QoL was assessed at 3 months, 9 months, and 2 years after admission, and then annually. Patients who were unable to understand written questionnaires and those with

dementia were excluded. Patients with dementia were identified using clinical records where the dementia diagnosis was previously established and through cognitive assessment using the Mini-Cog and Mini Mental State Examination. The Mini-Cog test was part of the HF management program and was applied to all patients during their first visit to the HF clinic and, subsequently, every year. Patients with an abnormal Mini-Cog test were further evaluated using the Mini Mental State Examination to identify dementia. The inability to understand written questionnaires was assessed by the nurse administering the questionnaires.

The MLHFQ is a validated instrument for evaluating HF-specific QoL; it consists of 21 questions specific to HF and appraises QoL over the previous four weeks. Questions are answered using a Likert scale ranging from 0–5; 0 indicates that the question has no impact on the patient or is not applicable, whereas 5 indicates the greatest adverse impact. The score range is 0–105 points; a higher score represents a poorer QoL. The MLHFQ was validated in the Portuguese language [14]. The translation and validation of the Portuguese version of MLHFQ used in this research were finalized before 2013, even though its validation in a larger sample of HF patients was published more recently.

The baseline was defined as the first MLHFQ administration. Demographic data were collected at HF clinic admission. Comorbidities were collected at clinical admission or were diagnosed at follow-up. Other variables were collected: HF aetiology; NYHA class; systolic blood pressure (SBP); heart rate; heart rhythm on the last electrocardiogram; last transthoracic echocardiogram parameters: left ventricle ejection fraction (LVEF), right ventricle (RV) systolic dysfunction, pulmonary artery systolic pressure (PASP), and severe tricuspid regurgitation; HF literacy; self-care behaviour; poor adherence to recommendations and treatments; HF hospitalizations (HFHs); urgent HF visits; last laboratory results: haemoglobin, blood creatinine, estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation and N-terminal-pro-B type natriuretic peptide (NT-proBNP); HF medications and devices; completed cardiac rehabilitation program; and nocturnal non-invasive ventilation.

2.3. Study Outcomes

The primary outcome was to measure the impact of demographic factors, comorbidities, and other clinical variables on the total score of the MLHFQ. The effect of each factor on QoL was measured between patients and within-patient, by measuring QoL changes over time.

The secondary outcome was to identify factors that resulted in clinically important changes in QoL. Clinically important changes were classified using previously proposed ranges of 5, 10 or 15 points to refer to small-to-moderate, moderate-to-large, and large-to-very-large changes in QoL, respectively [9,10].

2.4. Statistical Analysis

The categorical variables are presented as frequencies and percentages. The normality of the data was assessed through visual graphic verification and the Shapiro–Wilk test. Non-skewed continuous variables were described using means and standard deviations (SDs). Variables with skewed distributions were described using medians and interquartile ranges (IQRs). Considering the longitudinal nature of the data, we used linear mixed effect (LME) models with random intercept and random time slope to account for the dependence of score measurements within-patient. Five LME models were parameterized: Model 1 was adjusted for time and time squared; Model 2 added adjustments for age, sex and self-reported low income; Model 3 included adjustments for chronic kidney disease (CKD), anaemia at HF admission, chronic pulmonary condition, anxiety, and depression; Model 4 added adjustments for self-care adherence; and Model 5 incorporated adjustments for NYHA class and NT-proBNP.

The nested models were constructed considering structure: i.e., Model 2 included sociodemographic factors, Model 3 added comorbidities, Model 4 included self-care adherence and Model 5 incorporated HF severity. Each model included a small number of variables to reduce the probability of multicollinearity. We assumed that missing data occurred at random (Missing at Random—MAR). As mixed-effects models provide valid estimates under the MAR assumption and have demonstrated robustness in the presence of incomplete data, individuals with fewer time points were retained in the analysis.

To identify clinically important changes in QoL, the magnitude of the impact of each factor on the MLHFQ score was obtained by comparing the fixed regression coefficient with 5, 10 and 15 when categorical variables were considered. For continuous variables, the fixed regression coefficient was multiplied by the SD of each variable, and the results were compared with 5, 10 and 15.

A significance level of 5% was assumed. Statistical analysis was performed using R version 4.3.0 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient Demographic and Clinical Characteristics

A total of 595 patients were observed at the HF clinic during the study period. Follow-up was less than 3 months for 79 patients and 97 patients met the exclusion criteria for MLHFQ administration. The remaining 419 patients composed the study sample. At baseline, patients had a median follow-up of 3 months. During the study, 70 (16.7%) patients died. The average follow-up was 22 months, and the maximum was 84 months. At follow-up, there were 348 MLHFQ observations between 2 and 5 months, 244 between 8 and 12 months, 115 between 22 and 27 months, and 167 observations between 27 and 84 months of follow-up.

The patients' characteristics are presented in Table 1 and in more detail in Supplementary Table S1.

Table 1. Baseline characteristics [a].

		n
Demographics [b]		
Age (years), median (IQR)	78 (14)	419
Female, *n* (%)	228 (54.4)	419
Formal education (years), *n* (%)		363
0	52 (14.3)	
1–4	231 (63.6)	
>4	80 (22.0)	
Low income [c], *n* (%)	53 (12.6)	419
Comorbidities, *n* (%)		
Hypertension [b]	357 (85.2)	419
Diabetes *mellitus*	225 (54.1)	416
Pre-diabetes	66 (15.8)	419
Dyslipidemia	318 (75.9)	419
Obesity [b]	129 (30.9)	418
Smoking [b]		419
Current	40 (9.5)	
Past	110 (26.3)	
Atrial flutter/fibrillation [b,d]	247 (58.9)	419
Chronic kidney disease [b]	230 (54.9)	419
Cerebrovascular disease	93 (22.2)	419
Peripheral arterial disease	58 (13.8)	419
Chronic pulmonary condition	156 (37.2)	419
Sleep-related breathing disorder	154 (36.8)	419
Anaemia [b]	218 (52.2)	418
Iron deficiency	218 (71.5)	305

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Table 1. *Cont.*

		n
Cancer	14 (3.3)	419
Anxiety	25 (6.0)	419
Depression	124 (29.6)	419
Heart failure		
Etiology [b], *n* (%)		419
Hypertensive	178 (42.5)	
Ischemic	163 (38.9)	
Valvular	146 (34.8)	
NYHA functional class, *n* (%)		419
I	65 (15.5)	
II	262 (62.5)	
III	47 (11.2)	
IV	2 (0.5)	
SBP (mmHg), mean (SD)	126.7 (21.1)	399
Heart rate (bpm), mean (SD)	71.8 (12.1)	403
LVEF, *n* (%)		419
≥50%	216 (51.6)	
41–49%	40 (9.5)	
≤40%	163 (38.9)	
HF self-care, *n* (%)		
HF literacy	98 (25.7)	381
Self-care literacy	146 (37.5)	389
Self-care adherence	132 (33.9)	389
Exercice adherence	72 (20.7)	348
Poor adherence, *n* (%)	169 (40.3)	419
HF events [e], *n* (%)		419
HF hospitalization	39 (9.3)	
Urgent HF visit	4 (1.0)	
Laboratory		
Haemoglobin (g/dL), mean (SD)	12.5 (1.8)	419
Creatinine (mg/dL), mean (SD)	1.35 (0.64)	419
eGFR (mL/min/1.73 m^2), *n* (%)		419
≥60	167 (39.9)	
45–59	78 (18.6)	
30–44	113 (27.0)	
<30	61 (14.6)	
NT-proBNP (pg/mL), median (IQR)	1454 (2546)	415
Medications, *n* (%)		419
ACEi	203 (48.4)	
ARNi	11 (2.6)	
ARB	41 (9.8)	
MRA	136 (32.5)	
BB	326 (77.8)	
SGLT2i	14 (3.3)	
Furosemide (mg/day), mean (SD)	80.0 (41.5)	
Other treatments, *n* (%)		
Cardiac rehabilitation	9 (2.1)	419
Nocturnal non-invasive ventilation	55 (13.1)	419
Cardiac devices	72 (17.2)	419
CRT-P	9 (2.1)	
CRT-D	8 (1.9)	
ICD	11 (2.6)	
Pacemaker	44 (10.5)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter–defibrillator; IQR, interquartile range; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; NYHA, New York Heart Failure; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium–glucose co-transporter 2 inhibitor. [a] Baseline represents the moment of the first MLHFQ administration. [b] Data collected at HF clinic admission. [c] Self-reported. [d] Past or present history of atrial fibrillation or atrial flutter. [e] HF events on the previous 28 days.

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Briefly, the patients' median age was 78 years, with a female predominance (54.4%). At HF clinic admission, 49.6% of the patients had preserved LVEF (≥50%), and 40.6% had a reduced LVEF (≤40%). The HF aetiology was primarily hypertensive (42.5%), ischemic (38.9%), and/or valvular (34.8%). At baseline, most patients had NYHA class II symptoms (62.5%), and the median NT-proBNP level was 1454 pg/mL. Most patients had several cardiovascular and non-cardiovascular comorbidities. Hypertension, dyslipidaemia, iron deficiency, a history of atrial flutter or fibrillation, CKD, diabetes mellitus and anaemia were the most frequent comorbidities, each of which was present in more than half of the patients. At baseline, 60.6% of the patients were taking at least one renin–angiotensin–aldosterone system inhibitor (RAASi). Only 33.9% of patients adhered to HF self-care behaviour, 17.2% had a cardiac device implanted, and 9.3% had had HFH in the previous 28 days (Table 1). In the follow-up, a total of 16 patients received a CRT-P device.

3.2. QoL Trajectory

The mean MLHFQ total score at baseline was 25 points (95%CI: 22.97–27.60). We found a nonlinear association between scores and time. The generalized additive model revealed higher scores at baseline and a rapid decline, stabilizing at 10 months of follow-up. The time trend of the score was a decrease of 0.59 points/month. The inclusion of a quadratic term ($\beta = 0.009$) to account for that nonlinearity resulted in an inverse J-curve. Both the linear and quadratic terms were statistically significant (95%CI: −0.80–−0.38 and 95%CI: 0.005–0.013, respectively) (Figure 1).

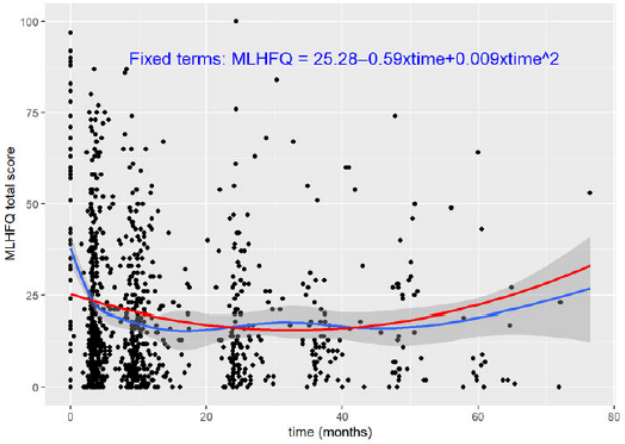


Figure 1. MLHFQ total score trajectory over time. The blue line represents the generalized additive model with smooth term for time. The red line indicates the linear and fixed terms for time of the LME model.

3.3. Factors Associated with Significant QoL Changes

The results of the univariate analysis (Model 1) and multivariate analysis (Models 2 to 5) are presented in Tables 2 and 3. The detailed results of the statistical analysis are reported in the Supplementary Tables S2–S4.

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Table 2. Mixed-effects models with MLHFQ total score, patient demographics and comorbidities [a].

Variable	Model 1			Model 2 [b]			Model 3 [c]			Model 4 [d]			Model 5 [e]		
		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value
Age															
<65	Ref			Ref			Ref			Ref			Ref		
65–79	3.09	−1.25–7.42	0.162	2.82	−1.32–6.95	0.181	2.45	−1.78–6.68	0.255	2.37	−1.91–6.65	0.277	−0.09	−3.87–3.69	0.965
≥80	1.86	−2.57–6.28	0.409	2.26	−2.08–6.61	0.307	0.255	−2.08–6.86	0.294	2.20	−2.34–6.74	0.342	−2.15	−6.25–1.96	0.304
Sex															
Female	Ref			Ref			Ref			Ref			Ref		
Male	−4.69	−7.69–−1.68	**0.002**	−4.30	−7.30–−1.30	**0.005**	−4.46	−7.53–−1.39	**0.005**	−4.73	−7.85–−1.62	**0.003**	−1.50	−4.34–1.33	0.298
Low income															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.19	−0.43–8.81	0.076	4.67	0.08–9.25	**0.046**	4.39	−0.19–8.97	0.060	4.03	−0.61–8.67	0.089	3.74	−0.38–7.86	0.075
Diabetes *mellitus*															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.95	−0.09–5.99	0.057	2.28	−0.66–5.22	0.128	2.06	−0.92–5.04	0.175	2.25	−0.75–5.26	0.141	3.00	0.29–5.70	**0.030**
Smoking															
Never	Ref			Ref			Ref			Ref			Ref		
Past	−5.09	−8.53–−1.65	**0.004**	−2.90	−7.17–1.38	0.184	−5.01	−9.52–−0.51	**0.029**	−4.95	−9.51–−0.40	**0.033**	−4.36	−8.44–−0.27	**0.037**
Current	−2.20	−7.46–3.07	0.413	−0.43	−6.43–5.58	0.889	−3.30	−9.66–3.07	0.309	−3.15	−9.58–3.29	0.337	−2.52	−8.31–3.27	0.393
CKD															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.23	−0.84–5.30	0.154	2.38	−0.64–5.41	0.122	2.11	−0.92–5.15	0.172	1.95	−1.12–5.02	0.212	0.06	−2.72–2.85	0.963
Chronic pulmonary condition															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.06	−1.04–5.17	0.192	2.60	−0.47–5.67	0.097	3.02	−0.06–6.10	0.055	3.14	0.03–6.26	**0.048**	1.49	−1.33–4.32	0.300
Sleep-related breathing disorder															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−0.86	−3.59–1.86	0.534	−0.74	−3.43–1.95	0.588	−0.77	−3.44–1.91	0.573	−0.68	−3.36–1.99	0.616	−2.84	−5.34–−0.35	**0.026**
Anxiety															
No	Ref			Ref			Ref			Ref			Ref		
Yes	7.05	0.73–13.37	**0.029**	6.33	0.20–12.46	**0.043**	5.96	−0.31–12.24	0.063	5.52	−0.87–11.90	0.090	4.36	−1.38–10.10	0.136
Depression															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.92	1.70–8.14	**0.003**	4.63	1.44–7.83	**0.005**	4.27	1.04–7.50	**0.010**	4.22	0.96–7.49	**0.011**	2.46	−0.53–5.46	0.107
Anaemia															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.32	0.26–6.38	**0.033**	3.49	0.54–6.43	**0.020**	3.75	0.78–6.72	**0.013**	3.72	0.72–6.73	**0.015**	2.75	0.05–5.46	**0.046**

CKD, chronic kidney disease; CI, 95% confidence interval; MLHFQ, Minnesota Living with Heart Failure Questionnaire. [a] All models were adjusted to time and time^2. [b] All variables were adjusted to model 1, age, sex, and low income. [c] All variables were adjusted to model 2, CKD, anaemia, CPD, anxiety, and depression. [d] All variables were adjusted to model 3 and selfcare adherence. [e] All variables were adjusted to model 4, NYHA, and NT-proBNP.

Table 3. Mixed-effects models with MLHFQ total score, HF, laboratory and treatment variables [a].

Variable	Model 1			Model 2 [b]			Model 3 [c]			Model 4 [d]			Model 5 [e]		
		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value
NYHA class															
I	Ref			Ref			Ref			Ref			Ref		
II	9.78	6.96–12.60	**<0.001**	10.58	7.64–13.51	**<0.001**	10.52	7.55–13.50	**<0.001**	10.20	7.20–13.19	**<0.001**	9.74	6.74–12.75	**<0.001**
III	29.94	25.67–34.22	**<0.001**	30.18	25.71–34.65	**<0.001**	29.53	25.01–34.05	**<0.001**	29.13	24.58–33.67	**<0.001**	28.39	23.82–32.96	**<0.001**
IV	59.48	33.04–85.93	**<0.001**	61.40	35.05–87.76	**<0.001**	61.89	35.58–88.21	**<0.001**	61.88	35.55–88.22	**<0.001**	60.59	34.46–86.72	**<0.001**
SBP	−0.06	0.12–0.00	0.052	−0.08	−0.14–−0.02	**0.010**	−0.08	−0.14–−0.02	**0.009**	−0.08	−0.15–−0.02	**0.008**	−0.06	−0.12–−0.00	**0.045**
LVEF															
≥50%	Ref			Ref			Ref			Ref			Ref		
41–49%	5.96	1.36–10.56	**0.011**	7.16	2.56–11.76	**0.002**	6.37	1.76–10.98	**0.007**	6.09	1.49–10.70	**0.010**	4.88	0.60–9.17	**0.026**
≤40%	−3.23	−6.18–−0.28	**0.032**	−2.12	−5.18–0.94	0.174	−1.68	−4.75–1.39	0.282	−1.68	−4.77–1.42	0.287	−1.78	−4.74–1.19	0.239
PASP	0.24	0.12–0.36	**<0.001**	0.23	0.11–0.35	**<0.001**	0.20	0.08–0.32	**0.001**	0.20	0.08–0.32	**0.001**	0.11	−0.00–0.23	0.057
HF literacy															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−2.97	−5.90–−0.03	**0.047**	−2.82	−5.73–0.08	0.057	−2.95	−5.86–−0.03	**0.047**	−2.24	−5.17–0.70	0.135	−2.50	−5.26–0.25	0.074
Self-care literacy															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−4.47	−7.29–−1.65	**0.002**	−4.07	−6.91–−1.23	**0.005**	−3.90	−6.74–−1.07	**0.007**	−0.76	−4.83–3.30	0.713	−1.07	−5.04–2.91	0.599
Self-care adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−4.75	−7.28–−2.23	**<0.001**	−4.50	−7.05–−1.95	**0.001**	−4.33	−6.87–−1.79	**0.001**	−4.33	−6.87–−1.79	**0.001**	−2.26	−4.68–0.17	0.069
Exercise adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−3.43	−6.24–−0.62	**0.017**	−3.48	−6.32–−0.65	**0.016**	−2.99	−5.83–−0.14	**0.040**	−2.03	−4.99–0.92	0.177	−2.12	−4.87–0.63	0.130
Poor adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.31	0.18–6.43	**0.038**	3.23	0.13–6.32	**0.041**	3.22	0.12–6.32	**0.042**	2.79	−0.37–5.95	0.083	3.36	0.53–6.20	**0.020**
HF hospitalization [f]															
No	Ref			Ref			Ref			Ref			Ref		
Yes	32.75	27.46–38.03	**<0.001**	32.66	27.38–37.93	**<0.001**	32.00	26.74–37.26	**<0.001**	31.21	25.95–36.46	**<0.001**	26.91	21.80–32.03	**<0.001**
Urgent HF visit [f]															
No	Ref			Ref			Ref			Ref			Ref		
Yes	15.25	3.78–26.71	**0.009**	17.05	6.44–27.67	**0.002**	16.37	5.75–26.99	**0.003**	16.47	5.83–27.10	**0.002**	8.79	−0.99–18.57	0.078
Haemoglobin [g]															
Normal	Ref			Ref			Ref			Ref			Ref		
Low	4.46	1.92–7.00	**0.001**	4.59	2.04–7.15	**<0.001**	4.24	1.47–7.01	**0.003**	4.44	1.68–7.20	**0.002**	2.37	−0.27–5.00	0.078
eGFR															
≥60	Ref			Ref			Ref			Ref			Ref		
45–59	0.39	−2.90–3.68	0.816	0.50	−2.88–3.89	0.770	0.40	−3.17–3.97	0.825	0.46	−3.09–4.02	0.798	1.07	−2.25–4.39	0.529
30–44	2.14	−1.25–5.52	0.215	2.04	−1.43–5.50	0.249	1.76	−2.20–5.72	0.383	1.73	−2.22–5.68	0.390	−0.33	−4.04–3.37	0.860
<30	9.77	5.53–14.02	**<0.001**	9.33	5.06–13.60	**<0.001**	9.44	4.57–14.32	**<0.001**	9.60	4.73–14.47	**<0.001**	5.82	1.17–10.47	**0.014**
NT-proBNP/1000	0.37	0.20–0.54	**<0.001**	0.37	0.20–0.54	**<0.001**	0.37	0.20–0.54	**<0.001**	0.35	0.18–0.52	**<0.001**	0.20	0.03–0.36	**0.023**
ACEi															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−4.67	−7.37–−1.96	**0.001**	−4.79	−7.50–−2.08	**0.001**	−4.20	−6.93–−1.48	**0.003**	−3.83	−6.58–−1.07	**0.007**	−3.45	−6.00–−0.91	**0.008**
Furosemide dose/40	3.78	2.64–4.92	**<0.001**	3.95	2.82–5.07	**<0.001**	3.80	2.65–4.94	**<0.001**	3.76	2.61–4.91	**<0.001**	2.29	1.09–3.49	**<0.001**
Cardiac rehabilitation															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−5.82	−9.70–−1.94	**0.003**	−6.17	−10.02–−2.32	**0.002**	−5.92	−9.80–−2.05	**0.003**	−5.38	−9.24–−1.52	**0.006**	−2.90	−6.48–0.67	0.112

Table 3. *Cont.*

Variable	Model 1			Model 2 [b]			Model 3 [c]			Model 4 [d]			Model 5 [e]		
		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value		CI	*p*-Value
Cardiac device															
None	Ref			Ref			Ref			Ref			Ref		
ICD	−6.69	−14.36–0.98	0.087	−4.37	−12.17–3.42	0.271	−2.83	−10.59–4.93	0.474	−3.84	−11.61–3.93	0.332	−5.29	−12.34–1.77	0.142
CRT-P	−10.39	−19.71–−1.08	**0.029**	−9.49	−18.63–−0.35	**0.042**	−8.56	−17.61–0.50	0.064	−9.44	−18.41–−0.47	**0.039**	−13.55	−22.45–−4.65	**0.003**
CRT-D	0.03	−8.39–8.45	0.995	1.34	−6.76–9.44	0.745	−0.09	−8.20–8.02	0.982	−0.28	−8.32–7.76	0.945	0.61	−6.75–7.97	0.872
Pacemaker	−0.20	−4.65–4.26	0.931	0.30	−4.07–4.67	0.892	−0.19	−4.57–4.18	0.931	−0.65	−5.03–3.74	0.772	−1.88	−5.87–2.11	0.354

ACEi, angiotensin-converting enzyme inhibitor; CI, 95% confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left ventricle ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal-pro-B type natriuretic peptide; NYHA, New York Heart Failure; PASP, pulmonary artery systolic pressure; RV, right ventricle; SBP, systolic blood pressure. [a] All models were adjusted to time and time^2. [b] All variables were adjusted to model 1, age, sex, and low income. [c] All variables were adjusted to model 2, CKD, anaemia, CPD, anxiety, and depression. [d] All variables were adjusted to model 3 and selfcare adherence. [e] All variables were adjusted to model 4, NYHA, and NT-proBNP. [f] HF events on the previous 28 days. [g] Normal haemoglobin is defined as ≥12 g/dL in female and ≥13 g/dL in male patients.

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Multivariate analysis adjusted for patient characteristics is represented in Model 2 and the adjustment for comorbidities is represented in Model 3. Model 4 was adjusted for self-care adherence and Model 5 was adjusted for two surrogate markers of HF severity, NYHA class and NT-proBNP level (Tables 2 and 3).

The final model (Model 5) revealed that past smokers, patients with sleep-related breathing disorder, those with higher SBP, those taking an ACEi, and those with an implanted CRT-P had significantly better QoL (Figure 2).

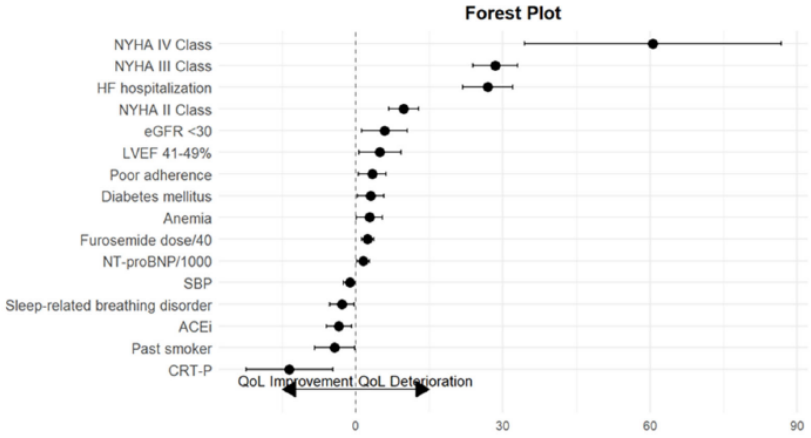


Figure 2. MLHFQ total score changes and factors associated with significant QoL improvement (on the left) and deterioration (on the right).

The only factor associated with clinically important improvement in QoL was having an implanted CRT-P (−13.55 points, 95%CI: −22.45–−4.65). Considering that only 16 patients had an implanted CRT-P, we performed a power simulation based on 200 simulations, using the simr package in R. We found that the estimated power to detect the effect of CRT-P was 44% (95% CI: 37.0-51.2%). Although this is below the conventional 80% threshold, it still provides some statistical power to detect an effect of CRT-P, suggesting that it is not a random effect.

Patients with diabetes, anaemia, NYHA class II to IV, LVEF between 41% and 49%, poor adherence, HFH in the previous 28 days, eGFR < 30 mL/min/1.73 m^2, high NT-proBNP and high furosemide dose were associated with significantly worse QoL (Figure 2). The factors associated with clinically important deterioration in QoL were NYHA class (9.74 points, 95%CI: 6.74–12.75; 28.39 points, 95%CI: 23.82–32.96; and 60.59 points, 95%CI: 34.46–86.72, for classes II, III and IV, respectively), HFH (26.91 points, 95%CI: 21.80–32.03) and eGFR < 30 mL/min/1.73 m^2 (5.82 points, 95%CI: 1.17–10.47) (Tables 2 and 3, Model 5). The detailed results of the statistical analysis are reported in Supplementary Tables S2–S4. We performed sensitivity analyses using several factors, such as HF literacy, self-care literacy, self-care adherence, exercise adherence, all-cause hospitalizations and HFH, which did not change the results.

CRT-P implantation was associated with a moderate-to-large improvement in QoL. NYHA class II and eGFR < 30 mL/min/1.73 m^2 were associated with small-to-moderate QoL deterioration, whereas NYHA class III or IV and a recent HFH were associated with large-to-very-large QoL deterioration (Figure 3).

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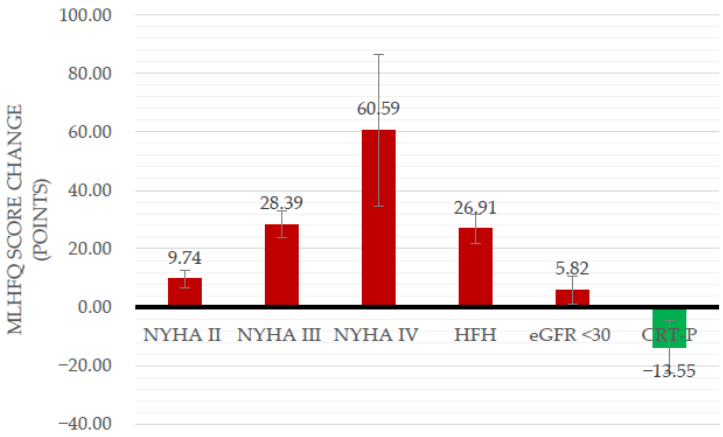


Figure 3. Factors associated with clinically important deterioration (red bars) or improvement (green bar) in MLHFQ total score.

Furthermore, we found that in patients with NYHA classes I-III, the improvement or worsening of one NYHA class was associated with a median decrease of 10.5 points (P25 =−36.2, P7 = −2) and an increase of 6 points (P25 =−9, P7 = 19) in MLHFQ score, respectively (Figure 4).

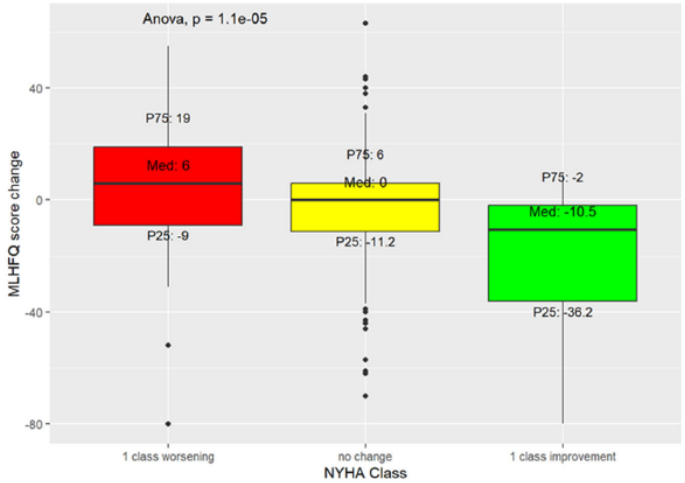


Figure 4. MLHFQ median score changes resulting from one NYHA class deterioration (red box), no change (yellow box), or one NYHA class improvement (green box).

4. Discussion

This study reports QoL assessment of a cohort of 419 HF outpatients admitted to a multidisciplinary HF clinic over more than seven years. QoL assessment was part of the structured follow-up program and routine clinical practice. After analysing a comprehensive group of demographic and clinical factors, the only factor associated with clinically important improvement in QoL was the implantation of a CRT-P, which resulted in a moderate-to-large improvement. NYHA class II and an eGFR < 30 mL/min/1.73 m^2 were associated with small-to-moderate clinically important QoL deterioration, whereas

NYHA class III or IV and a recent HFH were associated with large-to-very-large clinically important QoL deterioration.

Most patients in the study were female, had LVEF ≥ 50%, and had hypertensive and/or ischaemic heart disease, reflecting the Portuguese HF population. In Portugal, HF prevalence is twice as high in women as it is in men, and 93% of HF patients aged 50 years or older have LVEF ≥ 50% [4]. Not surprisingly, we found a high burden of comorbidities in an elderly population with preserved LVEF [15]. At baseline, most patients were NYHA class II, had high levels of NT-proBNP, and were taking a RAASi and/or a beta-blocker. Notably, this study began before the approval of sacubitril/valsartan and sodium–glucose co-transporter 2 inhibitors (SGLT2i) for treatment of HF.

The mean MLHFQ total score at baseline was 25 points, and the score improved over time, until 10 months of follow-up. This finding is better than that in other reports [16,17], and is expected in patients under optimized care and follow-up [18,19].

We found that some factors traditionally associated with better or worse QoL in HF patients lost their impact on QoL when other factors were taken into consideration in the LME models [20,21]. The positive effect of male sex on QoL was captured after adjustment for NYHA and NT-proBNP. This probably reflects fewer symptoms reported by men, improving NYHA. We observed a similar pattern with self-care adherence and cardiac rehabilitation. The improvement in symptoms is the likely explanation for the improved QoL of patients who adhere to self-care and/or exercise. In contrast, the negative effect of depression on QoL was captured after adjustment for NYHA and NT-proBNP. Probably, worse symptoms in depressed patients explain this finding. Other authors who also reported a strong correlation of symptoms with QoL did not find an effect of depression on QoL [21]. The negative effects of higher PASP and recent urgent HF visits on QoL were also captured in the final model. Diabetic patients constitute a subgroup of HF patients experiencing worse QoL, as reported by other authors [20,22]. Nevertheless, we did not verify a negative impact on QoL of other comorbidities, as found in a recent literature review [20].

We found some intriguing associations with QoL improvement and deterioration. Past smokers had better QoL, possibly reflecting healthier behaviour in patients who stopped smoking. Accordingly, we confirmed the negative impact of poor adherence to healthcare on QoL. Patients with LVEF between 41 and 49% at follow-up had worse QoL than patients with preserved LVEF. This is surprising, because an LVEF ≤ 40% at HF clinic admission was associated with better QoL in the univariate analysis, but its effect was captured in multivariate analyses. Patients with sleep-related disorders had better QoL, even though non-invasive ventilation had no impact on QoL. The negative impact of anaemia at clinic admission on QoL persisted throughout all the models. However, the negative effect of low haemoglobin at follow-up was captured in the final model, probably because patients with anaemia were classified with a higher NYHA class. The reasons behind these unexpected findings are not clear, but encourage further research.

In this study, age and HF aetiology had no effect on QoL. Patients with higher SBP and those taking an ACEi had significantly improved QoL. No impact was observed on QoL of the few patients taking sacubitril/valsartan or SGLT2i, contrary to the published evidence [23–25]. Clinical trials that measured the impact of ACE inhibitors on the QoL of patients with HF and reduced LVEF reported results that were confounded by a placebo effect, high noncompletion rates, different measurement tools, and evaluations of different QoL domains. Typically, QoL measurements in patients receiving ACEi showed small improvements or did not differ significantly from those in placebo-treated patients over long-term follow-up [26]. We found that higher furosemide doses and NT-proBNP levels are associated with worse QoL, as expected [21], since they are surrogate markers of severe HF.

Importantly, we found that NYHA class III and HFH were associated with large-to-very-large clinically important deterioration in QoL, whereas NYHA class II and an eGFR < 30 mL/min/1.73 m^2 were associated with small-to-moderate clinically important QoL deterioration. Despite the association between higher NYHA classes and worse QoL, which is widely reflected in the literature [10,16,21], improving QoL does not always imply that NYHA class has improved. In fact, recently, finerenone improved QoL, but not NYHA class, in patients with LVEF ≥ 40% [27]. On the other hand, vericiguat was shown to reduce HFH in HF patients with LVEF < 45%, but had no impact on QoL [18]. Moreover, the most recent positive drug trials in HF patients revealed a non-clinically important QoL improvement, which was driven mainly by a reduction in HFH [10,28]. These observations underscore the relevance of looking at QoL improvement as a key therapeutic target. Furthermore, we found that improvement in one NYHA class, compared with worsening, had a more pronounced effect on QoL, which is in line with findings in other studies [9,29].

Patients who received a CRT-P showed a moderate-to-large clinically important improvement in QoL. Despite its well-established clinical benefits and cost-effectiveness, CRT-P remains widely underutilized. European data suggest that only one in three eligible patients receives a CRT device [30]. Zeitler et al. demonstrated that the burden of comorbidities does not appear to compromise the clinical benefits of CRT in terms of morbidity and mortality [31]. Indeed, an ESC position paper regarding CRT states that clinical factors favoring the use of CRT-P could include advanced age, more severe symptoms, and life-shortening comorbidities, such as stage IV CKD [30]. In fact, these are the characteristics of our patients in the current study.

As a result of our findings, consideration should be given to earlier CRT-P implantation in eligible patients, especially elderly patients with diabetes or a high burden of comorbidities. Overall, our study results should lead us to diagnose and treat HF sooner and aggressively, with the aim of maintaining patients in NYHA class I and free of HFH. If we achieve this high standard of HF care, we can not only reduce mortality, but also improve QoL.

Our study has limitations to acknowledge. This was a single-centre observational study. Thus, residual confounding cannot be ruled out, nor can the results be generalized. Additionally, the effects of obesity and iron replacement on QoL were not assessed. Nevertheless, we analysed a wide range of factors retrieved from patients, nurses, physicians, and laboratory and treatment data. The latter, combined with a well-characterized real-world sample of HF patients across the entire range of the LVEF spectrum, are major strengths of this study. Finally, we showed that it is possible to include QoL assessment in routine clinical practice.

5. Conclusions

In conclusion, this study revealed that patients who received a CRT-P had moderate-to-large clinically important improvements in QoL and that NYHA class II-IV, HFH and eGFR < 30 mL/min/1.73 m^2 were associated with clinically important QoL deterioration. These were the only factors associated with clinically important QoL changes, considering a comprehensive number of factors studied and retrieved from patients, nurses, physicians, and laboratory and treatment data, while using a structured statistical analysis with nested LME models. These findings should lead clinicians to improve HF diagnosis and optimize treatment, including early CRT-P referrals for eligible patients. Consequently, clinically meaningful improvements in QoL may be expected. Future studies are needed to confirm our findings.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14145079/s1, Table S1: Patients' characteristics at HF clinic admission and at baseline; Table S2: Mixed-effects models with MLHFQ total score, patient's demographics and comorbidities; Table S3: Mixed-effects models with MLHFQ total score, HF and laboratory variables; Table S4: Mixed-effects models with MLHFQ total score and treatments.

Author Contributions: Conceptualization, I.M.; data curation, I.M.; formal analysis, I.M. and M.S.; funding acquisition, I.M.; investigation, I.M. and A.G.P.; methodology, I.M. and M.S.; project administration, I.M.; resources, I.M.; software, M.S.; supervision, I.M.; validation, I.M. and M.S.; writing—original draft, I.M.; writing—review and editing, I.M., M.S., A.G.P., C.F. and H.C.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Boards. The study protocol was approved by the local Ethics Committee. Ethic Committee name: Comissão de Ética para a Saúde (CES) do Centro Hospitalar do Porto; approval code: 2017.040 (040-DEFI/040-CES); approval date: 22 March 2017. The study protocol was approved also by institutional review boards: Gabinete Coordenador de Investigação, Direção de Departamento de Ensino, Formação e Investigação (DEFI), and Conselho de Administração do Centro Hospitalar do Porto; approval code: 2017.040 (040-DEFI/040-CES); approval date: 19 April 2017.

Informed Consent Statement: Patient consent was waived, in accordance with institutional requirements for observational studies. Written informed consent from the patients to publish this paper could not be obtained because many patients were deceased at the time the decision to publish was made.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin-receptor blocker
ARNi	Angiotensin receptor and neprilysin inhibitor
BB	Beta-blockers
CI	95% confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRT-D	Cardiac resynchronization-therapy defibrillator
CRT-P	Cardiac resynchronization-therapy pacemaker
DOAC	Direct-acting oral anticoagulant
eGFR	Estimated glomerular filtration rate
HF	Heart failure
HFH	Hearf failure hospitalization
ICD	Implantable cardioverter–defibrillator
IQR	Interquartile range
LME	Linear mixed effects
LVEF	Left ventricle ejection fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid receptor antagonists
NT-proBNP	N-terminal-pro-B type natriuretic peptide
NYHA	New York Heart Failure
PASP	Pulmonary artery systolic pressure
QoL	Quality of life

QUALIFIER	QUALIty oF lIfe in hEart failuRe
RAASi	Renin–angiotensin–aldosterone system inhibitor
RV	Right ventricle
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2i	Sodium–glucose cotransporter 2 inhibitor

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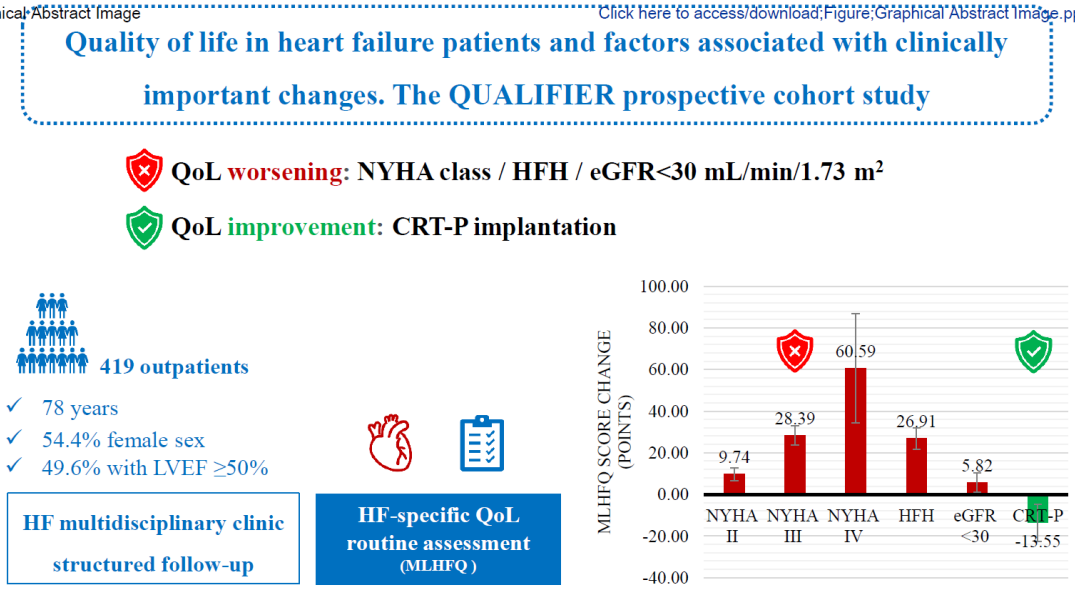
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Supplementary Table S1 Patients´characteristics at HF clinic admission and at baseline

Variable	HF clinic admission		Baseline[a]	
Demographics		n		n
Age (years), median (IQR)	78 (14)	419		
Female, n (%)	228 (54.4)	419		
Formal education (years), n (%)		363		
0	52 (14.3)			
1-4	231 (63.6)			
> 4	80 (22.0)			
Low income[b], n (%)	53 (12.6)	419		
Comorbidities, n (%)				
Hypertension	357 (85.2)	419		
Diabetes *mellitus*	224 (53.8)	416	225 (54.1)	416
Pre-diabetes	58 (13.8)	419	66 (15.8)	419
Dyslipidemia	314 (74.9)	419	318 (75.9)	419
Obesity	129 (30.9)	418		
Smoking		419		
Current	40 (9.5)			
Past	110 (26.3)			
Atrial flutter/fibrillation[c]	247 (58.9)	419		
CKD	230 (54.9)	419		
Cerebrovascular disease	93 (22.2)	419	93 (22.2)	419
Peripheral arterial disease	58 (13.8)	419	58 (13.8)	419
Chronic pulmonary condition	153 (36.5)	419	156 (37.2)	419
Sleep-related breathing disorder	72 (17.2)	419	154 (36.8)	419
Anaemia	218 (52.2)	418		
Iron deficiency	175 (63.4)	276	218 (71.5)	305
Cancer	12 (2.9)	419	14 (3.3)	419
Sexual dysfunction	17 (4.1)	419	17 (4.1)	419
Anxiety	25 (6.0)	419	25 (6.0)	419
Depression	121 (28.9)	419	124 (29.6)	419
Heart failure				
Etiology, n (%)		419		

Hypertensive	178 (42.5)			
Ischemic	163 (38.9)			
Valvular	146 (34.8)			
Dilated non-ischemic	32 (7.6)			
NYHA functional class, n (%)		419		419
I	58 (13.8)		65 (15.5)	
II	269 (64.2)		262 (62.5)	
III	70 (16.7)		47 (11.2)	
IV	4 (1.0)		2 (0.5)	
Not classified	18 (4.3)		43 (10.3)	
SBP (mmHg), mean (SD)			126.7 (21.1)	399
Heart rate (bpm), mean (SD)			71.8 (12.1)	403
Rhythm, n (%)		419		419
Sinus	227 (54.2)		225 (53.7)	
Atrial flutter/fibrillation	167 (39.9)		152 (36.3)	
Pacemaker	25 (6.0)		42 (10.0)	
LVEF, n (%)		419		419
≥50%	208 (49.6)		216 (51.6)	
41-49%	41 (9.8)		40 (9.5)	
≤40%	170 (40.6)		163 (38.9)	
RV systolic dysfunction, n (%)			72 (17.3)	415
PASP (mmHg), mean (SD)			40 (13)	315
Severe tricuspide regurgitation, n (%)			14 (3.4)	416
HF self-care, n (%)				
HF literacy			98 (25.7)	381
Self-care literacy			146 (37.5)	389
Self-care adherence			132 (33.9)	389
Exercice adherence			72 (20.7)	348
Poor adherence, n (%)			169 (40.3)	419
HF events[d], n (%)				419
HF hospitalization			39 (9.3)	
Urgent HF visit			4 (1.0)	
Laboratory				

Haemoglobin (g/dL), mean (SD)	12.3 (1.8)	418	12.5 (1.8)	419
Creatinine (mg/dL), mean (SD)	1.27 (0.62)	419	1.35 (0.64)	419
eGFR (mL/min/1.73 m^2), n (%)		419		419
≥60	175 (41.8)		167 (39.9)	
45-59	96 (22.9)		78 (18.6)	
30-44	106 (25.3)		113 (27.0)	
<30	42 (10.0)		61 (14.6)	
NT-proBNP (pg/mL), mean (SD)	2423 (4094)	383	1454 (2546)	415
Medications, n (%)				419
ACEi			203 (48.4)	
ARNi			11 (2.6)	
ARB			41 (9.8)	
MRA			136 (32.5)	
BB			326 (77.8)	
SGLT2i			14 (3.3)	
Ivabradine			13 (3.1)	
Furosemide (mg/day), mean (SD)			80.0 (41.5)	
Anticoagulants			218 (52.0)	
Other treatments, n (%)				
Cardiac rehabilitation			9 (2.1)	419
Nocturnal non-invasive ventilation			55 (13.1)	419
Cardiac devices			72 (17.2)	419
CRT-P			9 (2.1)	
CRT-D			8 (1.9)	
ICD			11 (2.6)	
Pacemaker			44 (10.5)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro-B type natriuretic peptide; NYHA, New York Heart Failure; PASP, pulmonary artery systolic pressure; RV, right ventricle; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

[a]Baseline represents the moment of the first MLHFQ administration.

[b]Self-reported.

[c]Past or present history of atrial fibrillation or atrial flutter.

[d]HF events on the previous 28 days.

Supplementary Table S2 Mixed effects models with MLHFQ total score, patient's demographics and comorbidities[a]

Variable	Model 1			Model 2[b]			Model 3[c]			Model 4[d]			Model 5[e]		
		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value
Age															
< 65	Ref			Ref			Ref			Ref			Ref		
65-79	3.09	-1.25 – 7.42	0.162	2.82	-1.32 – 6.95	0.181	2.45	-1.78 – 6.68	0.255	2.37	-1.91 – 6.65	0.277	-0.09	-3.87 – 3.69	0.965
≥ 80	1.86	-2.57 – 6.28	0.409	2.26	-2.08 – 6.61	0.307	0.255	-2.08 – 6.86	0.294	2.20	-2.34 – 6.74	0.342	-2.15	-6.25 – 1.96	0.304
Sex															
Female	Ref			Ref			Ref			Ref			Ref		
Male	-4.69	-7.69 – -1.68	**0.002**	-4.30	-7.30 – -1.30	**0.005**	-4.46	-7.53 – -1.39	**0.005**	-4.73	-7.85 – -1.62	**0.003**	-1.50	-4.34 – 1.33	0.298
Formal education															
0	Ref														
1-4	-1.50	-6.67 – 3.66	0.568												
>4	-2.76	-8.64 – 3.12	0.357												
Low income															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.19	-0.43 - 8.81	0.076	4.67	0.08 – 9.25	**0.046**	4.39	-0.19 – 8.97	0.060	4.03	-0.61 – 8.67	0.089	3.74	-0.38 – 7.86	0.075
Hypertension															
No	Ref			Ref			Ref			Ref			Ref		
Yes	0.50	-3.73 - 4.74	0.815	-0.50	-4.57 – 3.56	0.807	-0.12	-4.21 – 3.97	0.953	-0.20	-4.33 – 3.93	0.924	0.04	-3.61 – 3.70	0.981
Diabetes *mellitus*															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.95	-0.09 - 5.99	0.057	2.28	-0.66 – 5.22	0.128	2.06	-0.92 – 5.04	0.175	2.25	-0.75 – 5.26	0.141	3.00	0.29 – 5.70	**0.030**
Pre-diabetes															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-2.34	-6.08 - 1.41	0.221	-2.21	-5.84 – 1.41	0.230	-2.01	-5.65 – 1.62	0.277	-2.04	-5.70 – 1.61	0.273	-1.46	-4.79 – 1.88	0.391
Smoking															
Never	Ref			Ref			Ref			Ref			Ref		
Past	-5.09	-8.53 – -1.65	**0.004**	-2.90	-7.17 – 1.38	0.184	-5.01	-9.52 – -0.51	**0.029**	-4.95	-9.51 – -0.40	**0.033**	-4.36	-8.44 – -0.27	**0.037**
Current	-2.20	-7.46 – 3.07	0.413	-0.43	-6.43 – 5.58	0.889	-3.30	-9.66 – 3.07	0.309	-3.15	-9.58 – 3.29	0.337	-2.52	-8.31 – 3.27	0.393
CKD															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.23	-0.84 - 5.30	0.154	2.38	-0.64 – 5.41	0.122	2.11	-0.92 – 5.15	0.172	1.95	-1.12 – 5.02	0.212	0.06	-2.72 – 2.85	0.963
Cerebrovascular disease															
No	Ref			Ref			Ref			Ref			Ref		
Yes	0.32	-3.13 - 3.76	0.857	0.34	-3.02 – 3.70	0.843	0.04	-3.31 – 3.38	0.984	0.41	-2.96 – 3.78	0.812	-0.36	-3.45 – 2.73	0.819
Peripheral arterial disease															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.22	-2.09 - 6.53	0.313	2.71	-1.55 – 6.98	0.212	2.03	-2.25 – 6.30	0.352	1.71	-2.62 – 6.04	0.438	-1.74	-5.74 – 2.25	0.392
Chronic pulmonary condition															
No	Ref			Ref			Ref			Ref			Ref		

Yes	2.06	-1.04 - 5.17	0.192	2.60	-0.47 – 5.67	0.097	3.02	-0.06 – 6.10	0.055	3.14	0.03 – 6.26	**0.048**	1.49	-1.33 – 4.32	0.300
Sleep-related breathing disorder															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-0.86	-3.59 - 1.86	0.534	-0.74	-3.43 – 1.95	0.588	-0.77	-3.44 – 1.91	0.573	-0.68	-3.36 – 1.99	0.616	-2.84	-5.34 – -0.35	**0.026**
Anaemia															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.32	0.26 - 6.38	**0.033**	3.49	0.54 – 6.43	**0.020**	3.75	0.78 – 6.72	**0.013**	3.72	0.72 – 6.73	**0.015**	2.75	0.05 – 5.46	**0.046**
Iron deficiency															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.86	-0.05 - 7.78	0.053	2.46	-1.55 – 6.47	0.229	2.06	-1.98 – 6.09	0.317	2.46	-1.60 – 6.53	0.234	1.40	-2.40 – 5.19	0.471
Unknown	-0.36	-4.91 - 4.19	0.876	-0.53	-5.00 – 3.93	0.814	0.52	-3.98 – 5.02	0.819	0.88	-3.65 – 5.42	0.702	2.46	-1.68 – 6.61	0.243
Cancer															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.87	-2.57 - 12.31	0.199	5.83	-1.39 – 13.05	0.114	4.88	-2.34 – 12.11	0.185	4.23	-2.97 – 11.43	0.249	3.37	-3.16 – 9.91	0.310
Sexual dysfuntion															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-0.82	-8.37 - 6.73	0.832	1.11	-6.39 – 8.61	0.772	2.41	-5.06 – 9.87	0.527	2.84	-4.67 – 10.35	0.458	2.79	-3.86 – 9.44	0.410
Anxiety															
No	Ref			Ref			Ref			Ref			Ref		
Yes	7.05	0.73 - 13.37	**0.029**	6.33	0.20 – 12.46	**0.043**	5.96	-0.31 – 12.24	0.063	5.52	-0.87 – 11.90	0.090	4.36	-1.38 – 10.10	0.136
Depression															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.92	1.70 - 8.14	**0.003**	4.63	1.44 – 7.83	**0.005**	4.27	1.04 – 7.50	**0.010**	4.22	0.96 – 7.49	**0.011**	2.46	-0.53 – 5.46	0.107

CI, 95% confidence interval; CKD, chronic kidney disease; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

[a]All models were adjusted to time and time^2.

[b]All variables were adjusted to model 1, age, sex, and low income.

[c]All variables were adjusted to model 2, CKD, anaemia, CPD, anxiety, and depression.

[d]All variables were adjusted to model 3 and selfcare adherence.

[e]All variables were adjusted to model 4, NYHA, and NT-proBNP.

Supplementary Table S3 Mixed effects models with MLHFQ total score, HF and laboratory variables[a]

Variable	Model 1			Model 2[b]			Model 3[c]			Model 4[d]			Model 5[e]		
		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value
Ischemic etiology															
No	Ref			Ref			Ref			Ref			Ref		
Yes	0.81	-2.33 - 3.94	0.613	2.19	-0.95 – 5.33	0.172	1.29	-1.89 – 4.46	0.427	1.18	-2.03 – 4.40	0.470	0.41	-2.46 – 3.27	0.781
Hypertensive etiology															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-0.40	-3.50 – 2.71	0.802	-1.09	-4.16 – 1.98	0.485	-0.47	-3.56 – 2.61	0.763	-0.32	-3.44 – 2.80	0.841	0.49	-2.30 – 3.29	0.728
Valvular etiology															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.46	0.24 – 6.68	**0.035**	2.66	-0.54 – 5.87	0.103	2.21	-0.99 – 5.41	0.175	2.21	-1.03 – 5.44	0.181	-0.07	-3.00 – 2.87	0.965
Nonischemic dilated etiology															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-4.20	-9.60 - 1.21	0.128	-2.94	-8.34 – 2.46	0.286	-2.28	-7.73 – 3.16	0.410	-2.25	-7.78 – 3.29	0.426	-2.11	-6.83 – 2.60	0.379
NYHA class															
I	Ref			Ref			Ref			Ref			Ref		
II	9.78	6.96 - 12.60	**<0.001**	10.58	7.64 – 13.51	**<0.001**	10.52	7.55 – 13.50	**<0.001**	10.20	7.20 – 13.19	**<0.001**	9.74	6.74 – 12.75	**<0.001**
III	29.94	25.67 - 34.22	**<0.001**	30.18	25.71 – 34.65	**<0.001**	29.53	25.01 – 34.05	**<0.001**	29.13	24.58 – 33.67	**<0.001**	28.39	23.82 – 32.96	**<0.001**
IV	59.48	33.04 - 85.93	**<0.001**	61.40	35.05 – 87.76	**<0.001**	61.89	35.58 – 88.21	**<0.001**	61.88	35.55 – 88.22	**<0.001**	60.59	34.46 – 86.72	**<0.001**
SBP	-0.06	0.12 - 0.00	0.052	-0.08	-0.14 – -0.02	**0.010**	-0.08	-0.14 – -0.02	**0.009**	-0.08	-0.15 – -0.02	**0.008**	-0.06	-0.12 – -0.00	**0.045**
Heart rate	0.03	-0.07 - 0.13	0.602	0.02	-0.08 – 0.12	0.696	0.03	-0.07 – 0.13	0.603	0.02	-0.08 – 0.12	0.677	0.09	-0.01 – 0.19	0.069
Rhythm															
Sinus	Ref			Ref			Ref			Ref			Ref		
Atrial fibrillation	-0.35	-3.42 - 2.72	0.823	-0.06	-3.17 – 3.05	0.971	0.57	-2.54 – 3.67	0.721	0.93	-2.20 – 4.05	0.561	-0.49	-3.40 – 2.41	0.739
Pacemaker	1.28	-3.43 - 6.00	0.593	2.18	-2.49 – 6.86	0.360	1.94	-2.71 – 6.58	0.413	1.24	-3.41 – 5.88	0.601	-0.50	-4.87 – 3.87	0.822
LVEF															
≥ 50%	Ref			Ref			Ref			Ref			Ref		
41-49%	5.96	1.36 – 10.56	**0.011**	7.16	2.56 – 11.76	**0.002**	6.37	1.76 – 10.98	**0.007**	6.09	1.49 – 10.70	**0.010**	4.88	0.60 – 9.17	**0.026**
≤ 40%	-3.23	-6.18 – -0.28	**0.032**	-2.12	-5.18 – 0.94	0.174	-1.68	-4.75 – 1.39	0.282	-1.68	-4.77 – 1.42	0.287	-1.78	-4.74 – 1.19	0.239
RV systolic dysfunction															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.71	-1.12 - 6.53	0.166	3.71	-0.11 – 7.54	0.057	3.77	-0.02 – 7.57	0.051	3.65	-0.15 – 7.44	0.060	2.71	-0.88 – 6.30	0.138
PASP	0.24	0.12 - 0.36	**<0.001**	0.23	0.11 – 0.35	**<0.001**	0.20	0.08 – 0.32	**0.001**	0.20	0.08 – 0.32	**0.001**	0.11	-0.00 – 0.23	0.057
Severe Tricuspid regurgitation															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.24	4.54 -13.02	0.343	3.86	-4.78 – 12.50	0.380	2.53	-6.05 – 11.11	0.562	3.62	-4.96 – 12.19	0.408	1.70	-6.48 – 9.88	0.684
HF literacy															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-2.97	-5.90 – -0.03	**0.047**	-2.82	-5.73 – 0.08	0.057	-2.95	-5.86 – -0.03	**0.047**	-2.24	-5.17 – 0.70	0.135	-2.50	-5.26 – 0.25	0.074
Self-care literacy															

No	Ref			Ref			Ref			Ref			Ref	
Yes	-4.47	-7.29 – -1.65	**0.002**	-4.07	-6.91 – -1.23	**0.005**	-3.90	-6.74 – -1.07	**0.007**	-0.76	-4.83 – 3.30	0.713	-1.07	-5.04 – 2.91	0.599
Self-care adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-4.75	-7.28 – -2.23	**<0.001**	-4.50	-7.05 – -1.95	**0.001**	-4.33	-6.87 – -1.79	**0.001**	-4.33	-6.87 – -1.79	**0.001**	-2.26	-4.68 – 0.17	0.069
Exercice adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-3.43	-6.24 – -0.62	**0.017**	-3.48	-6.32 – -0.65	**0.016**	-2.99	-5.83 – -0.14	**0.040**	-2.03	-4.99 – 0.92	0.177	-2.12	-4.87 – 0.63	0.130
Poor adherence															
No	Ref			Ref			Ref			Ref			Ref		
Yes	3.31	0.18 - 6.43	**0.038**	3.23	0.13 – 6.32	**0.041**	3.22	0.12 – 6.32	**0.042**	2.79	-0.37 – 5.95	0.083	3.36	0.53 – 6.20	**0.020**
HF hospitalization[f]															
No	Ref			Ref			Ref			Ref			Ref		
Yes	32.75	27.46 – 38.03	**<0.001**	32.66	27.38 – 37.93	**<0.001**	32.00	26.74 – 37.26	**<0.001**	31.21	25.95 – 36.46	**<0.001**	26.91	21.80 – 32.03	**<0.001**
Urgent HF visit[f]															
No	Ref			Ref			Ref			Ref			Ref		
Yes	15.25	3.78 – 26.71	**0.009**	17.05	6.44 – 27.67	**0.002**	16.37	5.75 – 26.99	**0.003**	16.47	5.83 – 27.10	**0.002**	8.79	-0.99 – 18.57	0.078
Haemoglobin[g]															
Normal	Ref			Ref			Ref			Ref			Ref		
Low	4.46	1.92 -7.00	**0.001**	4.59	2.04 – 7.15	**<0.001**	4.24	1.47 – 7.01	**0.003**	4.44	1.68 – 7.20	**0.002**	2.37	-0.27 – 5.00	0.078
eGFR															
≥ 60	Ref			Ref			Ref			Ref			Ref		
45-59	0.39	-2.90 – 3.68	0.816	0.50	-2.88 – 3.89	0.770	0.40	-3.17 – 3.97	0.825	0.46	-3.09 – 4.02	0.798	1.07	-2.25 – 4.39	0.529
30-44	2.14	-1.25 – 5.52	0.215	2.04	-1.43 – 5.50	0.249	1.76	-2.20 – 5.72	0.383	1.73	-2.22 – 5.68	0.390	-0.33	-4.04 – 3.37	0.860
< 30	9.77	5.53 – 14.02	**<0.001**	9.33	5.06 – 13.60	**<0.001**	9.44	4.57 – 14.32	**<0.001**	9.60	4.73 – 14.47	**<0.001**	5.82	1.17 – 10.47	**0.014**
NT-proBNP/1000	0.37	0.20 - 0.54	**<0.001**	0.37	0.20 – 0.54	**<0.001**	0.37	0.20 – 0.54	**<0.001**	0.35	0.18 – 0.52	**<0.001**	0.20	0.03 – 0.36	**0.023**

CI, 95% confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricle ejection fraction; MLHFQMinnesota Living with Heart Failure Questionnaire, NT-proBNP, N-terminal-pro-B type natriuretic peptide; NYHA, New York Heart Failure; PASP, pulmonary artery systolic pressure; RV, right ventricle; SBP, systolic blood pressure.

[a]All models were adjusted to time and time^2.

[b]All variables were adjusted to model 1, age, sex, and low income.

[c]All variables were adjusted to model 2, CKD, anaemia, CPD, anxiety, and depression.

[d]All variables were adjusted to model 3 and selfcare adherence.

[e]All variables were adjusted to model 4, NYHA, and NT-proBNP.

[f]HF events on the previous 28 days.

[g]Normal haemoglobin is defined as ≥12 g/dL in female and ≥13 g/dL in male patients.

Supplementary Table S4 Mixed effects models with MLHFQ total score and treatments[a]

Variable	Model 1			Model 2[b]			Model 3[c]			Model 4[d]			Model 5[e]		
		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value		CI	*p*-value
ACEi															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-4.67	-7.37 – -1.96	**0.001**	-4.79	-7.50 – -2.08	**0.001**	-4.20	-6.93 – -1.48	**0.003**	-3.83	-6.58 – -1.07	**0.007**	-3.45	-6.00 – -0.91	**0.008**
ARNi															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-1.24	-8.17 – 5.69	0.726	-0.25	-7.17 – 6.68	0.944	-0.01	-6.93 – 6.90	0.997	-0.60	-7.54 – 6.35	0.866	0.07	-6.34 – 6.49	0.982
ARB															
No	Ref			Ref			Ref			Ref			Ref		
Yes	1.50	-3.63 – 6.63	0.566	0.76	-4.31 – 5.82	0.770	1.37	-3.68 – 6.41	0.595	1.32	-3.78 – 6.42	0.611	4.29	-0.22 – 8.80	0.062
MRA															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-0.50	-3.51 – 2.50	0.742	0.12	-2.86 – 3.09	0.938	1.00	-2.00 – 3.99	0.514	1.04	-1.96 – 4.04	0.495	-0.02	-2.84 – 2.79	0.987
BB															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-1.63	-4.85 - 1.58	0.319	-0.83	-4.08 – 2.42	0.616	-0.11	-3.36 – 3.13	0.946	-0.17	-3.42 – 3.08	0.919	0.87	-2.18 – 3.92	0.575
SGLT2i															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-3.91	-9.54 - 1.73	0.174	-4.65	-10.21 – 0.91	0.101	-4.74	-10.27 – 0.80	0.094	-5.22	-10.70 – 0.26	0.062	-1.94	-7.14 – 3.25	0.462
Ivabradine															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-1.48	-8.18 – 5.22	0.665	0.07	-6.53 – 6.66	0.985	-0.40	-6.93 – 6.14	0.905	-0.90	-7.42 – 5.61	0.785	-4.38	-10.47 – 1.71	0.158
Furosemide dose/40	3.78	2.64 - 4.92	**<0.001**	3.95	2.82 – 5.07	**<0.001**	3.80	2.65 – 4.94	**<0.001**	3.76	2.61 – 4.91	**<0.001**	2.29	1.09 – 3.49	**<0.001**
Anticoagulants															
No	Ref			Ref			Ref			Ref			Ref		
Dicumarinic	0.55	-2.76 - 3.87	0.743	0.87	-2.39 – 4.13	0.601	1.95	-1.31 – 5.21	0.240	2.27	-1.01 – 5.55	0.175	1.39	-1.62 – 4.41	0.364
DOAC	-3.50	-7.38 - 0.37	0.076	-2.58	-6.40 – 1.25	0.186	-1.54	-5.38 – 2.30	0.431	-1.66	-5.51 – 2.18	0.397	-1.35	-4.95 – 2.26	0.464
Cardiac rehabilitation															
No	Ref			Ref			Ref			Ref			Ref		
Yes	-5.82	-9.70 – -1.94	**0.003**	-6.17	-10.02 – -2.32	**0.002**	-5.92	-9.80 – -2.05	**0.003**	-5.38	-9.24 – -1.52	**0.006**	-2.90	-6.48 – 0.67	0.112
Nocturnal non-invasive ventilation															
No	Ref			Ref			Ref			Ref			Ref		
Yes	0.68	-2.71 - 4.07	0.694	1.10	-2.23 – 4.44	0.517	0.80	-2.52 – 4.12	0.635	0.96	-2.36 – 4.28	0.570	1.16	-1.96 – 4.28	0.465
Cardiac device															
None	Ref			Ref			Ref			Ref			Ref		
ICD	-6.69	-14.36 – 0.98	0.087	-4.37	-12.17 – 3.42	0.271	-2.83	-10.59 – 4.93	0.474	-3.84	-11.61 – 3.93	0.332	-5.29	-12.34 – 1.77	0.142
CRT-P	-10.39	-19.71 – -1.08	**0.029**	-9.49	-18.63 – -0.35	**0.042**	-8.56	-17.61 – 0.50	0.064	-9.44	-18.41 – -0.47	**0.039**	-13.55	-22.45 – -4.65	**0.003**
CRT-D	0.03	-8.39 – 8.45	0.995	1.34	-6.76 – 9.44	0.745	-0.09	-8.20 – 8.02	0.982	-0.28	-8.32 – 7.76	0.945	0.61	-6.75 – 7.97	0.872
Pacemaker	-0.20	-4.65 – 4.26	0.931	0.30	-4.07 – 4.67	0.892	-0.19	-4.57 – 4.18	0.931	-0.65	-5.03 – 3.74	0.772	-1.88	-5.87 – 2.11	0.354

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker, ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CI, 95% confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; DOAC, direct-acting oral anticoagulant; ICD, implantable cardioverter-defibrillator; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

[a]All models were adjusted to time and time^2.

[b]All variables were adjusted to model 1, age, sex, and low income.

[c]All variables were adjusted to model 2, CKD, anaemia, CPD, anxiety, and depression.

[d]All variables were adjusted to model 3 and selfcare adherence.

[e]All variables were adjusted to model 4, NYHA, and NT-proBNP.

6. DISCUSSION

6.1. Analysis of the results

The results of the line of research reported in this thesis made it possible to increase knowledge about the prognosis and QoL of HF patients in everyday clinical practice.

We found that elderly hospitalized HF patients have dismal and shortened survival and that multidisciplinary care can partially ameliorate this condition. It was possible to identify predictors of rehospitalization and all-cause mortality and of death without rehospitalization. During hospitalization, two separate measurements of NT-proBNP levels, one at admission and one at stabilization, can provide additional information about rehospitalization and the risk of death in the following 6 months. The focused work and expertise in the HF field led to the construction of bridges with other colleagues, clinicians from different specialties and other healthcare professionals and the state of our perspectives and recommendations to improve the lives of HF patients. These connections could improve research on the cost-efficient analysis of new drugs in HF care. Finally, answers were found to that crucial question: what matters to our HF patients, i.e. what can improve or decrease their QoL?

Article "*Characteristics and outcomes of heart failure hospitalization before implementation of a heart failure clinic: The PRECIC study*"

The PRECIC study revealed that our real-world HF patients were very elderly, being 10 years older than HF patients from a cardiology department. Additionally, 62.5% were female and 70.5% had an LVEF ≥40%, with an average of three comorbidities, among which hypertension and AF were the most common. The characterization of the population enabled us to tailor our management program and interventions to address the most urgent needs. The finding of a high burden of non-CV comorbidities, such as diabetes mellitus, dementia and sleep apnoea, was very relevant since it allowed us to identify those who needed more focused interventions.

Regarding the hard outcomes of all HF studies, mortality and HFH, we found that in-hospital mortality was 7.9%, and one-third of patients died or had at least one rehospitalization for HF in the year following discharge. Cardiovascular deaths were as common as non-CV deaths. This study shed light on the dismal prognosis of our HF patients and the significant problems we faced. With respect to the GEstIC, we aimed to improve patient prognosis, but in such a scenario, improving QoL was an urgent matter. When we examined the data back then, we primarily noticed the differences between our patients and

those included in European studies based on cardiology departments. Considering the same data today, the PRECIC study results were a preview of the results of the PORTHOS study. The reality consists of older HF patients, mostly women with HFpEF.

Article "*In-Hospital Mortality in Acute Heart Failure: Predicted ADHERE Risk vs. Observed Mortality*"

The bad news continued with the PRECIC sub-analysis concerning in-hospital mortality. After patients in the PRECIC study were assigned to the ADHERE risk group, the comparison of the predicted mortality with the observed mortality revealed that the overall observed in-hospital mortality was two to three times higher than the predicted mortality. This was especially worrisome when considering that our patients were admitted to a general ward. Consequently, patients who died in the emergency department or intensive care could have increased the in-hospital mortality even further. We found that our HF patients were older, more frequently female, had hypertension and AF, and had a substantially greater LVEF than did the ADHERE sample. The burden of age and comorbidities, particularly AF, along with the origin of patients (internal medicine versus cardiology departments), could explain the higher mortality we observed. We concluded that prediction models are important tools that need to be validated locally before they can be implemented in routine clinical practice. The QoL of older hospitalized patients at high risk of mortality was a concern. Fortunately, the mortality risk stratification can help us identify those for whom palliative care interventions are of utmost importance.

Article "*One-year mortality after hospitalization for acute heart failure: Predicting factors (PRECIC study subanalysis*)"

The search for one-year mortality predictors after HFH led to another PRECIC sub-analysis. We found that the independent predictors of increased one-year mortality risk at admission were age ≥80 years, active cancer, dementia, high urea levels, high red cell distribution width (RDW) (>16.3%), and low platelet cell distribution width (PDW). Among these variables, RDW was the strongest predictor of one-year mortality. Since the RDW consists of a simple, inexpensive, and widely available test reported in every blood count, this finding could have substantial implications for the risk stratification and clinical management of hospitalized HF patients. Risk stratification means personalized care. Person-centred care is a strong measure for improving the quality of care, the efficiency of

the healthcare system, and QoL at the individual level. Only multidisciplinary care can fill the individual needs, tailoring the intensity and spectrum of care.

Article "*One-year rehospitalization and mortality after acute heart failure hospitalization: a competing risk analysis*"

Considering the unpredictable trajectory of HF for individual patients, it is important to recognize that the most dreadful events, HFH and death, compete for the patient path. This led us to search for HFH predictors, keeping in mind that patients could die before being re-hospitalized. This was the rationale for the PRECIC sub-analysis using competing risk analysis. AF, renal dysfunction, and BB prescription at discharge were identified as independent risk factors for one-year rehospitalization for HF. After adjusting for sex, age, and LVEF, the risk of death without rehospitalization was greater in men, patients aged ≥80 years, those with dementia, and those with RDW >16.3% at admission. Notably, taking a BB at discharge was associated with a greater risk of rehospitalization and a lower risk of death without rehospitalization. Additionally, renal dysfunction at the index HF admission was identified as a risk factor for overall mortality and rehospitalization but not for death without rehospitalization. On the other hand, dementia was identified as a risk factor for overall mortality and death without rehospitalization, but not for rehospitalization. The knowledge of such predictors allows clinicians to tailor both the treatment and follow-up of patients at higher risk of death or rehospitalization. Additionally, risk prediction enables us to consider the patient's values, either preferring symptomatic relief or extended survival. In the context of short survival, patients with dementia represent a subgroup of HF patients to whom palliative care is essential to improve care and QoL.

In summary, the PRECIC study was a landmark observational study that enriched our understanding of the reality of HF in our setting, and likely in other internal medicine departments of Portuguese hospitals. It characterizes the patients hospitalized for HF, their in-hospital mortality, HF rehospitalizations, and mortality in the year following discharge. Additionally, showed that HFH is a turning point in the HF trajectory, setting the scenario for the HF events at least for the following year. Unless death first occurs, those events determine the QoL of each patient's life. However, the identification of predictors of HF events gives us the ability to stratify risk and allows to us tailor follow-up and implement person-centred care, improving QoL.

Article "*Multidisciplinary Heart Failure Clinic: How to Implement*"

This article mainly served as a tool to increase awareness to HF in the internal medicine community. Reviewing the scientific evidence regarding HF multidisciplinary teams and clinics, along with testimonials of implementing such an organization, was a powerful means of promoting better HF care in other hospitals. Over the years, the GEstIC has become recognized as an exemplary model of organization and multidisciplinary work. We received visits from internists, cardiologists, nurses, and internal medicine residents for training in HF. We reported that the one-year mortality rate of patients admitted to the GEstIC between 2013 and 2015 was 10.4%, while was 16.1% in patients of the PRECIC study with similar characteristics. The one-year rehospitalization rates for HF were 25.9% and 30.5% for GEstIC and PRECIC patients, respectively. This was the first sign of success of our work.

Notably, HF clinic management programs include QoL assessment. The domains that constitute the setting of HF clinics are essential to person-centred care. The interventions in each domain will translate into better self-care, functional capacity and nutritional status, which potentiate QoL improvement.

Article "*NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)- Guided Therapy in Acute Decompensated Heart Failure: PRIMA II Randomized Controlled Trial*"

The PRIMA II trial provided several important lessons. First, it is possible to implement an investigator-initiated randomized international trial, given the logistical support and motivated investigators. Second, the variation in the NT-proBNP level between the hospital admission and stable phase plays an important role in the prognosis after hospital discharge, independent of the magnitude of its level. We found that patients with decompensated chronic HF who achieved an NT-proBNP reduction of > 30% without NT-proBNP-guided therapy, from admission to discharge, had a better prognosis. Third, patients treated to target a reduction of > 30% in NT-proBNP levels showed no benefit compared with patients receiving standard-of-care therapy, in terms of event rates for all-cause mortality and readmissions for HF within 180 days after randomization. This occurred despite a greater proportion of patients in the NT-proBNP-guided therapy arm achieving the target of >30% reduction in NT-proBNP levels. Fourth, a *post hoc* analysis revealed that differences in HF event rates were reflected by differences in NT-proBNP reduction percentages. Non-guided patients had a significantly greater reduction in NT-proBNP levels than did both successfully and unsuccessfully guided patients. Finally, we found that it was not possible to lower NT-proBNP levels in 20% of patients. Unfortunately, we demonstrated that NT-proBNP-guided therapy targeting an NT-proBNP reduction of > 30% did not improve

clinical outcomes, and probably not QoL, in hospitalized HF patients. However, this highlights the need for transition care after discharge, optimized by a HF clinic. Additionally, the risk stratification given by NT-proBNP level variation is useful for person-centred care and QoL improvement.

Article "*External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure*"

Using the PRIMA II patients, we proceeded with the external validation of the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score, which confirmed the predictive proportional value of the risk score and demonstrated that 6-month mortality increases with increasing score. This made it possible to predict 6-month all-cause mortality in patients hospitalized for acute decompensated HF, using NT-proBNP values in addition to easily obtained clinical and laboratory characteristics, namely: 1) absolute NT-proBNP levels at discharge; 2) a change in NT-proBNP of ≤ 30% from admission to discharge values; 3) age, peripheral edema, systolic blood pressure and sodium levels at admission; and 4) serum urea and NYHA class at discharge. This reliable bedside score can be used in daily clinical practice for patients with both HFpEF and HFrEF, regardless of their NYHA class at discharge. The message is once more that risk stratification may be used to further intensify therapies, intensify follow-up and improve the care of those patients at greater risk. Additionally, it can anticipate the need for palliative care which represents the most tailored QoL-improving intervention we can offer to patients.

Article "*Impact of a heart failure multidisciplinary clinic on the reduction of healthcare-related events and costs: the GEstIC study*"

The GEstIC study served as a proof of the value of the multidisciplinary clinic implementation in our hospital. The analysis of HF events and all-cause hospitalizations in the year following the first visit to the clinic, compared with the previous year, ultimately demonstrated the significance of our work. We studied 287 HF patients admitted to GEstIC between 2013 and 2019 with a minimum of 365 days of follow-up. Their characteristics were similar to those of the PRECIC study sample. We observed a decrease of 71.7% in HFH, 53.7% in all-cause hospitalizations, and 39.1% in urgent HF visits at the end of the first year of follow-up, in comparison to the previous year. In addition to the reduction in the number of events, we found a significant reduction of 12.6 days of days passed in-hospital per patient. Fewer days in the hospital are associated with less complications, such as

infections and falls, which are frequent in elderly patients. Fewer complications are likely associated with better QoL. The 287 patients led to a total reduction of 3,624 days of hospitalization due to HF, which translates into the release of 9.9 hospital beds in the year following admission to the GEstIC. Considering only the reduction in HF events (hospitalizations and urgent visits) over the first year of follow-up in the GEstIC, we achieved an average savings of 5,439.77 euros per patient.

We believe that the combined effects of specialized multidisciplinary care and improved organizational aspects in the GEstIC HF clinic, led to the results of the GEstIC study. We demonstrated that our HF clinic implementation was a cost reduction initiative. In addition, we could reduce the discomfort and complications related to hospitalization, offering patients a better QoL. We also believe that offering optimized medical and device therapies was a means to improve the QoL of HF patients across the entire range of LVEF. At that time, there was no disease-modifying treatment for patients with HFpEF. However, there was still a need for a better understanding of the influence of our interventions on QoL.

Article "*conTemporary reflectiOns regarding heart failure management - How to ovERcome the PorTuguese barriers (TOGETHER-PT*)"

TOGETHER-PT was a multidisciplinary initiative panel of twelve Portuguese HF experts, including cardiologists, internists, and general practitioners, that formed the study steering committee. This committee designed a questionnaire to collect the opinions of a group of HF experts on how to improve HF management in Portugal. The questions focused on four areas of HF care: 1) HF awareness and literacy, 2) early HF diagnosis, 3) HF guideline-oriented treatment, and 4) HF organization of care. A group of 174 healthcare professionals with interest, expertise, and experience in HF care were invited to participate. This group included a balanced number of cardiologists, general practitioners, internists, and nurses working at primary healthcare facilities and regional or central hospitals all over Portugal. A total of 152 (87.4%) professionals answered the questionnaire. The participants identified HF literacy as an important unmet need among Portuguese HF patients and recognized the need to promote patient/caregiver education and empowerment. HF patients should have simplified access to healthcare facilities and patient care optimization. This could have a potential impact on HFH and QoL, namely reducing symptoms and improving functional capacity. The study participants had a high level of agreement regarding the healthcare organization statements. Strategies to coordinate different healthcare levels and develop optimized care and effective prevention programs were identified as needed to decrease the economic and social impact of HF. This project aimed

to promote changes in HF landscape in Portugal to improve Portuguese HF patients' QoL. It was a joint effort of three medical societies and actively involved nurses, representing cooperative work and a truly multidisciplinary perspective of HF care, reinforcing the relevance of HF clinics.

Article "*Beyond clinical trials - The cost saving associated with dapagliflozin use in Portugal hospital clinical practice*"

This article reported a multicentric study aimed at projecting the economic impact of dapagliflozin on HFH when dapagliflozin was started on patients who were hospitalized for HF. Dapagliflozin was one of the first drugs, alongside empagliflozin, to demonstrate to reduce HF events and mortality in HF patients across the entire range of LVEF. The study gathered information from six Portuguese hospitals and included patients hospitalized for HF. GEstIC represented one of two hospitals that had an established HF clinic. Dapagliflozin was associated with HFH cost savings of 32,986.12 euros when applied to HF clinics in 2019, considering a conservative approach. Given the ability of dapagliflozin to improve HF-related outcomes, its implementation can also contribute to improvements in-patients' QoL. Additionally, 19% of the patients were re-hospitalized at least once. The characteristics of the study patients were similar to those of the PRECIC and GEstIC studies.

Articles

"*A Portuguese expert panel position paper on the management of heart failure with preserved ejection fraction - Part I: Pathophysiology, diagnosis and treatment*"

"*A Portuguese Expert Panel Position Paper on HFpEF Management - Part II: Unmet needs and Organization of Care in Portugal*"

The two publications that reported a Portuguese expert panel position statement on the management of HFpEF represent another call-to-action, such as TOGETHER-PT, and the study concerning the impact of dapagliflozin on hospitalized HF patients. The publications resulted from the collaborative work of cardiologists, internists and general practitioners that represent their medical societies and HF dedicated working groups, which includes me. Given the very high prevalence of HFpEF in Portugal, as reported by the PORTHOS study, the position document is relevant for increasing awareness and guiding the care of this group of patients. The specific challenges in the diagnosis, treatment and management of patients with HFpEF are addressed step-by-step. The importance of multidisciplinary teams

and their essential role in addressing the multiple HF dimensions are reinforced to reduce morbidity and mortality and improve patients' functional capacity and QoL.

The second publication on HFpEF focused on the unmet need for the organization of care for HF patients with HFpEF in Portugal. The expert panel defined an ideal person-centred HFpEF journey with seamless, multidisciplinary, holistic and integrated care. QoL assessment and promotion, as well as palliative care are relevant elements in that journey. Additionally, the ideal management of HFpEF patients was defined as a roadmap for screening, diagnosis, referral and treatment. Person-centred multidisciplinary care was promoted, through multidisciplinary integrated care teams involving cardiologists, internists, primary care physicians, nurses, and other health professionals, which were linked together in a seamless care system. The suggestions to improve care through reducing mortality and HFH, integrating palliative care, and empowering patients and caregivers likely result in the improvement of QoL.

Article "*Quality of Life Scores Association with other Patient Reported Outcomes: Validating Minnesota Living with Heart Failure to Portuguese*"

The validation of MLHFQ to Portuguese was the accomplishment of an unmet need: regularly assess QoL alongside the routine HF care. The MLHFQ is easy to administer, has a simple structure with 21 questions, answers displayed on a Likert scale, fits to one page only and takes approximately five minutes to complete. We revealed that the MLHFQ total score was associated with other PROMs, namely: 1) 6MWD, 2) Borg fatigue score at the end of the six-minute walking test (6MWT), 3) Hospital Anxiety and Depression Scale (HADS) depression score and 4) HADS anxiety score. We reported the existence of three sub-scores: physical, emotional and social. Furthermore, we found associations between the physical score and both the Borg fatigue score and the 6MWD and between the emotional score and the anxiety and depression HADS scores. We believe that this MLHFQ validated version can help to overcome the challenge of QoL assessment in everyday clinical practice of Portuguese HF clinics through a pragmatic approach.

Article "*Quality of life in heart failure patients: factors associated with clinically important changes. The QUALIFIER prospective cohort study*"

Finally, the QUALIFIER (QUALIty oF lIfe in hEart failuRe) study provided answers to the crucial question of this thesis - QoL in HF: what matters? We found that having an implanted CRT-P was the only factor associated with clinically important improvement in QoL.

Additionally, other factors were associated with improved QoL: past smokers, patients with a sleep-related breathing disorder, those with higher systolic blood pressure (SBP) and those taking an ACEi. With respect to QoL deterioration, NYHA class II-IV, an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 and recent HFH were associated with clinically important QoL changes. After analysing a comprehensive group of demographic and clinical factors and using a nested model approach with adjustments for sociodemographic factors, comorbidities, self-care adherence and HF severity factors, the results were expected and surprisingly.

The QoL of HF patients in the QUALIFIER study was relatively good at 3 months of follow-up in the GEstIC, 25 points considering a score range of 0-105 points, with higher points indicating worse QoL. Notably, the QoL improved rapidly in the first months and then more slowly, until a nadir at 10 months of follow-up. The nested models used revealed that some factors that were previously reported to negatively or positively affect the QoL of HF patients did not influence QoL after adjusting for markers of HF severity. This is the case for age, male sex, depression, poor self-care, cardiac rehabilitation, recent urgent HF visits, HFpEF, and greater pulmonary artery systolic pressure (PASP). The results of this study should prompt us to consider earlier CRT-P implantation in eligible patients, especially elderly patients with diabetes, CKD, a high burden of comorbidities, more severe symptoms and recent HFH. The findings are also a call-to-action to organization of care for HF patients in Portugal, for which a group of healthcare professionals, including me, have been fostering in the recent years.

Importantly, despite the strong relation between QoL and HF severity markers, such as the NYHA class, QoL changes are not predictable based on those markers. This was shown in two of the most recent drug trials in HF, with vericiguat and finerenone. Thus, in clinical practice, it is imperative to assess QoL regularly irrespective of other clinical evaluations and PROs. QoL assessment provides independent information about how the patient is doing and simultaneously tells us how bad the prognosis is, predicting HF events and death. This knowledge is a powerful tool for illuminating patients' path and offering them person-centred care and a good life, regardless of how long it lasts.

6.2. Unmet needs

Throughout the last 12 years, motivation, commitment and resilience have brought GEstIC and their professionals to a higher level of patient care. We are happy to know that we make a difference in patients' lives. We conquered a team with strong relationships, have included one physician and one nurse from palliative care on the team, admitted patients from primary care, and proved the importance of day-care hospital for patient management. Today, we are 26 healthcare professionals, including 11 physicians from different specialties and 13 nurses. The team has embraced clinical research since the first years despite the adverse conditions we faced. Motivated professionals have progressively increased their expertise not only in HF but also in critical areas related to chronic patient care, such as physical rehabilitation, community care, chronic disease, mental health, ultrasound, and geriatrics.

However, it is possible to identify several unmet needs. First, we need enough human and logistic resources to ensure the time and places to listen to every patient and their caregivers, define an individualized care plan and work with them to accomplish it in a timely manner. Only then can we achieve truly person-centred care. Second, we urgently need more professionals on the multidisciplinary team: phycologists, nutritionists, social workers, and a pharmacist. Third, we need to build a model to improve the care of patients during HF events, in the Emergency Department and during hospitalization, with differentiated care and resources. Finally, we need adequate resources to include clinical research in daily clinical practice, empowering professionals and promoting better patient care.

6.3. Ongoing and future research

At present, there are research projects that I have not been able to finish and to publish before the writing of this thesis. This is the case for the article "Right Ventricle Systolic Dysfunction in Chronic Heart Failure: Real World Data from a Heart Failure Clinic. The REFRAME Study", that composed the master thesis of António Gomes Pinto, a medical student and junior investigator, argued in 2024 at ICBAS. The long-term experience with patients with HFpEF and predominantly right heart failure, severe systemic congestion and frequent HF events raised new research questions. We were able to answer some of them. We found that HF patients with right ventricle systolic dysfunction represent approximately 20.3% of HF patients at GEstIC and that they have a particularly poor prognosis, with high risk of HF events and death. We were also able to identify predictive factors for HFH and mortality in the first year of follow-up in this group of patients. In the future, I expect to

compare their HF trajectory, QoL and response to treatments with those of the other HF patients we follow.

Another ongoing research project is the “PROMs From GEstIC Heart Failure Patients (PROFIC-HF)”, protocol number 2020.032(024.DEFI/026.CE) at Centro Hospitalar Universitário de Santo António (CHUdSA), ClinicalTrials.gov Identifier: NCT06938698. This was a prospective cohort study aiming to assess the feasibility of digitally recording PROMs at home in HF patients from the GEstIC. Two HF-specific PROMs, the KCCQ and the MLHFQ, and two PROMs for anxiety and depression assessment, the Patient Health Questionnaire -2 (PHQ-2) and HADS, were collected remotely using a digital platform, that could be accessed online using a smartphone or a computer. The aim was also to evaluate the correlation between QoL changes and changes in clinically reported outcomes: assess QoL and quantify the impact of HFH events on patients' QoL. The study enrolled 155 patients for 6 months. Each patient had a minimum follow-up of 6 months, which could increase in HFH occured. Patients were invited to access the platform and answer the PROMs at baseline and at 1 month and 6 months of follow-up. If HFH occurred, more PROMs were given until 6 months after the event. The study began in December 2022 and ended in March 2024. During this time, 256 patients were screened, 155 signed informed consent forms, and 140 were randomized to one of the QoL questionnaires, the KCCQ or MLHFQ. Given the age and low literacy of most HF patients followed in the GEstIC, we were happily surprised by the successful implementation of the study and we are eager to analyse the results.

Another ongoing study is the “NutrIC – Nutrition and functional status in heart failure” study, protocol number 2020.032(024.DEFI/026.CE) in CHUdSA. This project is a cross-sectional, multicentric study that was developed by investigators of the Faculty of Nutrition and Food Sciences of the University of Porto. The NutrIC aims to study new indicators of hand grip strength in HF patients. Investigators believe that these muscle strength measurements, that go beyond the maximum exerted strength, can be useful in the diagnosis and treatment of HF and its associated comorbidities. Researchers are looking for associations between novel indicators of hand grip strength and clinical, functional, and nutritional variables in HF patients. In CHUdSA the study began in October 2023 and ended in April 2024; 74 HF patients were recruited at GEstIC. The study recruited approximately 680 community-dwellers and 216 HF outpatients. The preliminary results revealed that HF patients have a high prevalence of sarcopenia and frailty and are at high risk of undernutrition.

In my mind, the future is full of research. Building upon previous findings, we identified new gaps in knowledge that need to be addressed in the future. Research in the field of QoL and HF, of course, but also in other areas.

The QUANTIFIER study is a milestone in the line of QoL research. We collected a large amount of data that need to be analysed from different perspectives, in much detail. As always, more knowledge raises more questions, and some of these questions will necessarily motivate sub-analyses: Are there different individual trajectories of QoL? How do the studied factors impact the physical and emotional sub-scores of the MLHFQ? Are diabetic patients and other patients suffering from cardiometabolic syndrome a group of patients with especially poor QoL? Should we implant CRT-P early in HF patients with ventricular desynchrony? What happens to the QoL of patients with sleep apnoea when non-invasive ventilation is prescribed? These and other inciting research questions are what makes the future exciting.

Finally, I aim to motivate others, professionals in my department and hospital and medical students, to embrace clinical research and the quality improvement that is underneath the enduring questioning and answering in our clinical practice.

7. CONCLUSIONS

In conclusion, the research reported in this thesis shows that real-world HF patients are elderly people with a high burden of symptoms and comorbidities and are at high risk of death and HFH. We found that it is possible to predict the individual risk of events using data collected at routine clinical practice such as age, sex, active cancer, dementia, AF, renal dysfunction, RDW, NT-proBNP levels, and treatment with BB and ACEi. We reported the benefits of a multidisciplinary HF clinic for person-centred care, reduction on HF events, days passed in the hospital, and costs. The promotion of person-centred care and a tailored pathway for patients with HFpEF was actively pursed and communicated. We validated the MLHFQ, which enables QoL assessment in routine clinical practice. Finally, by assessing QoL regularly, we could determine what matters most to the QoL of our HF patients: living without HF symptoms and events and receiving a CRT-P when eligible. It is important to apply this acquired knowledge to each clinical encounter to lighten patients' path and offer them a good life.

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9. AWARD AND FUNDING

9.1. Award

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