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Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study

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Aim

To assess adverse outcomes attributable to non-cardiac co-morbidities and to compare their effects by left ventricular ejection fraction (LVEF) group [LVEF <50% (heart failure with reduced ejection fraction, HFrEF), LVEF ≥50% (heart failure with preserved ejection fraction, HFpEF)] in a contemporary, unselected chronic heart failure population.

Methods and results

This community-based cohort enrolled patients from October 2009 to December 2013. Adjusted hazard ratio (HR) and the population attributable fraction (PAF) were used to compare the contribution of 15 non-cardiac co-morbidities to adverse outcome. Overall, 2314 patients (mean age 77 ± 10 years, 57% men) were recruited [$n = 941$ (41%) HFrEF, $n = 1373$ (59%) HFpEF]. Non-cardiac co-morbidity rates were similarly high, except for obesity and hypertension which were more prevalent in HFpEF. At a median follow-up of 31 (interquartile range 16–41) months, 472 (20%) patients died. Adjusted mortality rates were not significantly different between the HFrEF and HFpEF groups. After adjustment, an increasing number of non-cardiac co-morbidities was associated with a higher risk for all-cause mortality [HR 1.25; 95% confidence interval (CI) 1.10–1.26; $P < 0.001$], all-cause hospitalization (HR 1.17; 95% CI 1.12–1.23; $P < 0.001$), heart failure hospitalization (HR 1.28; 95% CI 1.19–1.38; $P < 0.001$), non-cardiovascular hospitalization (HR 1.16; 95% CI 1.11–1.22; $P < 0.001$). The co-morbidities contributing to high PAF were: anaemia, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, and peripheral artery disease. These findings were similar for HFrEF and HFpEF. Interaction analysis yielded similar results.

Conclusions

In a contemporary community population with chronic heart failure, non-cardiac co-morbidities confer a similar contribution to outcomes in HFrEF and HFpEF. These observations suggest that quality improvement initiatives aimed at optimizing co-morbidities may be similarly effective in HFrEF and HFpEF.

Keywords Heart failure • Prognosis • Co-morbidities • Ejection fraction

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Introduction

Heart failure (HF) is a highly prevalent syndrome that occurs across the entire range of left ventricular ejection fraction (LVEF), from patients with preserved LVEF (HFpEF) to those with reduced LVEF (HFrEF). HF prevalence steeply increases with aging, from <1% in the 20 to 39-year-age group to >20% in individuals aged >80 years.[1,2] With the aging of the population, there is an increase in concomitant non-cardiac conditions affecting chronic HF (CHF) patients.[3] These co-morbidities frequently complicate management and may contribute to adverse outcomes. However, there are limited data evaluating the relative prognostic impact of multiple non-cardiac co-morbidities in unselected patients with CHF.[4–6] In particular, the prognostic implications of non-cardiac co-morbidities in HFpEF patients, compared to patients with HFrEF, are still controversial. With the exception of the recent data reported by van Deursen *et al.*,[6] most previous studies suggested a higher prevalence of non-cardiac chronic illnesses among HFpEF patients when compared to HFrEF patients.[5,7] This has led to the belief that improving management of specific co-morbidities may have a greater impact on patients with HFpEF.[8] However, the relative contribution of non-cardiac co-morbidity burden to outcomes in HFrEF vs. HFpEF is unclear, particularly in contemporary 'real-world' cohorts. A more nuanced understanding of these relationships could have important implications for disease management programmes, quality improvement initiatives, and future clinical intervention trials. To better understand the public health impact of non-cardiac chronic illnesses, we explored the differential prevalence and the attributable risk of non-cardiac co-morbidities on outcomes between HFrEF and HFpEF patients in a large contemporary, community-based population.

Methods

Study setting

Between October 2009 and December 2013, all consecutive ambulatory CHF patients that attended the Outpatient Clinics of the Cardiovascular Center and Cardiovascular Department of Trieste (Italy) were recruited. The public health system in the Trieste area is largely inclusive (87.1% of all cardiovascular ambulatory clinical evaluations), thus facilitating population-based cardiovascular research. The study was registered at ClinicalTrials.gov (NCT02946476).

Data sources

To select patients and clinical variables, coding data derived from the E-chart of the Outpatient Clinic (Cardionet®) were utilized. The E-chart includes medical information collected by cardiologists during routine clinical practice, including diagnostic codes, laboratory tests, procedures, and drug prescriptions sorted out using electronic indexes. The E-chart allows electronic access to folders including clinic consultations, emergency department visits, instrumental procedures, laboratory analyses, and hospital admissions. Medical records are routinely reviewed by clinicians during each clinical evaluation to update medical history, diagnostic procedures, and treatment. Additionally, the E-chart is collected in a Data Warehouse that includes regional databases, such as the Registry of Births and Deaths, the Hospital Discharge, the District Healthcare Services (intermediate and home care), and the Public Drug Distribution System. We implemented the data of the E-chart with discharge codes of previous hospitalizations (within the previous 5 years), based on the standard nomenclature of the International Classification of Diseases-Ninth Revision (ICD-9-CM), available laboratory data, interventional procedures, and prescribed treatments. This integrated database established the Trieste Observatory of Cardiovascular Diseases. The institutional ethical board approved the study and the informed consent was obtained under the institutional review board policies of hospital administration.

Study population

We studied all consecutive HF patients included in the E-chart. For the identification of HF patients, we followed several steps. Firstly, we searched the electronic medical records using the keywords 'chronic heart failure', 'systolic,' 'diastolic' to select patients with clinical findings compatible with HF. In order to avoid diagnostic underestimation, we implemented the data of the medical E-chart with discharge codes of previous hospital access based on the standard nomenclature of the ICD-9-CM, interventional procedures for HF patients (i.e. cardioverter-defibrillator implantation) and prescribed treatments. Subsequently, the potential cases were manually reviewed by clinicians to validate the diagnosis of HF using the 2012 criteria of the European Society of Cardiology and confirmed by the most recent 2016 European Society of Cardiology guidelines.[9,10] We included in the present analysis patients with LVEF determinations before or within 3 months of the index visit. We also excluded all patients who had severe left-sided primary valvular disease. Patients were classified as having valvular heart disease if the degree of left-sided primary valve disease was moderate or severe according to standard echocardiographic criteria.[11] The patients were divided into two groups according to LVEF: preserved LVEF (≥50%) and reduced LVEF (<50%). Additionally, we also performed a comparison of non-cardiac co-morbidities considering the HF population grouped according to three LVEF strata: HF with mid-range ejection fraction (HFmrEF, 40–49%), HFpEF (≥50%), and HFrEF (<40%). The investigation complies with the Declaration of Helsinki.[12]

Clinical variables and co-morbidities

Clinical variables, including cardiac and non-cardiac co-morbidities, were determined according to the data of the E-chart medical records. We considered the non-cardiac co-morbidities included in the Charlson co-morbidity index because of their reported important prevalence and prognostic impact in the HF population.

On the basis of the Charlson co-morbidity index,[13] we included the following non-cardiac co-morbidities: peripheral artery disease (PAD), cerebrovascular accident, dementia, chronic obstructive pulmonary disease (COPD), rheumatologic disorders, acquired immunodeficiency syndrome, peptic ulcer disease, diabetes mellitus, liver disease, malignancy, chronic kidney disease (CKD), psychiatric disorders, and anaemia. In accordance with Ather *et al.*,[5] we also included obesity and hypertension, because of their prognostic significance in HF patients. None of our patients had an acquired immunodeficiency syndrome, hence, a total of 14 co-morbidities were considered. Body mass index was calculated as the ratio of weight to square height (kg/m^2), and obesity was defined as a body mass index ≥30 kg/m^2. Hypertension was defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg at the time of enrolment, and/or as

a history of hypertension.[5] Renal failure was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease formula.[14] Anaemia was defined according to the World Health Organization criteria (haemoglobin <13 g/dL in men and < 12 g/dL in women).[15]

Outcome

Study outcomes of interest included death from any cause, all-cause hospitalization, HF hospitalization, and non-cardiovascular hospitalization. Deaths were collected from the regional Registry of Births and Deaths. First all-cause hospitalization, HF hospitalization, and non-cardiovascular hospitalization were collected from the Hospital Discharge Registry. HF hospitalization was assessed using primary ICD-9-CM code from the first discharge diagnosis. Conversely, non-cardiovascular hospitalizations were identified on the basis of standard diagnosis-related group codes.

Statistical analysis

We report percentages for categorical variables and mean with standard deviation (SD) or median and interquartile range (IQR) for continuous variables according to the shape of corresponding distribution. Categorical variables were compared between HFpEF and HFrEF using chi-square tests. Continuous variables were compared with two-sample *t*-tests for variables with Gaussian distribution and the non-parametric median test for non-Gaussian distributions. To evaluate whether the impact of each co-morbidity was different among the HFpEF and HFrEF groups, we performed several steps. First, in order to examine the relationship between non-cardiac co-morbidities and outcomes, we estimated the population attributable fraction (PAF) of each non-cardiac co-morbidity in the overall HF population and in the LVEF subgroups. The attributable fraction is generally defined as the proportion of events in a population that could be prevented by eliminating the risk factor from the population and is generally expressed as a percentage. In the present work, PAFs have been computed using the R package 'NestedCohort': this package provides functions that perform survival analysis on cohort studies to estimate hazard ratios (HR), survival probabilities and attributable risks, all standardized for confounders. Survival probability is estimated for each level of the co-morbidity (presence vs. absence) taking into account confounders (i.e. standardized for age and sex), and the 'crude' survival probability is also estimated, which is the observed survival in the population (so not standardized). Then, the PAF at time *t* (in our case *t* was fixed at the last observed event time) is estimated as:

$$PAF(t) = \frac{P(T \leq t) - P(T \leq t|Z = z^*)}{P(T \leq t)}$$

where T denotes the time to event, Z a p-vector of risk factors and z* the p-vector of their chosen target values in order to quantify the potential impact of modifying the current distribution of Z to z* (i.e. absence of the co-morbidity). Using the crude survival function $S(t) = P(T > t)$ and the standardized one $S(t)_{adj} = S(T > t|Z = z^*)$, the PAF for time-to-event outcomes can be written as follows:[16]

$$PAF(t) = 1 - \frac{1 - S(t)_{adj}}{1 - S(t)}$$

In order to assess the interaction between LVEF groups and co-morbidities (both individually, and as a sum of co-morbidities per patients) the HR of the interaction term in a Cox model adjusted for sex and age was calculated. The covariates for the multivariable models of mortality were selected on the basis of a backward stepwise algorithm in a Cox proportional hazards model. To examine the effect of co-morbidity load on all-cause mortality, the HFrEF and HFpEF populations were divided into groups with different co-morbidity loads (0, 1, 2, ≥3 co-morbidities); estimated survival curves obtained from the Cox multivariable models were plotted to represent the effect of co-morbidity load in the two groups. The model included demographic (age, sex), medical history (atrial fibrillation), laboratory values (serum sodium levels), number of co-morbidities (0, 1, 2, ≥3), and the interaction between co-morbidity burden (0, 1, 2, ≥3) and LVEF groups. All analyses were performed using SPSS version 18 (SPSS, Inc., Chicago, IL, USA). Data are presented as mean (SD) unless otherwise specified, and *P*-values <0.05 were considered statistically significant.

Results

A total of 2765 patients met the pre-defined HF criteria during the study period. Of these, 353 (13%) patients were excluded because quantitative LVEF had not been documented, and 98 (4%) were excluded because of left-sided severe primary valvular disease (*Figure 1*). When we performed sensitivity analysis by excluding patients with LVEF available after clinical visit, no significant difference was found. Further, performing the comparison analysis between patients with and without available LVEF, similar characteristics as well as a similar proportion of non-cardiovascular co-morbidities between the two groups were found (online supplementary *Table S1*). A total of 2314 patients met the study selection criteria. Of these, 1373 (59%) patients were identified as having HFpEF (i.e. LVEF ≥50%) and 941 (41%) as having HFrEF. Clinical characteristics of the whole HF population, as well as by LVEF groups, are presented in *Table 1*. Overall, mean age was 77 years with a substantial proportion of female patients, significant background prevalence of ischaemic heart disease, hypertension, and atrial fibrillation. During a median follow-up of 31 (IQR 16–41) months, 472 (20%) patients died. Overall, there was a high morbidity burden, with first hospitalizations from any cause in 1533 (66%), hospitalizations for HF in 510 (22%), hospitalizations for non-cardiovascular cause in 1422 (61%) (*Table 1*).

Relevant differences between HFrEF and HFpEF groups were observed with respect to demographics, cardiac co-morbidities, aetiology, and pharmacological treatment. Patients with HFpEF were older, with a higher prevalence of women and atrial fibrillation, but a lower rate of ischaemic heart disease. Furthermore, HFpEF patients were less frequently treated with beta-blockers and renin–angiotensin–aldosterone system inhibitors. Conversely, non-cardiac co-morbidities had a similar prevalence between HFrEF and HFpEF groups, except for obesity and hypertension which were more frequent in HFpEF (*Table 1*). A similar proportion of non-cardiac co-morbidities per patient was observed within each LVEF group (*Figure 2*). Additionally, we performed a comparison of non-cardiac co-morbidities considering the HF population grouped according to three HF-LVEF types: HFmrEF (40–49%), HFpEF (≥50%), and HFrEF (<40%). Specifically, the description analysis (online supplementary *Table S2*) and the interaction term analysis showed no significant difference in prevalence and prognostic impact of non-cardiac co-morbidities between HFmEF vs.

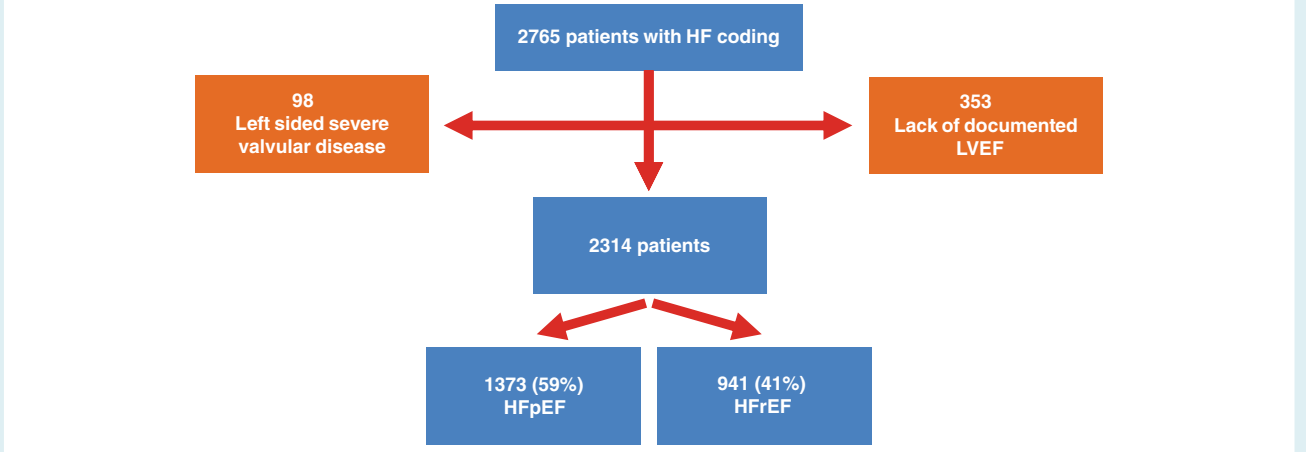

Figure 1 Flowchart of patient selection. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

HFpEF and HFrEF (online supplementary *Table S3*). Additionally, performing a sensitivity analysis for LVEF threshold, we confirmed a 50% LVEF as significant threshold (online supplementary *Figure S1*).

Population attributable risk of non-cardiac co-morbidities

Among all non-cardiac co-morbidities, anaemia, CKD, COPD, diabetes mellitus, and PAD were strongly associated with mortality in the overall HF population (*Table 2*). Similar findings were seen for all-cause, non-cardiovascular, and HF hospitalizations (data not shown). Considering PAF for all-cause mortality, anaemia, CKD, diabetes mellitus, and COPD showed the highest quantitative contribution. Findings were similar for all-cause hospitalization, with exception of PAD which showed a high contribution only for all-cause hospitalization. For each LVEF group, non-cardiac co-morbidities presented similar quantitative contribution (*Table 2*). Concordantly, for all-cause mortality, non-cardiac co-morbidities had no significant interactions by LVEF, confirming no differences in their prognostic impact (*Table 3*). This was confirmed to be similar for all-cause, HF, and non-cardiovascular hospitalizations (online supplementary *Table S4*).

Non-cardiac co-morbidity burden and prognosis

When HF patients were grouped according to co-morbidity burden, the presence of ≥3 co-morbidities was related with increased risk for all-cause mortality [HR 2.32, 95% confidence interval (CI) 2.11–3.46; $P < 0.001$]. This trend was similarly observed in both LVEF groups ($P = 0.81$ for interaction) (*Figure 3*). After adjustment for several variables, an increasing number of non-cardiac co-morbidities was associated with a higher risk for all-cause mortality (HR 1.25, 95% CI 1.10–1.26; $P < 0.001$), all-cause hospitalization (HR 1.17, 95% CI 1.12–1.23; $P < 0.001$), HF hospitalization (HR 1.28, 95% CI 1.19-1.38; $P < 0.001$), non-cardiovascular hospitalization (HR 1.16, 95% CI 1.11–1.22; $P < 0.001$) (online supplementary *Table S5*). The unadjusted and adjusted mortality and hospitalization rates according to LVEF groups are summarized in *Table 4*. The adjusted model revealed no significant difference in mortality rates between the two LVEF groups (HR 0.95, 95% CI 0.63–1.42; $P = 0.81$). This trend was confirmed also for morbidity outcomes (*Table 4*).

Discussion

This study confirms, in a contemporary community-based population, previous observations by demonstrating that non-cardiac chronic illnesses confer significant risk for mortality and hospitalization in CHF patients.[17,18] For the first time, we demonstrate the effect of a wide range of non-cardiac co-morbidities, by estimating associated attributable risks in a CHF community setting within LVEF phenotype. Prior population-based HF studies were confined to studying specific global regions, and thus direct comparative real-world data from different countries are not widely available.[19] Specifically, robust region-specific registry data are available from Olmsted County (USA)[20] and Sweden[21] (online supplementary *Table S6*). Given the span in temporal period of HF patients included in previous population-based studies,[19–23] the comparison with previous studies could result difficult, especially for different definitions of some co-morbidities and HF itself. However, in line with previous population-based studies,[19–23] our population included a high proportion of elderly patients and women, high rates of non-cardiac co-morbidities, and a large proportion of HFpEF patients. Although HFpEF management was based on targeting symptoms and/or signs of congestion using diuretics, in this patient subset there was a high percentage of administration of HF drugs (beta-blockers, mineralocorticoid receptor antagonists and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). This may reflect that trial results in the specific context of HFpEF are still not fully considered conclusive by clinicians.

Table 1 Characteristics of the overall population and of patients with heart failure with reduced and preserved ejection fraction

Clinical characteristics	Overall ($n = 2314$)	HFrEF ($n = 941$; 41%)	HFpEF ($n = 1373$; 59%)	*P*-value (HFrEF vs. HFpEF)
Age, years, mean (SD)	77 (10)	76 (10)	79 (9)	<0.001
Male gender, *n* (%)	1325 (57)	658 (70)	667 (49)	<0.001
NYHA class, *n* (%)				
I	790 (34)	302 (32)	488 (35)	0.06
II	993 (43)	392 (42)	601 (44)	0.05
III–IV	531 (23)	178 (19)	235 (17)	0.05
Body mass index, kg/m^2, mean (SD)	28 (5)	27 (4)	28 (5)	0.001
Systolic blood pressure, mmHg, mean (SD)	134 (19)	130 (20)	136 (20)	<0.001
Heart rate, b.p.m., mean (SD)	73 (16)	73 (17)	73 (16)	0.42
Left ventricular ejection fraction, %, mean (SD)	51 (15)	36 (8)	61 (7)	
eGFR, mL/min/1.73 m^2, mean (SD)	66 (25)	65 (25)	66 (25)	0.37
Sodium, mEq/L, mean (SD)	139 (12)	139 (12)	139 (12)	0.91
Haemoglobin, g/dL, mean (SD)	13.2 (3)	13 (2)	13 (4)	0.32
Ischaemic heart disease, *n* (%)	1116 (46)	572 (61)	544 (40)	0.001
Atrial fibrillation, *n* (%)	1235 (54)	437 (46)	798 (58)	<0.001
Non-cardiac co-morbidities, *n* (%)				
Hypertension	1863 (80)	732 (79)	1131 (82)	0.01
Obesity (≥30 kg/m^2)	609 (26)	200 (21)	409 (30)	0.01
Diabetes mellitus	797 (34)	335 (35)	462 (34)	0.14
Peripheral artery disease	422 (18)	187 (20)	237 (17)	0.08
Chronic kidney disease	804 (41)	341 (42)	463 (40)	0.46
Chronic obstructive pulmonary disease	547 (24)	210 (22)	337 (24)	0.36
Anaemia	586 (25)	229 (24)	357 (26)	0.44
Liver disease	95 (4)	37 (4)	58 (4)	0.75
Cancer	283 (12)	113 (12)	170 (12)	0.75
Dementia	19 (1)	10 (1)	9 (1)	0.91
Rheumatologic disorders	66 (3)	19 (2)	47 (3)	0.06
Peptic ulcer disease	42 (2)	14 (2)	28 (2)	0.34
Psychiatric disorders	62 (3)	32 (3)	30 (2)	0.06
Cerebrovascular accident	324 (14)	133 (14)	191 (14)	0.91
Medication use, *n* (%)				
ACEi/ARB	1712 (74)	742 (79)	970 (71)	<0.001
Digitalis	544 (23)	244 (26)	300 (22)	0.01
Beta-blocker	1198 (52)	536 (57)	662 (48)	<0.001
Aldosterone antagonist	528 (23)	274 (29)	254 (19)	<0.001
Outcomes, *n* (%)				
Mortality	472 (20)	225 (24)	247 (18)	0.001
All-cause hospitalization	1533 (66)	611 (65)	922 (67)	0.33
Heart failure hospitalization	510 (22)	222 (24)	288 (21)	0.07
Non-cardiovascular hospitalization	1422 (61)	543 (57)	879 (64)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

Clinical differences between LVEF groups were similar to previous epidemiological studies, albeit differences in the current study were generally less pronounced than previously reported.[6,21] Of note, similarly to reports from population-based studies in Olmsted County,[20] the prevalence of non-cardiac co-morbid conditions was high, regardless of LVEF. However, none of the population studies to date has attempted to compare the relative prognostic impact of individual non-cardiac co-morbidities in patients with CHF.

Remarkably, the adverse impact of non-cardiac chronic diseases appears similarly significant, irrespective of LVEF. This trend was confirmed similarly across the LVEF phenotypes, also considering the subset of patients with HFmrEF (online supplementary *Table S3*). Although our analysis was not focused specifically on HFmrEF, these results are of interest and contrast with those of previous studies that reported a different frequency and prognostic impact across the three LVEF phenotypes.[24,25] However, these studies included mixed patients (hospitalized for HF and CHF) derived

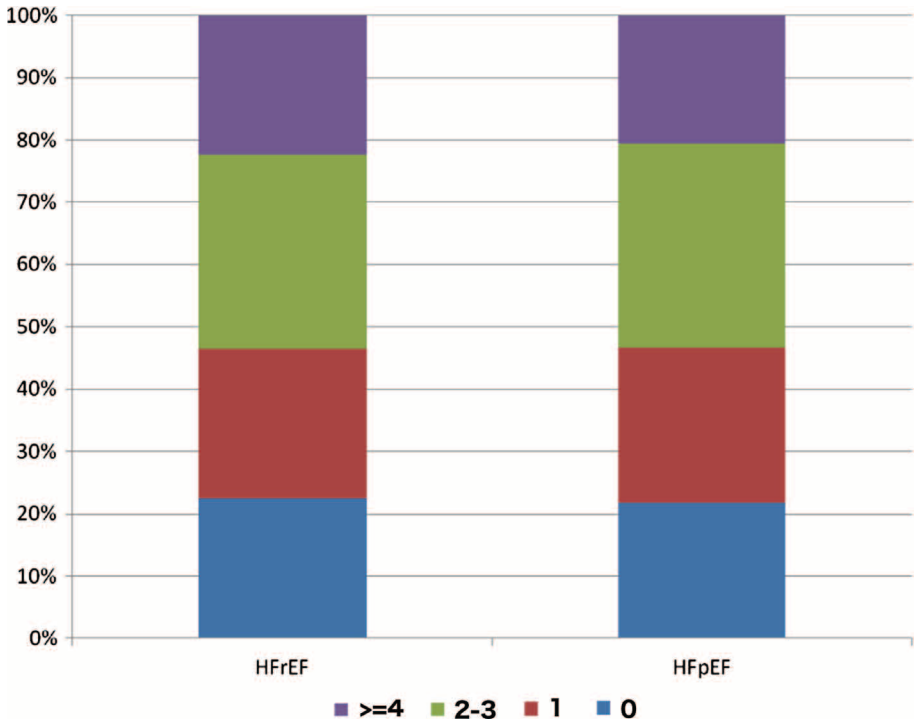

Figure 2 Co-morbidity load (0, 1, 2, 3, ≥4 co-morbidities) according to left ventricular ejection fraction groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

from cardiology registry or trials, thus referring to HF populations that differ from our study cohort.[24–26]

Herein, to quantitatively evaluate and compare the contribution of non-cardiac co-morbidities to the outcomes among HFrEF and HFpEF patients, we estimated the PAF. Of all individual non-cardiac co-morbidities, CKD, anaemia, diabetes mellitus, COPD, and PAD showed the highest significant association with mortality and morbidity. To date, PAF has been one of the most applied measures for estimating the association between cardiovascular risk factors and clinical outcomes, allowing policy makers to anticipate the potential impact of preventive strategies targeting certain risk factors.[2,23,27] When assessing attributable risks using PAF, we found a higher contribution of anaemia, COPD, diabetes mellitus, CKD, and PAD. The present study addressed, for the first time, the PAF within each LVEF groups (HFrEF and HFpEF) showing a similar quantitative effect of non-cardiac co-morbidities in both LVEF groups. After performing a direct comparative analysis with interaction test, we confirmed no significant differences in the prognostic impact of various non-cardiac co-morbidities between LVEF groups. Ather *et al.*[5] estimated the interaction between 15 non-cardiac conditions and LVEF groups in a retrospective study of an HF ambulatory cohort of veterans including predominantly male (91%) patients with HFrEF (30% HFpEF vs. 70% HFrEF). They found no significant interaction between non-cardiac co-morbidities and LVEF groups, with exception of COPD. Unlike this prior study, the present analysis includes a more heterogeneous population, allowing better application to the contemporary real-world CHF population.

Current data are also consistent with the 3C-HF score that combined cardiac and non-cardiac co-morbidities and showed a similarly good predictive performance in both LVEF groups, thus underscoring the prognostic impact of co-morbidities regardless of LVEF.[28] Other previous reports, addressing the comparative prognostic role of co-morbidities across LVEF groups, were focused on a single or limited number of non-cardiac conditions and reported conflicting results.[17,29–33] Concordant with the high co-morbidity burden, the rate of non-cardiovascular hospitalizations in our population was high. This is consistent with recent reports highlighting an increasing rate of non-cardiovascular hospitalizations in HF patients.[34,35] Indeed, despite previous observations,[5,7] non-cardiovascular hospitalizations occurred similarly in the two LVEF groups. This trend may reflect contemporary epidemiology, involving a change in the clinical profile of LVEF phenotypes. The present findings suggest that a greater focus on recognition and treatment of co-morbidities in HF patients appears warranted, irrespective of LVEF.

Although there is a wide heterogeneity in the context of the HFpEF population, the coexistence of HFpEF patients with advanced age and a high prevalence of non-cardiac co-morbidities has led to the pathophysiologic hypothesis linking HFpEF to these clinical conditions.[29] In particular, a major role was speculated for chronic inflammation, which could mechanistically tie aging and co-morbidities with HFpEF development.[30,31] However, chronic inflammation and other mechanisms induced by non-cardiac co-morbidities may similarly cause progression of

Table 2 Crude hazard ratio, adjusted hazard ratio and population attributable fraction for all-cause mortality and all-cause hospitalization

Non-cardiac co-morbidities		Crude HR (95% CI)	Adjusted* HR (95% CI)	PAF*, % (95% CI)
All-cause mortality				
Chronic obstructive pulmonary disease	Overall	1.7 (1.3–2.1)	1.6 (1.3–1.9)	12 (6–17)
	HFpEF	1.7 (1.3–2.3)	1.4 (1.1–1.8)	13 (4–21)
	HFrEF	1.7 (1.2–2.3)	1.3 (1.2–1.8)	12 (3–21)
Anaemia	Overall	2.0 (1.6–2.5)	1.9 (1.5–2.4)	21 (13–22)
	HFpEF	1.6 (1.2–2.1)	1.9 (1.4–2.6)	20 (2–24)
	HFrEF	2.7 (2.0–3.8)	1.9 (1.2–2.5)	23 (14–30)
Chronic kidney disease	Overall	1.9 (1.5–2.3)	1.7 (1.3–2.0)	22 (9–32)
	HFpEF	1.6 (1.2–2.1)	1.6 (1.3–2.1)	20 (6–30)
	HFrEF	2.4 (1.7–3.3)	1.9 (1.7–2.3)	26 (11–42)
Diabetes mellitus	Overall	1.3 (1.1–1.6)	1.4 (1.2–1.7)	18 (12–23)
	HFpEF	1.3 (1.1–1.6)	1.6 (1.4–2.4)	15 (5–25)
	HFrEF	1.7 (1.3–2.3)	1.8 (1.3–2.2)	22 (11–33)
Peripheral artery disease	Overall	1.3 (1.1–1.7)	1.1 (0.9–1.5)	–
	HFpEF	1.1 (1.1–1.5)	1.2 (1.1–1.9)	–
	HFrEF	1.7 (1.3–2.5)	1.3 (1.1–1.8)	–
All-cause hospitalization				
Chronic obstructive pulmonary disease	Overall	2.0 (1.6–2.5)	1.9 (1.6–2.4)	14 (11–16)
	HFpEF	1.8 (1.4–2.4)	1.3 (1.1–1.5)	13 (7–19)
	HFrEF	2.2 (1.6–3.2)	1.5 (1.2–1.9)	15 (11–19)
Anaemia	Overall	2.2 (1.8–2.7)	2.0 (1.7–2.7)	14 (1–6)
	HFpEF	2.2 (1.7–3.1)	1.6 (1.4–1.8)	14 (1–7)
	HFrEF	2.1 (1.6–3.1)	1.5 (1.3–1.8)	15 (1–7)
Chronic kidney disease	Overall	1.8 (1.4–2.1)	1.6 (1.3–1.9)	17 (11–23)
	HFpEF	1.8 (1.4–2.4)	1.4 (1.3–1.7)	19 (10–28)
	HFrEF	1.7 (1.3–2.3)	1.3 (1.1–1.5)	15 (2–28)
Diabetes mellitus	Overall	1.4 (1.1–1.6)	1.4 (1.2–1.7)	11 (8–15)
	HFpEF	1.3 (1.1–1.6)	1.2 (1.1–1.4)	12 (5–16)
	HFrEF	1.6 (1.2–2.1)	1.4 (1.2–1.6)	15 (7–22)
Peripheral artery disease	Overall	2.1 (1.7–2.7)	2.1 (1.7–2.7)	12 (8–14)
	HFpEF	1.7 (1.3–2.3)	1.3 (1.1–1.6)	14 (4–16)
	HFrEF	2.8 (1.9–4.4)	1.5 (1.3–1.8)	16 (11–21)

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PAF, population attributable fraction.
*HR and population attributable risk were adjusted for age and sex.

cardiac deterioration in patients with HFrEF.[30,32] Regardless of the underlying mechanism, the 'new concept' that emerges from our work is that non-cardiac co-morbidities play an important role irrespective of HF-LVEF type, and so appropriate care of HF patients should always include screening, stratification and treatment of the main non-cardiac co-morbidities. Therefore, HF patients who are often older and with multiple chronic diseases, may benefit from care models targeting non-cardiac co-morbidities. On the other hand, although we did not evaluate the effects of high co-morbidity burden on advanced therapies (such as defibrillator implantation), our findings may confirm previous observations,[36] suggesting that the potential benefit of some therapies may be limited in patients with HFrEF and high co-morbidity burden.

Finally, our results support the current move towards multidisciplinary care to develop disease management systems that span cardiology and non-cardiology health care providers.

Limitations

This study has limitations inherent to observational studies where the analyses were performed without adjustment for measured or unmeasured confounders. All patients in the present analysis were white, thus preventing application of these data to other racial groups. The identification of chronic conditions was done through review of the ICD-9-CM codes and coding practices may differ across geographic regions and hospital systems. However, ICD-9-CM codes were confirmed by chart review, as well as instrumental, laboratory and pharmaceutical data defining chronic disease. Another limitation is the absence of a direct comparison between HFmrEF and the other HF-LVEF types (HFrEF and HFpEF). Although the topic is intriguing, our aim was to extend previously published results, which compared HFpEF and HFrEF populations, assessing population attributable risk of co-morbidities in a contemporary, community-based cohort of HF patients. Furthermore,

Table 3 **Adjusted hazard ratio of non-cardiac co-morbidities for mortality in patients with heart failure with reduced and preserved ejection fraction**

Non-cardiac co-morbidities	Adjusted* HR (95% CI)		*P*-value for interaction (HFpEF vs. HFrEF)
	HFrEF	HFpEF	
Diabetes mellitus	1.8† (1.3–2.2)	1.6† (1.4–2.4)	0.07
Hypertension	0.5 (0.7–0.93)	0.7 (0.5–1.6)	0.69
Peripheral artery disease	1.3§ (1.1–1.8)	1.2§ (1.1–1.9)	0.96
Cerebrovascular disease	1.0 (0.7–1.6)	1.3 (0.5–1.1)	0.74
Chronic kidney disease	1.9† (1.7–2.3)	1.6‡ (1.3–2.1)	0.19
Anaemia	1.9† (1.2–2.5)	1.9† (1.4–2.6)	0.63
Chronic pulmonary disease	1.3† (1.2–1.8)	1.4† (1.1–1.8)	0.66
Obesity	0.6 (0.4–0.9)	0.6 (0.4–0.8)	0.43
Dementia	2.5§ (1.2–6.9)	1.6§ (1.3–4.8)	0.96
Liver disease	1.3 (0.7–2.6)	0.8 (0.4–1.6)	0.60
Cancer	1.3 (0.9–3.7)	1.2‡ (1.2–2.9)	0.95
Rheumatologic disorders	0.9 (0.9–7.9)	1.1 (0.2–9.3)	0.99
Peptic ulcer disease	1.9 (0.7–5.0)	1.3 (0.6–2.8)	0.94
Psychiatric disorders	1.3 (0.6–2.6)	0.6 (0.2–1.5)	0.67

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
*Data were adjusted for age and sex.
†$P < 0.001$; ‡$P = 0.01$; §$P = 0.05$.

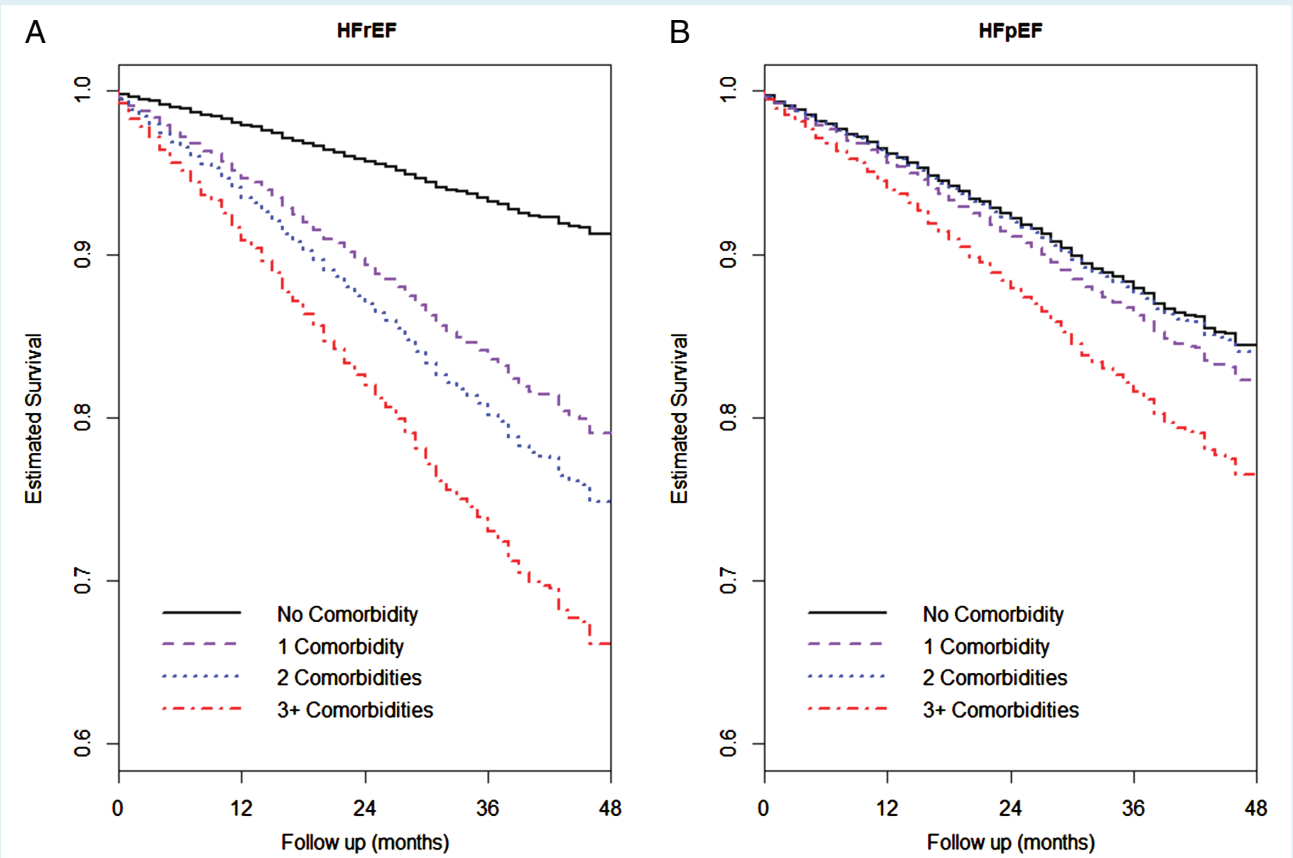

Figure 3 Estimated survival curves from the Cox model according to co-morbidity load (0, 1, 2, ≥3 co-morbidities) in patients with heart failure with reduced (HFrEF, *A*) and preserved ejection fraction (HFpEF, *B*).

Table 4 Crude and adjusted hazard ratio for mortality and hospitalization according to left ventricular ejection fraction groups

Outcomes	Crude HR (95% CI)	*P*-value (HFpEF vs. HFrEF)	Adjusted* HR (95% CI)	*P*-value (HFpEF vs. HFrEF)
All-cause mortality	0.71 (0.59–0.85)	0.001	0.95 (0.63–1.42)	0.81
Heart failure hospitalization	0.84 (0.71–1.05)	0.06	1.06 (0.72–1.51)	0.74
Non-cardiovascular hospitalization	1.05 (0.94–1.17)	0.36	1.05 (0.84–1.32)	0.62
All-cause hospitalization	0.62 (0.88–1.10)	0.61	1.07 (0.86–1.33)	0.52

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
*Data were adjusted for age, sex, atrial fibrillation, serum sodium levels, number of co-morbidities (0, 1, 2, ≥3 co-morbidities), interaction term (left ventricular ejection fraction groups*co-morbidities).

a preliminary sensitivity analysis resulted in an ejection fraction threshold of 50%. Another limitation may result from the fact that other co-morbidities (e.g. hypothyroidism) were not tested for their prognostic impact in the two HF types; otherwise, dedicated future studies are encouraged on this topic. In addition, the grade of some co-morbidities were not tested for their prognostic impact in the two types of HF, but dedicated future studies are encouraged on this intriguingly topic. Although the method used to identify HF patients minimizes the risk of underestimation, diagnosis of HFpEF is more challenging than that of HFrEF and could more easily be influenced by mistakes because of the lack of standardized and universally accepted diagnostic criteria. Therefore, relying mainly on physician diagnosis for the identification of HFpEF patients may determine misclassification errors, in particular when obesity and/or COPD coexist. Further, 353 (13%) patients were excluded because quantitative LVEF had not been documented leading to a potential bias; otherwise it is a real representation of the clinical picture of population variability. Additionally, this bias may be considered irrelevant since patients without known LVEF presented similar characteristics to those of included patients.

Some patients may not have received a discharge diagnosis of HF once their ejection fraction was known to be normal, even though their symptoms and signs were consistent with the presence of HF, thus leading to underestimation of HF-related hospitalization rates. Finally, patients with HFrEF with LVEF recovery were not examined in this study, which represents another important goal for future studies.

Conclusion

In a contemporary community population with CHF, non-cardiac co-morbidities are common and give a similar contribution to the outcome of patients with HFrEF and HFpEF. These observations suggest that interventions and quality improvement initiatives aimed at optimizing non-cardiac co-morbidities may be effective for both the HFrEF and HFpEF populations.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical characteristics of heart failure patients included in the study cohort and in heart failure patients excluded with missing left ventricular ejection fraction.
Table S2. Non-cardiac co-morbidities in patients with heart failure with reduced, mid-range and preserved ejection fraction.
Table S3. Adjusted hazard ratio of non-cardiac co-morbidities for mortality in patients with heart failure with reduced, mid-range and preserved ejection fraction.
Table S4. Adjusted hazard ratio of non-cardiac co-morbidities for hospitalization in patients with heart failure with reduced and preserved ejection fraction.
Table S5. Multivariate model for mortality and hospitalizations.
Table S6. Baseline patient characteristics by region.
Figure S1. Sensitivity analysis for left ventricular ejection fraction threshold.

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