

Comprehensive characterization of non-cardiac comorbidities in acute heart failure: an analysis of ESC-HFA EURObservational Research Programme Heart Failure Long-Term Registry

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Aims

To evaluate the prevalence and associations of non-cardiac comorbidities (NCCs) with in-hospital and post-discharge outcomes in acute heart failure (AHF) across the ejection fraction (EF) spectrum.

Methods and results

The 9326 AHF patients from European Society of Cardiology (ESC)-Heart Failure Association (HFA)-EURObservational Research Programme Heart Failure Long-Term Registry had complete information for the following 12 NCCs: anaemia, chronic obstructive pulmonary disease (COPD), diabetes, depression, hepatic dysfunction, renal dysfunction, malignancy, Parkinson's disease, peripheral vascular disease (PVD), rheumatoid arthritis, sleep apnoea, and stroke/transient ischaemic attack (TIA). Patients were classified by number of NCCs (0, 1, 2, 3, and ≥ 4). Of the AHF patients, 20.5% had no NCC, 28.5% had 1 NCC, 23.1% had 2 NCC, 15.4% had 3 NCC, and 12.5% had ≥ 4 NCC. In-hospital and post-discharge mortality increased with number of NCCs from 3.0% and 18.5% for 1 NCC to 12.5% and 36% for ≥ 4 NCCs.

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Anaemia, COPD, PVD, sleep apnoea, rheumatoid arthritis, stroke/TIA, Parkinson, and depression were more prevalent in HF with preserved EF (HFpEF). The hazard ratio (95% confidence interval) for post-discharge death for each NCC was for anaemia 1.6 (1.4–1.8), diabetes 1.2 (1.1–1.4), kidney dysfunction 1.7 (1.5–1.9), COPD 1.4 (1.2–1.5), PVD 1.2 (1.1–1.4), stroke/TIA 1.3 (1.1–1.5), depression 1.2 (1.0–1.5), hepatic dysfunction 2.1 (1.8–2.5), malignancy 1.5 (1.2–1.8), sleep apnoea 1.2 (0.9–1.7), rheumatoid arthritis 1.5 (1.1–2.1), and Parkinson 1.4 (0.9–2.1). Anaemia, kidney dysfunction, COPD, and diabetes were associated with post-discharge mortality in all EF categories, PVD, stroke/TIA, and depression only in HF with reduced EF, and sleep apnoea and malignancy only in HFpEF.

Conclusion

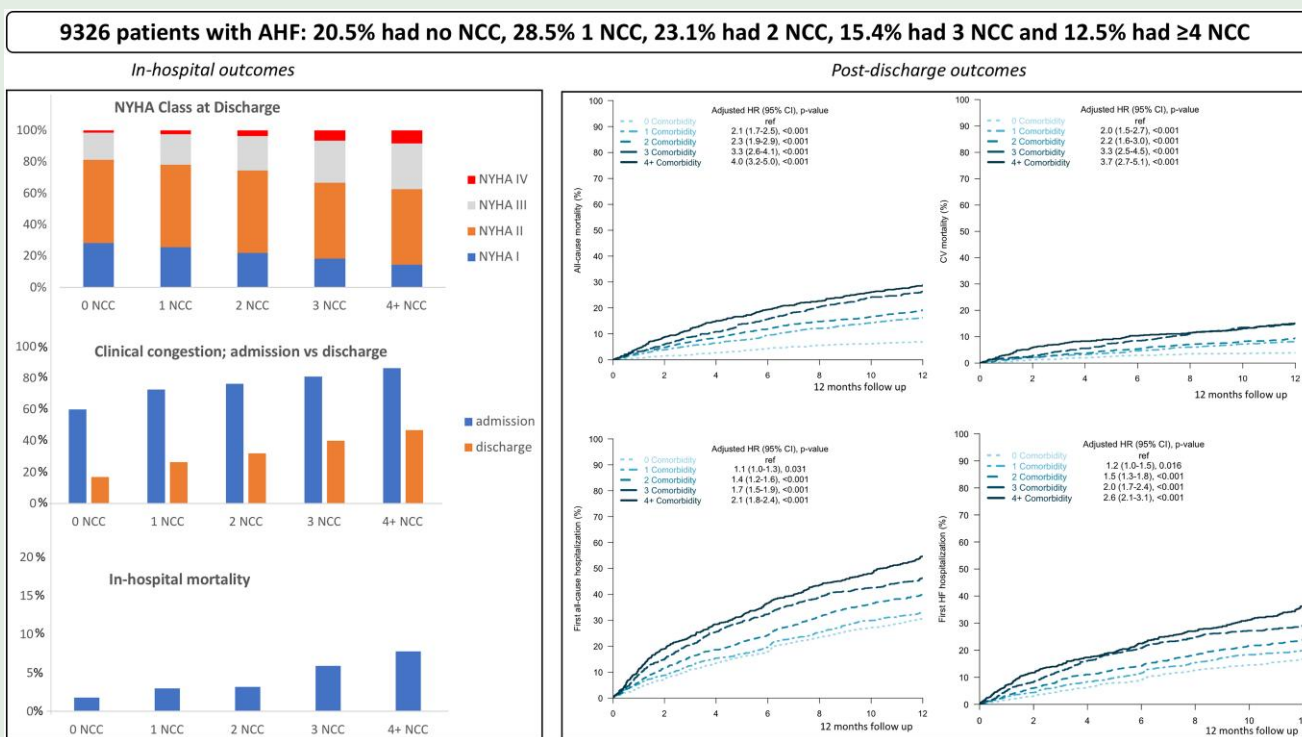
Multiple NCCs conferred poor in-hospital and post-discharge outcomes. Ejection fraction categories had different prevalence and risk profile associated with individual NCCs.

Lay summary

The current analysis from ESC-Heart Failure Long-Term Registry represents the largest and most comprehensive study in an acute heart failure (AHF) population with HF with reduced ejection fraction (HFrEF), HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF), on prevalence and association with in-hospital and post-discharge outcomes of a large number of non-cardiac comorbidities.

- A greater number of non-cardiac comorbidities (CNNs) were associated at admission with older age, preserved EF, more severe NYHA class, and longer duration of HF. In-hospital and post-discharge mortality gradually increased with number of CNNs.
- The association between each individual comorbidity and post-discharge outcomes varied substantially in AHF patients with HFrEF, HFmrEF, and HFpEF, suggesting that an ‘EF-specific’ multidisciplinary approach with distinct comorbidity management programs should be applied in post-discharge phase.

Graphical Abstract



Keywords

Acute heart failure • Comorbidities • Prognosis

Introduction

Acute heart failure (AHF) is a multifactorial syndrome associated with a high rate of in-hospital and long-term mortality, as well as recurrent HF admission.^{1–4} Heart failure is commonly accompanied by a broad range of cardiac and non-cardiac comorbidities (NCCs), complicating the management and unfavourably affecting the prognosis.^{5–9} Hospitalization for AHF represents a change in the trajectory of the disease process, and clinical severity is determined by the complex interplay between precipitants, the underlying cardiac substrate, and the patient's associated cardiac and NCCs.⁵ Following hospitalization for AHF, short-term readmissions are due to residual or rapidly recurring congestion.¹⁰ However, long-term readmissions are the consequence of the continuous deterioration of cardiac substrate, worsening of the associated cardiac and NCCs and subsequent difficulties in implementing in guideline-directed medical therapy.^{10,11}

Cardiac comorbidities such as ischaemic heart disease^{6,7} and atrial fibrillation (AF)^{7,8} have been extensively studied in chronic HF in relation to ejection fraction (EF) category (HF with reduced EF, HFrEF, $\leq 40\%$; mildly reduced EF, HFmrEF, 41–49%; and preserved EF, HFpEF, $\geq 50\%$).⁹ Also addressed by the recent guidelines,^{5,12} ischaemic heart disease is more common in HFrEF,⁶ while AF is distinctly more common in HFpEF.^{7,8} Although the prevalence of NCCs and association between NCCs and clinical outcomes in chronic HF have been studied,^{13–15} very few studies focused specifically on the burden and prognostic impact of NCCs in patients who are hospitalized for AHF.^{16–18}

Detailed information on the impact of NCCs in AHF is critical, since about half of hospitalizations are not due to cardiovascular reasons.¹¹ Furthermore, since the hospitalized HF patients are generally elderly,¹ the burden of NCCs will continue to increase. In a US study, among patients hospitalized for HF in real-world clinical practice, there was an increase in patients with multiple (≥ 3) comorbidities from 18% to 29% and a decrease in patients with no comorbidities, from 22% to 16%, from 2005 to 2014.¹⁹

The ESC-Heart Failure Long-Term (ESC-HF-LT) Registry is the largest cohort providing contemporary generalizable information about acute and chronic HF across the spectrum of EF, from all regions of Europe and from Mediterranean countries.^{20–23} In the present manuscript, we studied a large number of NCCs in AHF across the full EF spectrum and assess prevalence and characteristics, clinical associations, and in-hospital and post-discharge cause-specific outcomes.

Methods

Study design

The ESC-HFA EURObservational Research Programme (EORP)-HF-Long-Term (LT) Registry was an international, multicentre, prospective registry of patients with HF and any EF. The study was conducted from 2011–2018 in a broad range of cardiology centres from 33 ESC member countries.^{20–23} All patients provided written informed consent, and the registry was approved by local ethical review boards according to the regulations of each participating country. A follow-up visit at 12 months after the entry visit was mandatory for all patients in order to allow information on morbidity and mortality to be collected. The follow-up clinical visit could be replaced by a telephone call if the patient was unable to travel to the clinical centre. During the course of the year, patients were followed up according to the usual practice of the respective centres.

Patients

In the present analysis, we included patients with AHF who had non-missing data on EF and had complete information about presence of the 12 predefined NCCs. Patients who survived to hospital discharge, and who were not lost to post-discharge follow-up, were included in post-discharge outcome analysis (see [Supplementary material online, Appendix S1](#)). Acute

heart failure was defined as signs and symptoms of HF, evidence of cardiac dysfunction, and need for intravenous (i.v.) treatment for HF (inotropes, vasodilators, and/or diuretics). There were no specific exclusion criteria, with the exception that all patients had to be older than 18 years. In the ESC-HFA EORP-HF-LT Registry, the following 12 NCCs were studied: anaemia (haemoglobin <12 g/L for women and <13 g/L for men), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), depression, hepatic dysfunction, kidney dysfunction (glomerular filtration rate <60 mL/min/m²), current malignancy, Parkinson's disease, peripheral vascular disease (PVD), rheumatoid arthritis, sleep apnoea, and stroke/transient ischaemic attack (TIA). Patients were classified by overall burden of NCC score (0, 1, 2, 3, and ≥ 4).

Data collection

All baseline data (at hospital admission), in-hospital course, and outcomes at a 12-month post-discharge follow-up were collected and entered into an online database using a web-based electronic case report form. Automated electronic data checks were performed to prevent duplicate entries or entering invalid data. Several training meetings were organized for national co-ordinators and study investigators to assure consistency in data collection among participating centres. Furthermore, in each participating country, all data sources were subjected to verification by principal investigators, and for a random sample of 5% of enrolled patients, by EURObservational Research Programme (EORP) monitors.

Ejection fraction is defined as EF by Echo-Doppler recorded during hospitalization, or if this is missing, last known EF recorded in *Characteristics*. Ejection fraction categories were $<41\%$, 41–49%, and $\geq 50\%$ for HFrEF, HFmrEF, and HFpEF.⁵

Clinical signs of congestion, pulmonary rales, peripheral bilateral oedema, jugular venous distension >6 cm, hepatomegaly, and hepatojugular reflux were collected at admission and discharge. Target doses of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), Mineralocorticoid Receptor Antagonists (MRA), and beta-blockers (BB) were adopted from the ESC guidelines on HF. The in-hospital outcomes were all-cause mortality, length of stay (LOS), and NYHA class at discharge. Patients discharged alive were followed for 12 months, and post-discharge outcomes included all-cause mortality, cardiovascular mortality, first any cause hospitalization, and first HF rehospitalization.

Statistical analysis

All results were summarized by number of NCCs in five groups (0, 1, 2, 3, ≥ 4 NCCs). The purpose of this 'score' was to provide a clinically relatable number, rather than e.g. tertiles/quartiles, which would be specific to this cohort and less useful to clinicians. Categorical data are presented as n (%) and compared with the χ^2 test. Continuous variables are reported as median and interquartile range and compared with Kruskal–Wallis tests.

The binomial in-hospital outcomes were modelled using a generalized linear mixed-effects model with a logit link and a random effect for country. In the models including the NCC score, adjustment was performed for age, sex, primary aetiology, systolic blood pressure at admission, NYHA class, history of myocardial infarction, and AF whereas in the models including the individual comorbidities, no adjustment was performed.

The long-term outcomes were presented with cumulative incidence curves. Proportions were estimated using the Kaplan–Meier method, and incidence rates with 95% Poisson confidence intervals were calculated. Time was from date of discharge. Cox proportional hazards regressions with a frailty term for country were used to model the time to first event analysis. As a consistency analysis, the long-term outcomes were modelled using a sub-distributional hazards model (Fine and Gray²⁴) where death from other causes than the event was treated as a competing event. All-cause mortality, cardiovascular (CV) mortality, and HF hospitalization were also modelled, as above, separately in each EF group. Similar to above, in the models including the NCC score, the adjustment was performed for age, gender, primary aetiology, systolic blood pressure, NYHA class, history of myocardial infarction, and AF whereas in the models including the individual comorbidities, no adjustment was performed. Missing values were not imputed.

All analyses were performed using R version 4.0.2 (R Core Team²⁵). The level of significance is set to 5%, two-sided. The R code for all data

management and statistical analyses is found at <https://github.com/KIHeartFailure/esccomorb>.

Results

Patients and non-cardiac comorbidities

Among 25 621 patients enrolled in the ESC-HFA EORP-HF-LT Registry from 2011 to 2018, 10,879 were enrolled with AHF (defined as hospitalized with HF requiring i.v. treatment). Of these, 9326 had non-missing data on EF, and the 12 had pre-specified NCCs. A total of 359 patients (3.9%) died during hospitalization, and 8967 were discharged alive. The median (min–max) follow-up for the long-term outcomes was 12.8 (1.0–43.4) months.

Distribution of NCCs shows that 1907 patients (20.5%) had no NCCs, 2658 patients (28.7%) had one, 2154 patients (23%) had two, 1441 patients (15.4%) had three, and 1166 patients (12.5%) had \geq four NCCs. Patients with HFpEF had a higher number of NCCs (Figure 1A). Patients from the Middle East and Southern Europe had a higher NCC number compared to other regions (see Supplementary material online, Figure S1). The most common NCCs were anaemia, DM, kidney dysfunction, and COPD. The prevalence of each individual NCCs across EF categories is presented in Figure 1B.

Baseline characteristics

Patients with higher comorbidity score were significantly older and more likely to have a HF diagnosis of longer duration and higher NT-proBNP at admission (Table 1). Ischaemic aetiology as well as history of percutaneous coronary intervention (PCI) and coronary artery by-pass graft (CABG) were more common in the group of patients with higher NCC score. In patients with greater number of NCCs, NYHA class at discharge was higher (see Supplementary material online, Figure S2A), and signs of congestion at admission were more frequent and less likely to resolve (see Supplementary material online, Figure S2B). A greater number of NCCs were associated with smaller left ventricular but larger left atrial dimensions, and a greater prevalence of moderate–severe tricuspid regurgitation (TR) (Table 1).

In-hospital therapies and procedures

The proportion of patients treated with i.v. inotropes and/or i.v. diuretics (but not i.v. vasodilators) increased steeply with number of NCCs (Table 2). Particularly, i.v. inotropes were used in 17% of patients with \geq 4 NCCs. A lower proportion of AHF patients with three and four NCCs underwent coronary angiography (18% and 17%) and PCI (9.4% and 8.2%) during hospitalization as compared to patients with no, one, or two NCCs. There were no significant differences in *de novo* implantation of ICD or cardiac resynchronization therapy (CRT). In patients with HFrEF, utilization of disease modifying HF medications was lower at admission, increased more during hospitalization, and was greater at discharge in those with fewer NCCs. Similarly, the proportion of patients receiving $>$ 50% target dose of these therapies decreased with greater number of NCCs. Oral diuretics were more frequently used in patients with more NCCs, both at admission and at discharge (see Supplementary material online, Figure S3).

In-hospital course and outcomes

In-hospital mortality increased with number of NCCs, with 1.8%, 3.0%, 3.2%, 5.9%, and 7.8% for none, one, two, three, and \geq four NCCs, respectively. Association between each individual comorbidity and in-hospital mortality is presented in Supplementary material online, Figure S4. In-hospital LOS was longer in patients with higher NCC score (see Supplementary material online, Table). Clinical congestion at discharge were more commonly reported in patients with higher NCC

score irrespective of EF category, and patients with multiple NCCs were discharged with more advanced NYHA class (see Supplementary material online, Figure S2).

Long-term outcomes

One-year all-cause mortality ranged from 7.8% with no NCCs to 36% with \geq 4 (see Supplementary material online, Table). Similarly, the rate of all-cause hospitalization increases with number of NCCs from 30% to 56%.

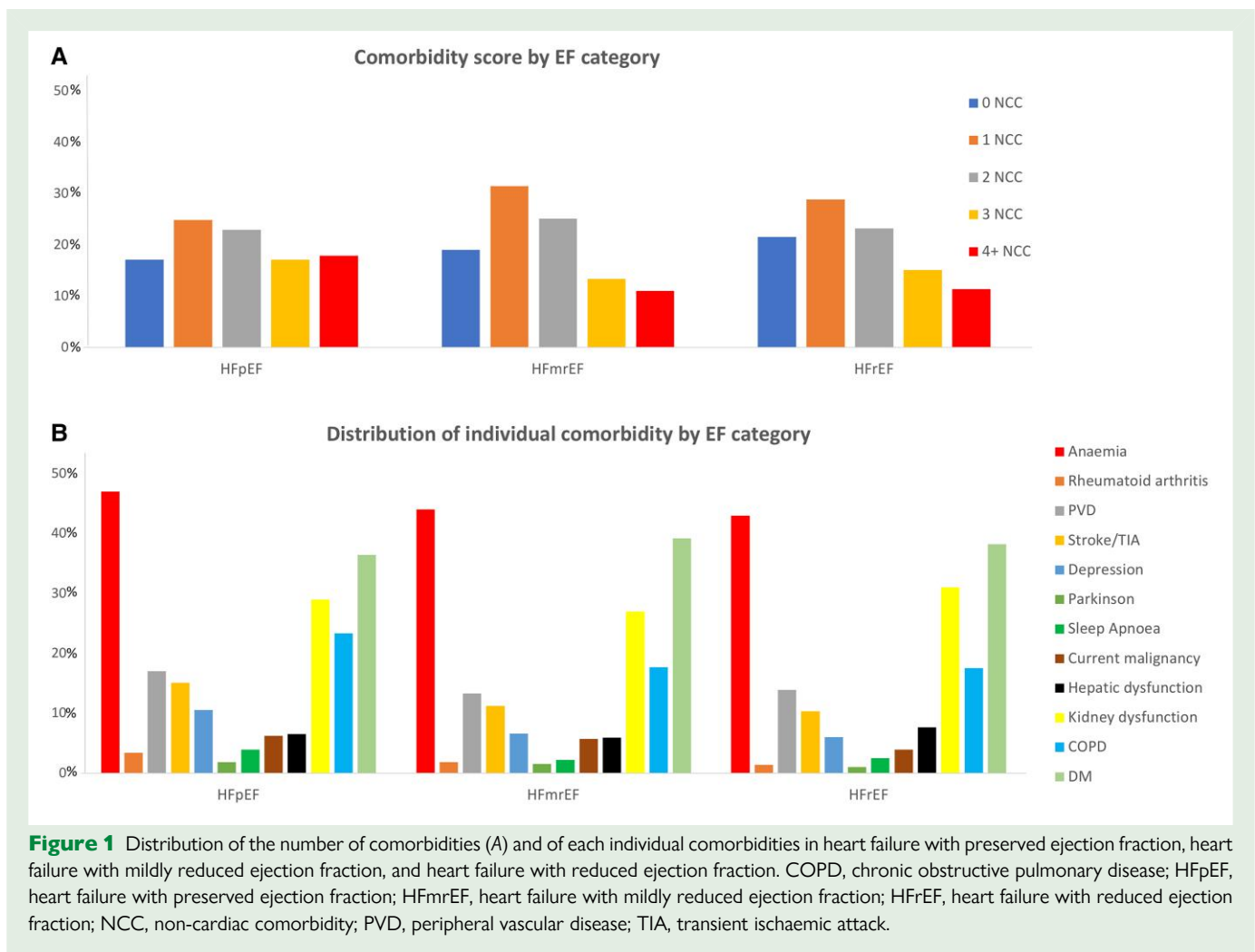
Using Cox regression, the adjusted association of each individual NCC with long-term outcomes is presented in Figure 2. Several NCCs, such as anaemia, stroke/TIA, hepatic dysfunction, kidney dysfunction, and diabetes were associated with four all long-term outcomes studied, while other NCCs were associated with some but not all outcomes. Hepatic dysfunction [hazard ratio (HR) = 2.1 (1.8–2.5)] and kidney dysfunction [HR = 1.7 (1.5–1.9)] had the strongest association with 1-year-all-cause mortality.

Figure 3 shows the cumulative incidence curves for the long-term outcomes and adjusted HR [95% confidence interval (CI)] from the Cox proportional hazard models for AHF patients stratified by number of NCCs. Compared with patients without NCCs, used as reference in this analysis, HRs for 1-year all-cause mortality gradually increased with number of NCCs, HR = 2.1; (95% CI = 1.7–2.5) for 1 NCC, HR = 2.3; (CI = 1.9–2.9) for 2 NCCs, HR = 3.3; (CI = 2.6–4.1) for 3 NCCs, and HR = 4.0; (CI = 3.2–5.0) for \geq 4 NCCs (Figure 3). This association persisted after stratification by EF categories (Figure 4). The association of each individual NCC with the 1-year all-cause mortality in the three EF categories (Figure 4) showed that the prognostic role of the individual NCCs varied substantially in AHF patients stratified by EF. Association between each individual NCC and CV mortality and HF hospitalization is presented for each category of EF in Supplementary material online, Figure S5.

Discussion

The current analysis from ESC-HF-LT Registry represents the largest and most comprehensive study in an AHF population with HFpEF, HFmrEF, and HFrEF, on prevalence of, associations with, and in-hospital course and post-discharge prognostic role of, a large number of NCCs. The main findings were as follows: (i) the prevalence of 0, 1, 2, 3, and \geq 4 NCCs was 20%, 28%, 23%, 15%, and 13%, respectively, and the most common NCCs were anaemia, diabetes, and kidney dysfunction; (ii) a greater number of NCCs were associated at admission with higher age, higher EF, longer duration of HF and more severe HF, ischaemic heart disease, less use of disease modifying HF medications, and more use of loop diuretics; (iii) patients with higher comorbidity score had greater in-hospital mortality, longer LOS, less intensification of HF therapy and more severe NYHA class, and greater residual congestion at discharge; (iv) a greater number of NCCs were independently associated with higher risk of post-discharge all-cause death and hospitalization and CV death and HF hospitalization, with the greatest impact on all-cause death; and (v) the associations with in-hospital and post-discharge outcomes varied by EF, with hepatic and kidney dysfunction associated with the greatest risk overall.

In this registry, 80% of patients admitted for AHF had at least one NCC, a proportion higher than reported in ambulatory patients from ESC-HF-pilot study.¹³ This suggests not only that AHF is a marker of increased risk but also NCCs are associated with greater risk of HF hospitalization. Similarly to the ASCEND-HF trial,¹⁶ in our registry, patients with higher NCC score were older, more commonly having HFpEF, and presenting with worsening HF of longer duration. They had smaller LV diameters but larger LA dimensions and notably, more likely associated with moderate/severe TR. A larger LA size



with normal LV dimensions typically characterizes HFpEF,⁵ a phenotype more prevalent than HFrEF in patients with high comorbidity score. The different pathophysiologic mechanisms associated to the two phenotypes, as well as the higher prevalence of AF,²⁶ may explain echocardiographic abnormalities reported in patients with higher NCC score.

The prevalence of some NCCs that varied substantially among EF categories, COPD, anaemia, PVD, sleep apnoea, rheumatoid arthritis, stroke/TIA, Parkinson, and depression were more prevalent in HFpEF, while diabetes, kidney dysfunction, and liver dysfunction were more frequent in HFrEF. In a previous analysis from ESC-HFA HF-LT Registry,²³ patients with AHF and HFpEF had older age, finding that may explain the higher prevalence of stroke/TIA, Parkinson, and depression, while a higher body mass may explain the association with sleep apnoea.²⁷ Other comorbidities, such as anaemia, COPD, and rheumatoid arthritis, interrelate with HFpEF substrate by several common mechanisms, especially inflammation.²⁷ In patients with HFrEF, a higher prevalence of diabetes might relate to ischaemic heart disease, more prevalent among HFrEF.²³ Furthermore, in addition to diabetes, patients with HFrEF as compared to those with HFpEF have higher neurohormonal activation,^{7,27} sympathetic and renin-angiotensin-aldosterone systems, which may contribute to more frequent kidney dysfunction.

Overall, the prevalence of the most common NCCs, such as anaemia, renal dysfunction and diabetes was similar to that reported by the contemporary global REPORT-HF registry.¹⁶ However, the

prevalence of NCCs was higher than reported by clinical trials.^{16,28} To note, in ASCEND-HF trial,¹⁶ all reported NCCs were less prevalent, except anaemia (60.3% vs. 45.4%), but this disparity is explained by different definitions and more restrictive inclusion criteria used in clinical trial compared to registry.

The proportion of patients treated with i.v. diuretics increased in parallel with number of NCCs, but clinical improvement and successful decongestion were nevertheless less often achieved in these patients. Some particular NCCs and possible their aggregation in a specific patient may limit the possibility of achieving decongestion. In a previous analysis of the ESC-HF-LT registry, moderate/severe TR, more severe NYHA class, worsening vs. *de novo* HF, anaemia, diabetes, and no beta-blockers at admission were independent predictors of residual congestion at discharge after multivariable adjustment analysis.²² Notably, inadequate decongestion was reported despite of a median LOS that was longer in patients with multiple NCCs. Comorbidities contribute directly to prolonged hospitalization, and COPD, liver and renal dysfunction, and signs of right HF were associated to longer LOS in AHF patients in different studies.^{28,29} Increasing prevalence of these high-risk variables in addition to older age and more altered biological profile at admission may explain why in-hospital mortality increases considerably with number of NCCs, from 1.8% to 7.8%.

Despite of the potential survival benefit associated with optimal dosing of HF therapies, the results of the present analysis are in the line with

Table 1 Epidemiology and baseline characteristics by number of non-cardiac comorbidities

	0 NCC (n = 1906)	1 NCC (n = 2657)	2 NCC (n = 2156)	3 NCC (n = 1441)	≥ 4 NCC (n = 1166)	P-value
Age	65.0 [56.0, 75.0]	69.0 [59.0, 78.0]	71.0 [62.0, 79.0]	73.0 [64.0, 80.0]	74.0 [67.0, 80.0]	<0.001
Age > 65 years (%)	50.8	60.6	67.7	74.3	80.3	<0.001
Female (%)	36.7	38.9	35.7	38.5	36.4	0.154
History (%)						
De novo HF	40.0	34.2	26.9	23.6	16	<0.001
Worsening HF	60.0	65.8	73	76.4	84	<0.001
HF diagnosis > 12 m	27.0	28.9	34.1	33.0	37.6	<0.001
Previous MI	46.9	51.4	55.0	58.6	63.6	<0.001
PCI	19.6	18.9	21.6	22.7	24.3	0.001
CABG	4.9	8.5	12.1	13.4	18.4	<0.001
PM	3.9	5.2	7.7	8.4	9.0	<0.001
CRT/ICD	8.1	9.1	9.2	9.1	10.4	0.06
Valvular surgery	4.2	6.5	6.4	6.5	6.4	0.08
Comorbidities						
Anaemia	0	36.8	58.8	70.7	77.0	<0.001
Diabetes	0	26.9	47.1	63.8	75.1	<0.001
PVD	0	4.3	12.0	25.9	54.4	<0.001
Stroke/TIA	0	4.3	11.8	18.8	40.0	<0.001
Rheumatoid arthritis	0	0.6	1.5	3.5	8.1	<0.001
CKD	0	7.8	28	40.4	71.4	<0.001
Hepatic dysfunction	0	2.6	6.2	11.1	25.2	<0.001
COPD	0	10.5	21.2	31.2	52.5	<0.001
Sleep apnoea	0	1.0	2.7	5.1	8.1	<0.001
Parkinson	0	0.3	0.8	1.5	5.7	<0.001
Depression	0	2.9	5.8	10.8	29.0	<0.001
Current malignancy	0	1.7	4.5	8.3	12.5	<0.001
Primary aetiology (%)						
Ischaemic heart disease	56.6	58.1	54.4	75.8	63.5	<0.001
Hypertension	8.1	7.8	8.9	6.1	5.2	<0.001
Dilated cardiomyopathy	13.6	15.0	13.1	12.1	14.7	0.266
Valve disease	12.0	7.6	13.0	6.1	10.6	<0.001
Other	9.7	11.5	10.6	0.0	6.0	<0.001
Clinical presentation						
Pulmonary oedema	10.1	13.3	12.8	12.9	13.0	
Cardiogenic shock	2.5	2.5	2.5	2.1	3.1	
Decompensated HF	61.9	60.9	64.3	65.9	63.9	
Hypertensive HF	5.9	5.4	4.8	4.4	3.0	
Right HF	1.8	2.6	3.1	4.0	3.9	

Continued

Table 1 Continued

	0 NCC (n = 1906)	1 NCC (n = 2657)	2 NCC (n = 2156)	3 NCC (n = 1441)	≥ 4 NCC (n = 1166)	P-value
SBP (mmHg)	130.0 [110.0, 150.0]	130.0 [110.0, 150.0]	130.0 [110.0, 150.0]	130.0 [110.0, 150.0]	130.0 [112.0, 150.0]	0.640
Body weight (kg)	80.0 [70.0, 90.0]	80.0 [70.0, 90.0]	80.0 [70.0, 90.0]	80.0 [70.0, 90.0]	82.0 [71.0, 92.0]	<0.001
HR (beats/min)	85.0 [70.0, 104.0]	88.0 [74.0, 108.0]	87.0 [70.8, 102.0]	85.0 [70.0, 100.0]	84.0 [70.0, 100.0]	<0.001
Biology						
Creatinine (mg/dL)	1.0 [0.8, 1.2]	1.1 [0.9, 1.3]	1.2 [1.0, 1.6]	1.4 [1.1, 1.9]	1.6 [1.2, 2.1]	<0.001
BUN (mg/dL)	21.5 [16.4, 28.5]	23.0 [17.1, 28.2]	25.5 [20.0, 38.0]	31.0 [21.0, 46.0]	35.1 [24.6, 53.3]	<0.001
Sodium (mmol/L)	139.0 [137.0, 141.0]	139.0 [135.0, 141.0]	138.0 [135.0, 141.0]	138.0 [135.0, 141.0]	138.0 [134.0, 140.2]	<0.001
Glycaemia (mg/dL)	93.3 [85.0, 105.0]	99.0 [87.0, 118.3]	103.3 [90.0, 130.0]	110.0 [91.7, 140.0]	116.0 [93.3, 145.0]	<0.001
Haemoglobin (g/dL)	14.2 [13.3, 15.1]	13.1 [11.8, 14.4]	12.2 [11.0, 13.6]	11.6 [10.2, 13.0]	11.5 [10.0, 12.7]	<0.001
BNP (pg/mL)	699.5 [382.8, 1433.1]	832 [350.0, 1420.0]	794.0 [333.0, 1393.0]	725.0 [359.0, 1377.0]	902.9 [428.8, 2131.2]	<0.001
NT-proBNP (pg/mL)	2768.0 [1210.5, 5576.0]	3268.0 [1733, 8352.8]	3966.5 [1729.5, 8758.5]	4663.0 [2107.8, 10362.0]	5173.0 [2096, 9113.0]	<0.001
ECG						
AF (%)	30.0	32.0	33.3	32.6	33.9	<0.001
QRS duration (ms)	104.0 [88.0, 121.0]	100.0 [86.0, 120.0]	100.0 [86.0, 122.0]	100.0 [84.0, 124.0]	100.0 [85.0, 130.0]	0.465
QT duration (ms)	392.0 [350.5, 420.0]	386.0 [328.0, 425.0]	388.0 [331.0, 426.0]	395.0 [320.0, 428.0]	400.0 [382.0, 440.0]	<0.001
LBbB (%)	14.5	14.8	13.8	16.6	18.6	0.003
Echo						
EF	36.0 [28.0, 50.0]	39.0 [30.0, 50.0]	40.0 [30.0, 52.0]	40.0 [30.0, 54.0]	40.0 [30.0, 56.0]	<0.001
EF <41% (%)	62.4	58.9	57.2	56.6	50.4	
EF = 41–49% (%)	11.6	13.5	12.9	10.5	10.0	
EF ≥ 50% (%)	26.0	27.6	29.9	32.9	39.6	
LVEDD (mm)	59.6 [53.0, 67.0]	58.0 [52.0, 66.0]	58.0 [52.0, 65.0]	58.0 [51.0, 65.0]	56.4 [51.0, 63.7]	0.01
LA dimension (mm)	4.6 [4.2, 5.1]	4.6 [4.1, 5.2]	4.7 [4.2, 5.2]	4.8 [4.3, 5.3]	4.8 [4.2, 5.3]	0.045
Mitral regurgitation (%) moderate–severe	47.9	51.9	51.0	53.2	52.6	0.144
Tricuspid regurgitation (%) moderate–severe	28.2	32.2	36.8	38.7	40.8	<0.001

ACSs, acute coronary syndromes; AF, atrial fibrillation; BNP, brain natriuretic peptide; CKD, chronic kidney dysfunction; COPD, chronic obstructive pulmonary dysfunction; CRT, cardiac resynchronization therapy; CS, cardiogenic shock; ICD, internal cardiac defibrillator; HTN, hypertension; LBbB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; PCI, percutaneous coronary intervention; PM, pacemaker; PVD, peripheral vascular disease; SBP, systolic blood pressure; VTE, venous thrombo-embolism; TIA, transient ischaemic attack.

Table 2 Intravenous vasoactive therapies, interventions, and oral CV therapies during hospitalization

	0 NCC (n = 1906)	1 NCC (n = 2657)	2 NCC (n = 2156)	3 NCC (n = 1441)	≥4 NCC (n = 1166)	P-value
i.v. therapies (%)						
Inotropes	9.	10.7	11.0	13.6	17.4	<0.001
Vasodilators	17.3	19.7	19.6	20.4	17.7	0.082
Diuretics	74.2	79.5	82.8	85.1	88.2	<0.001
Interventions (%)						
Coronary angiography	35.7	27.5	21.6	17.8	17.1	<0.001
PCI	15.9	10.8	10.3	9.4	8.2	<0.001
EPS	1.0	0.6	0.4	0.2	0.1	0.002
Transcatheter ablation	1.0	0.5	0.4	0.3	0.0	0.5
Right heart catheterization	3.2	2.3	2.4	1.6	1.4	0.005
IABP	1.2	0.8	0.8	0.7	1.1	0.53
CRT	2.9	4.3	4.7	4.8	4.3	0.155
ICD	6.3	6.5	7.2	6.7	6.5	0.105
Oral CV therapies (%)						
BB admission	56.2	55.9	59.5	59.0	54.4	<0.001
BB discharge	83.1	78.9	75.1	71.5	63.4	<0.001
ACE/ARBs admission	59.2	59.5	64.1	56.3	55.9	<0.001
ACE/ARBs discharge	84.3	79.8	75.2	68.2	65.2	<0.001
ARNI admission	0.6	0.6	2.2	0.0	0.0	0.284
ARNI discharge	1.7	2.6	3.3	2.3	1.1	0.861
MRA admission	33.6	36.2	33.9	33.5	33.1	<0.001
MRA discharge	62.3	61.5	57.9	47.1	41.2	<0.001
Ivabradine admission	1.2	1.4	1.9	1.8	1.9	0.421
Ivabradine discharge	3.3	3.5	3.6	3.9	4.5	0.725
Digoxin admission	15.9	17.9	18.3	21.1	17.7	0.009
Digoxin discharge	21.9	25.1	22.7	23.8	21.3	0.072
Diuretic admission	42.1	51.4	59.8	64.4	71.3	<0.001
Diuretic discharge	73.9	80.0	81.2	83.5	84.8	<0.001

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitors; BB, betablocker; CRT, cardiac resynchronization therapy; EPS, electrophysiological studies; IABP, intra-aortic balloon pump; ICD, intracardiac defibrillator; IABP, intra-aortic balloon pump; ICD, intracardiac defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary interventions.

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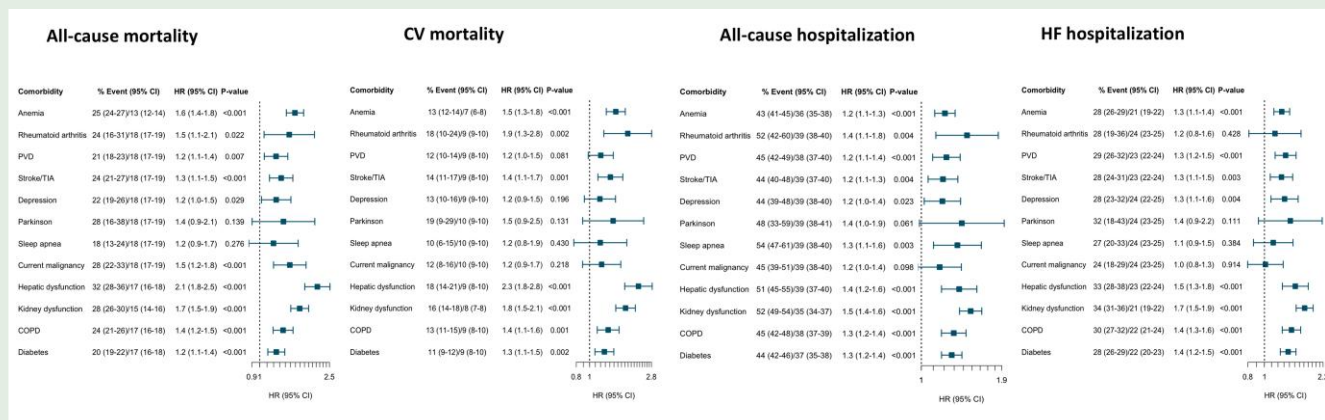


Figure 2 Associations between each individual non-cardiac comorbidities and long-term outcomes. Data are presented with % (95% confidence interval) with event in the variable yes/no and heart failure. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; NCC, non-cardiac comorbidity; PVD, peripheral vascular disease; TIA, transient ischaemic attack; HR, heart failure.

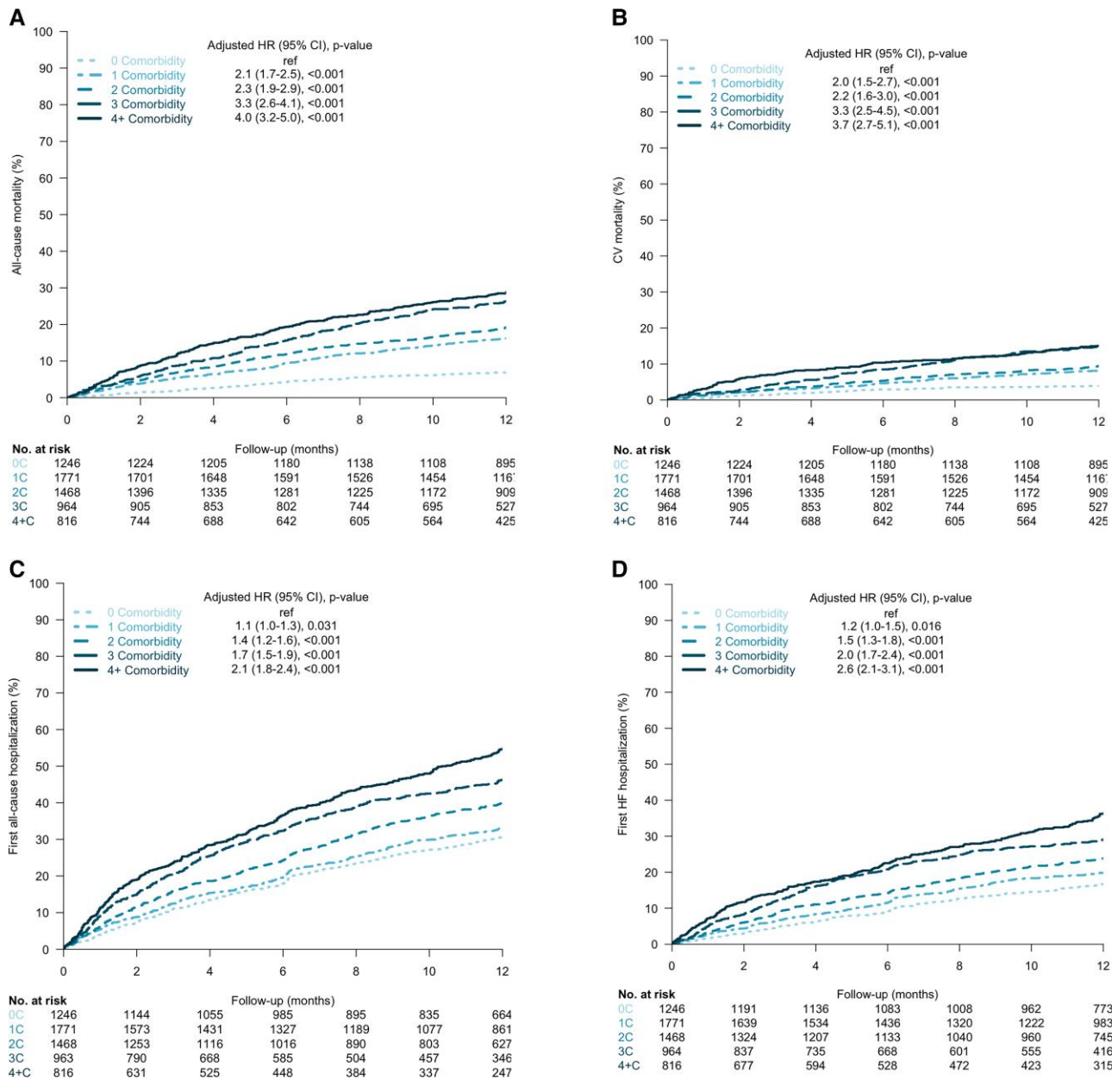


Figure 3 Cumulative incidence curves for the long-term outcomes and adjusted hazard ratio (95% confidence interval) from the Cox proportional hazard models for acute heart failure patients stratified by number of non-cardiac comorbidities. (A) All-cause mortality; (B) cardiovascular mortality; (C) all-cause hospitalization; (D) heart failure-hospitalization. CI, confidence interval; NCC, non-cardiac comorbidity; HR, hazard ratio; AHF, acute heart failure.

the multiple observations showing that suboptimal dosing of HF therapies is highly prevalent. Patient factors (e.g. older age, comorbid diseases, intolerance or contraindications, and medication cost) and physician factors (e.g. clinical inertia) have been suggested as potential reasons for suboptimal dosing of HF therapy.³⁰

Heart failure therapies at discharge were associated with lower 1-year mortality in patients with recent AHF, regardless of EF or the presence of comorbidities³¹ and in recent STRONG-HF trial, a rapid and intensified up-titration of neurohormonal antagonists at and early after discharge were associated with improved outcome.³² Also, in patients with HFrEF, benefits of ICD therapy in

primary prevention were seen on different strata of comorbidity burden.³³

We found a consistent and strong association between the number of NCCs and all long-term outcomes, irrespective of EF category and consistent with previous studies in patients with chronic^{9,13-15} and acute HF.^{16,17}

An important strength of the current analysis is the in-depth characterization of the association between each individual NCCs and the clinical outcomes, overall and in the three EF categories. In the whole population, anaemia, stroke/TIA, hepatic dysfunction, kidney dysfunction, and diabetes have been associated with all long-term outcomes.

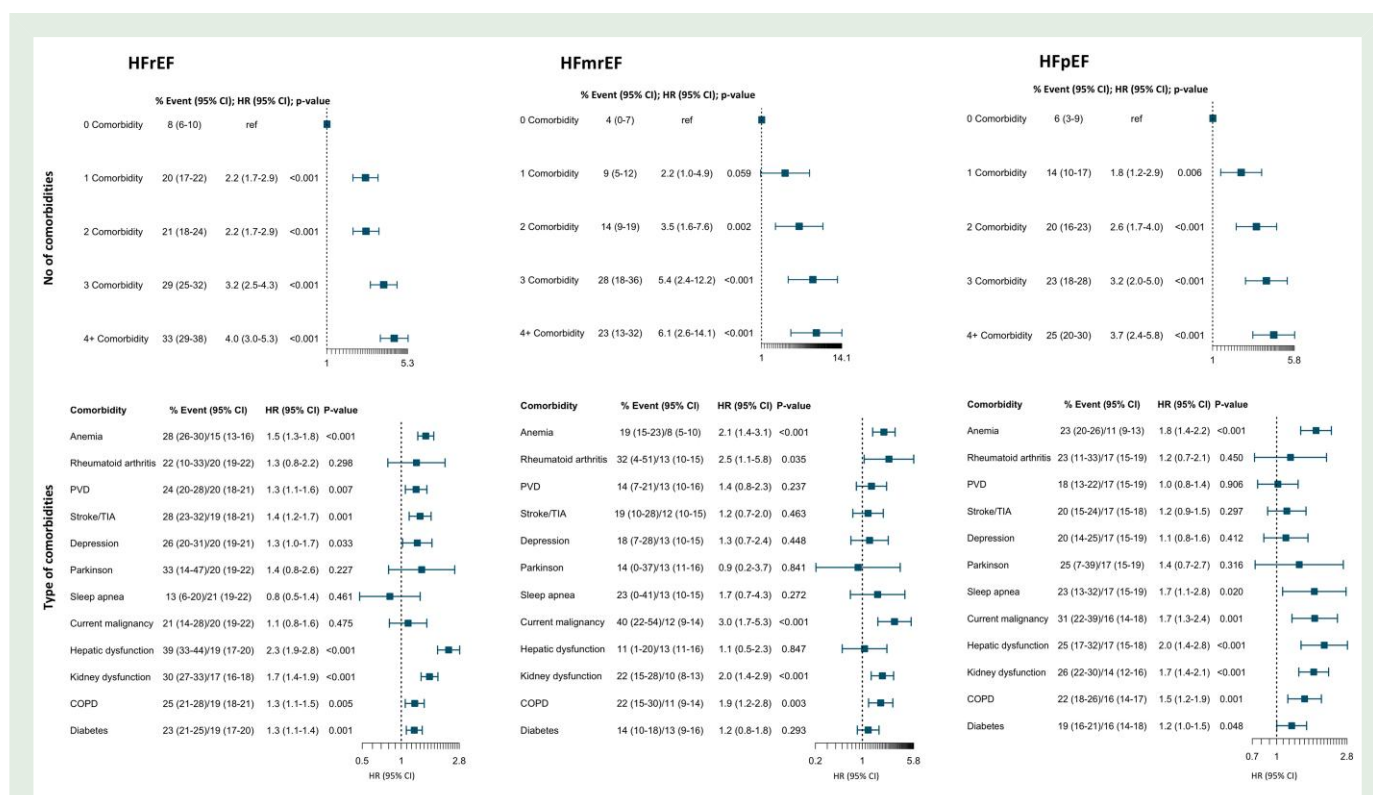


Figure 4 The association of the number of comorbidities and each non-cardiac comorbidity separately with the all-cause mortality in the three ejection fraction categories. Data are presented with % (95% confidence interval) with event in the variable yes/no and heart failure. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; NCC, non-cardiac comorbidity; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

Several other comorbidities, such as PVD, depression, and current malignancy were associated with the risk of all-cause mortality but not to CV mortality (Figure 2). This can be relevant for the understanding of the results of RCTs, which typically include younger patients without significant co-morbidities and more severe HF and have a composite of CV mortality or HF hospitalization as the primary endpoint. When included in future RCTs, these comorbidities may particularly increase the number of non-CV deaths and non-HF hospitalizations and may dilute the benefits of the investigated study intervention on CV outcomes. Even if a trial is favourable on CV events, the total burden of HF is not relevantly impacted due to the high rate of NCCs and their negative outcomes' consequences. Also, from a clinical practice perspective, translation of RCT results in an unselected HF population is not rigorously evidence-based, and assumption of a similar efficacy in HF patients, who usually have a higher comorbidity burden, is mostly based on extrapolations of these data, and the true benefit should be proved.

Of all comorbidities, hepatic and kidney dysfunction had the strongest association with both all-cause and CV-mortality, in both HFrEF and HFpEF patients. The two comorbidities are highly suggestive of systemic congestion, which is the main driver of the post-discharge outcomes, irrespective of EF.²²

Of note, each category of EF had a different risk profile associated with the individual NCCs. Peripheral vascular disease, stroke/TIA, and depression were associated with all-cause mortality only in patients with HFrEF, while sleep apnoea and current malignancy were only in patients with HFpEF. Diabetes was strongly associated to HF-hospitalization in any EF category, but less consistent with CV mortality in HFrEF and HFpEF. Patients with HFrEF are relatively homogenous, with the same comorbidities being associated to CV mortality and

HF-hospitalization, while in HFpEF, there are differences among comorbidities predictive for CV mortality or HF-hospitalization (see Supplementary material online, Figure S5). Identification of the comorbidities that are predictors of the specific outcomes may provide opportunities to explore potential interactions between possible treatment effects and cause-specific risk in each category of EF. This finding may probably explain the greater effect on HF hospitalization than on CV mortality in the RCTs including HFpEF patients.

On the basis of our findings, a greater focus on the recognition and treatment of comorbidities in all EF categories is justified. This approach may be particularly relevant for HFpEF where only SGLT2-inhibitors have been shown to improve outcomes but also for HFrEF where the burden of NCCs was also high and may interfere with optimization of guideline-directed medical therapy.

Interestingly, the individual comorbidities have a stronger association (higher odds ratios) with in-hospital mortality than with 1-year mortality. The presence of comorbidities may confer a particular vulnerability to worsening HF leading to admission, process attenuated during follow-up. It cannot be excluded that i.v. vasoactive therapies may worsen some comorbidities or interfere with their treatment.

Nevertheless, the mechanisms leading to the increased mortality risk observed in AHF patients with multiple comorbidities are probably multifactorial.³⁴ Although individual NCCs *per se* were previously³⁰ and in our study associated to long-term mortality, it remains unknown whether this represents primarily a clinical interaction between HF and the NCCs or some confounding related to lower use or poor tolerability of HF medications, or possibly some interaction with medications used to treat these comorbidities or with polypharmacy. To note, some NCCs may cluster and potentiate each other, and

their association may increase the overall risk beyond the risk of each NCC, creating high risk subgroups.¹⁸ In addition, patients with AHF and more NCCs have a higher probability of residual congestion at discharge, factor associated with long-term mortality.^{22,35,36}

Defining the prognostic role of comorbidities in AHF might help to improve assessment of patients' vulnerability and to inform in-hospital and post-discharge management and referrals. In addition to optimization of HF therapies, NCC management during HF hospitalization may improve outcomes and warrants evaluation in prospective studies. While severe comorbidities may impact eligibility for HF therapies, it is important to optimize medical therapy as tolerated and reduce clinical risk and to use admission as a trigger to initiate HF therapies with proven benefit that would permit long-term exposure to therapeutic beneficial effects.^{30,31}

When cardiac surgery is indicated, the association of the multiple and severe NCCs may place HF patient in a very-high/prohibitive surgical risk, which requires further evaluation for percutaneous interventions, either coronary, or valvular or palliative care.

Furthermore, since AHF patients with high NCC score are discharged with residual congestion, suboptimal therapeutic regimen, and have poor post-discharge outcome, an intensified follow-up visits program is required. All these results highlight the need for multidisciplinary team-based care and improved co-ordination with primary care and other specialists to manage these complex patients.

Future trials should focus on the comprehensive management of the patients with AHF with multiple comorbidities, rather than to study the isolated effects of single drugs in younger patients with few or no comorbidities. These trials should include HF patients with comorbidities, possibly applying complex interventions that target together CV substrate and associated comorbidities, despite the increased requirements for intensified monitoring and safety evaluations.³⁷

Limitations

The registry included only patients from cardiology departments or specialized HF units (and not internal medicine or geriatric departments), which introduces selection bias and may reduce external validity. Patients admitted to internal medicine or geriatric departments may be expected to be older, with more comorbidities and more often with HFpEF compared to HF patients admitted to cardiology departments.³⁸

Ejection fraction used for classification was based on a single EF assessment during hospitalization and was obtained per local protocol (there was no core laboratory) and without adjudication.

Also, there was no central committee to adjudicate the causes of death and type of rehospitalization.

Since the registry spanned between 2011 and 2018, data about SGLT2 inhibitor utilization are missing.

Other potentially important variables with well-known prognostic importance, such as natriuretic peptide level (data available only for 41% patients at admission), were not selected in adjusted analyses, as data were not available in many patients.

The set of NCCs were obtained from medical history collected in the registry as reported by the investigators. Some comorbidities, particularly kidney and hepatic dysfunction, may reflect both intrinsic organ pathologies as well as the organ dysfunction as result of of congestion or/and hypoperfusion during HF decompensation, but this analysis does not account for the relative contribution of each mechanism. Severity of comorbidities was not collected, and this was not considered to evaluate association with outcomes. Finally, we cannot exclude that some NCCs are under-reported.

Conclusions

In AHF patients enrolled in ESC-HFA EORP-HF-LT Registry, a greater number of NCCs were associated at admission with older age,

preserved EF, more severe NYHA class, and longer duration of HF. Despite of longer hospital stay and a more intense use of i.v. therapies, AHF patients with higher number of NCCs are discharged with sub-optimal HF therapies and more severe NYHA class and residual congestion. In-hospital and post-discharge mortality gradually increased with number of NCCs.

Overall, anaemia, renal dysfunction, and diabetes were the most commonly reported NCCs, but the prevalence of NCCs varied substantially among EF categories.

The association between each individual NCC and post-discharge outcomes varied substantially in AHF patients with HFrEF, HFmrEF, and HFpEF, suggesting that an 'EF-specific' multidisciplinary approach with distinct comorbidity management programs should be applied in post-discharge phase.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

O.C., S.D.A., A.J.S.C., A.M., G.S., M.F., R.F., M.M., G.F., G.M.C.R., A.P.M., and L.H.L. contributed to the conception or design of the work; M.C.-L., T.M., C.M., M.F.P., M.A., F.R., G.S., P.S., M.V., and R.F. contributed to analysis or interpretation of data for the work; L.B. contributed to the statistical analysis; O.C. drafted the manuscript; and O.C. and L.H.L. critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The following research was conducted using data from ESC-HFA EORP Heart Failure Long-Term Registry (2011–2018) on behalf of Executive Committee of the registry. eCRF is found at <https://www.euroheartsurvey.org/Surveys/News.aspx/>, and the R code for all data management and statistical analyses is found at <https://github.com/KIHeartFailure/esccomorb>.

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