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RESEARCH ARTICLE

A comprehensive characterization of acute heart failure with preserved versus mildly reduced versus reduced ejection fraction – insights from the ESC-HFA EORP Heart Failure Long-Term Registry

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Aims To perform a comprehensive characterization of acute heart failure (AHF) with preserved (HFpEF), versus mildly reduced (HFmrEF) versus reduced ejection fraction (HFrEF).

Methods and results Of 5951 participants in the ESC HF Long-Term Registry hospitalized for AHF (acute coronary syndromes excluded), 29% had HFpEF, 18% HFmrEF, and 53% HFrEF. Hospitalization reasons were most commonly atrial fibrillation (more in HFmrEF and HFpEF), followed by ischaemia (HFmrEF), infection (HFmrEF and HFpEF), worsening renal function (HFrEF), and uncontrolled hypertension (HFmrEF and HFpEF). Hospitalization characteristics included lower blood pressure, more oedema and higher natriuretic peptides with lower ejection fraction, similar pulmonary congestion,

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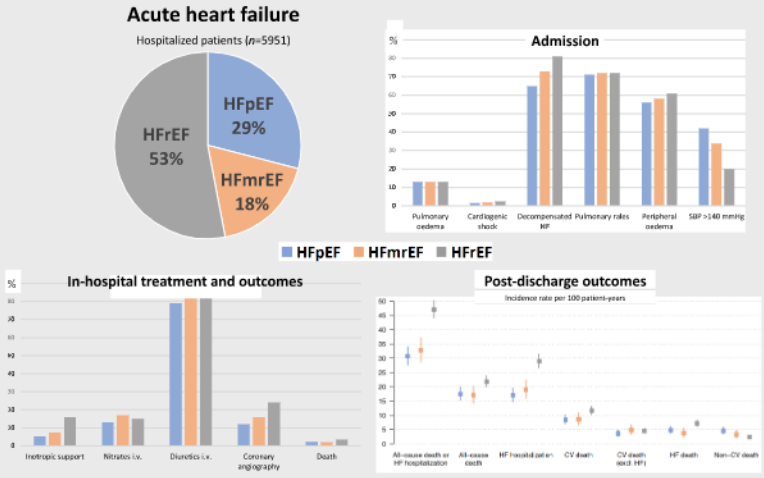
more mitral regurgitation in HFrEF and HFmrEF and more tricuspid regurgitation in HFrEF. In-hospital mortality was 3.4% in HFrEF, 2.1% in HFmrEF and 2.2% in HFpEF. Intravenous diuretic (~80%) and nitrate (~15%) use was similar but inotrope use greater in HFrEF (16%, vs. HFmrEF 7.4% vs. HFpEF 5.3%). Weight loss and estimated glomerular filtration rate improvement were greater in HFrEF, whereas reduction in natriuretic peptides was similar. Over 1 year post-discharge, events per 100 patient-years (95% confidence interval) in HFrEF versus HFmrEF versus HFpEF were: all-cause death 22 (20–24) versus 17 (14–20) versus 17 (15–20); cardiovascular (CV) death 12 (10–13) versus 8.6 (6.6–11) versus 8.4 (6.9–10); non-CV death 2.4 (1.8–3.1) versus 3.3 (2.1–4.8) versus 4.5 (3.5–5.9); all-cause hospitalization 48 (45–51) versus 35 (31–40) versus 42 (39–46); HF hospitalization 29 (27–32) versus 19 (16–22) versus 17 (15–20); and non-CV hospitalization 7.7 (6.6–8.9) versus 9.6 (7.5–12) versus 15 (13–17).

Conclusion In AHF, HFrEF is more severe and has greater in-hospital mortality. Post-discharge, HFrEF has greater CV risk, HFpEF greater non-CV risk, and HFmrEF lower overall risk.

Graphical Abstract



Acute heart failure in patients with preserved (HFpEF), mildly reduced (HFmrEF) and reduced ejection fraction (HFrEF): admission profiles, in-hospital treatment and outcomes.

Keywords Heart failure with mildly reduced ejection fraction • Heart failure with mid-range ejection fraction • Heart failure with preserved ejection fraction • Treatment • Hospitalization • Prognosis

Introduction

Heart failure (HF) is categorized by left ventricular ejection fraction (EF). Based on the 2016 European Society of Cardiology (ESC) guidelines on HF, and extensive subsequent research, there are three distinct entities: HF with EF that is reduced (HFrEF; <40%), mid-range or mildly reduced (HFmrEF; 40%–49%), or preserved (HFpEF; ≥50%).[1] HFmrEF is analogous to the 'borderline' EF category (EF 41%–49%) from the American College of Cardiology Foundation/American Heart Association guidelines.[2] In the 2016 ESC guidelines on HF, HFrEF was <40% and HFmrEF was 40%–49%, but in recent trials, HFrEF was generally defined as ≤40%, and in a recent global consensus statement, HFrEF was defined as ≤40% and HFmrEF as 41%–49%.[1,3,4]

Chronic HFmrEF has been well characterized. It appears intermediate between HFrEF and HFpEF in some regards, but more similar to HFrEF regarding younger age, lower proportion women, and higher prevalence of ischaemic aetiology, and more similar to HFpEF regarding milder HF severity, lower natriuretic peptide concentrations, and lower cardiovascular (CV) risk.[5–7] Effective medical therapy is well established in HFrEF but was unconvincing in HFpEF trials, generally including patients with EF ≥40% or ≥45%.[1] However, post-hoc and subgroup analyses suggest that HF drugs may be effective in HFmrEF.[7–10] Recently, a landmark study with a

sodium–glucose co-transporter 2 inhibitor met its primary endpoint in patients with EF >40%.[11]

In contrast to chronic HF, there is no evidence-based therapy in acute HF (AHF) of any EF.[1] Many trials have included HF regardless of EF, and characterization of HFrEF, HFmrEF, and HFpEF in AHF has not been performed, in particular with regard to in-hospital course and post-hospital outcomes.

The ESC Heart Failure Association (HFA) EURObservational Research Programme (EORP) HF Long-Term Registry is so far the largest international registry of HF patients in Europe. Most reports from the registry have focused on chronic HF, including comparative analyses of ambulatory HF patients stratified by EF category.[5,12,13] The aim of the current analysis was a comprehensive comparison of admission characteristics, in-hospital course, discharge characteristics, and detailed post-discharge cause-specific outcomes in patients hospitalized with acute HFpEF, HFmrEF and HFrEF.

Methods

Study design and patient selection

The ESC-HFA EORP HF Long-Term Registry was an international, multicentre, prospective survey of HF patients, conducted in years 2011–2018 in a broad range of cardiology centres from 33 ESC member countries (online supplementary *Appendix S1*), enrolling adult patients hospitalized for AHF, defined as signs and symptoms of AHF requiring intravenous treatment for HF (specifically inotropes, intravenous vasodilators and/or intravenous diuretics), and outpatients with chronic HF.[5,12,13] A broad spectrum of centres with varied complexity and level of reference was included to represent a balanced proportion across a different range of cardiology facilities. The number of participating centres for each country was decided according to the number of inhabitants in that country.[13] Data on survival and subsequent hospital admissions were obtained either at a follow-up visit or by a telephone call at 12 months. Detailed methodology of the ESC-HFA EORP HF Long-Term Registry was previously described,[5,12,13] and the protocol is available as online supplementary *Appendix S2*. The registry was approved by local ethical review boards according to the regulations of each participating country. All patients gave written, informed consent, unless exempt by the local ethics committee.

The current study was a retrospective analysis of data from the ESC-HFA EORP HF Long-Term Registry, and included patients hospitalized for AHF who had an echocardiogram with EF assessment performed during hospitalization. Patients with acute coronary syndromes (ACS), as well as patients with significant (moderate to severe) aortic stenosis were excluded. Patients were then categorized into three groups: HFpEF (≥50%), HFmrEF (40%–49%), and HFrEF (<40%) (CONSORT diagram, online supplementary *Figure S1*). These three groups were compared with respect to admission characteristics, in-hospital treatment and outcomes, and 1-year cause-specific outcomes. The number of different cause-specific outcomes was extensive: a composite of time to all-cause death or first HF rehospitalization, death from any cause, CV, HF, sudden cardiac, CV other than HF, and non-CV causes, and rehospitalization for any cause, CV, HF, CV other than HF, and non-CV causes.

Laboratory parameters and pharmacotherapy

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Changes in weight and laboratory parameters during hospitalization were calculated as difference between discharge and admission values. Dosing of loop diuretics was given as equivalent to furosemide doses (furosemide 40 mg equivalent to torsemide 10 mg equivalent to bumetanide 1 mg). Target doses of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and beta-blockers were adopted from the 2016 ESC guidelines on HF.[1]

Statistical analysis

Baseline characteristics were at time of hospital admission. Categorical data were presented as percentages and compared with the chi-square test. Continuous variables were reported as median and interquartile range (IQR) or as mean ± standard deviation (SD) as appropriate, and tested with Kruskal–Wallis test.

We report hospital duration and crude in-hospital mortality. Due to the low absolute number of in-hospital deaths, we did not perform an analysis of predictors of in-hospital death in EF subgroups.

Post-discharge outcome analyses were performed excluding patients who died in hospital or were lost to follow-up and the time was calculated from date of discharge. For all post-discharge deaths (except all-cause death) competing causes of death were censored unless stated otherwise. For all post-discharge hospitalizations, deaths were censored but competing hospitalizations were not, i.e. if a patient had e.g. a CV hospitalization the patient continued to be at risk and could experience a later non-CV hospitalization. Post-discharge outcomes were presented as incidence rates per 100 patient-years, calculated with 95% Poisson confidence intervals (CI). Differences between EF groups were tested with log-rank test. Kaplan–Meier curves were plotted for all-cause death and the composite of all-cause death or first HF rehospitalization and cumulative incidence curves, taking into account death as a competing risk, for first HF rehospitalization, the composite of CV death or first HF rehospitalization, non-CV death, and non-CV hospitalization for the three groups.

Multivariable Cox proportional hazards regressions were used (i) to detect independent relationships between EF category and selected post-discharge outcomes (all-cause death, first rehospitalization for HF, all-cause death or first rehospitalization for HF, CV death or first rehospitalization for HF, non-CV death, and non-CV hospitalization), and (ii) to evaluate possible independent predictors of post-discharge long-term outcomes for all-cause mortality and first HF hospitalization within each EF category. For the latter analysis, EF group and the variable presented were modelled using an interaction term, thereby displaying the results in the respective EF groups, at the same time making it possible to test for differences between EF groups. Additional variables included in the Cox regression analysis included baseline characteristics, reason for HF hospitalization, in-hospital treatment, clinical and laboratory status at hospital discharge, and pharmacotherapy at discharge. The variables included in the models were chosen based on clinical relevance, and are listed in online supplementary *Tables S1* and *S2*. Data on discharge concentrations of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) was missing in 84% and therefore natriuretic peptides were not included in the multivariable Cox regression. For patients with missing information on the date of rehospitalization (10% of all rehospitalizations), the time to hospitalization was imputed with half the time to last follow-up. This was

based on the observation that median time to rehospitalization in patients with available dates of rehospitalization, was 0.5 of the time to last follow-up. To avoid bias due to data not missing at random, we performed multiple imputation for the covariates included in the models using Multivariate Imputation by Chained Equations (MICE) for 10 datasets and 10 iterations.[14] Variables included in the imputation model were the same as included in the Cox regression analysis. The death outcome was included as the Nelson–Aalen estimator in the imputation model. The proportional hazards assumption was investigated using the scaled Schoenfeld residuals and possible outliers were visually inspected by plotting the dfbetas. For all tests, the level of significance was set to 0.05, two-sided. No adjustment for multiple comparisons were made and therefore the results should be viewed with some care.

All statistical analyses were conducted using R version 4.0.2 (2020-06-22) (R Core Team 2019). All code used to perform the data handling and statistical analysis can be found at https://github.com/KIHeartFailure/characteristicsOutcomesHeartFailureESC.

Results

Study population

A total of 25 621 patients were included in the ESC-HFA EORP HF Long-Term Registry between March 2011 and September 2018. Of those, 10 879 patients (43%) were hospitalized for AHF, including 8557 with EF assessed during hospitalization. After excluding 2015 patients with ACS and 591 patients with moderate to severe aortic stenosis, there were 5951 patients left for the current analysis, 1729 (29%) had HFpEF, 1082 (18%) HFmrEF, and 3140 (53%) HFrEF (*Figure S1*).

Admission characteristics and precipitating factors

Table 1 presents admission characteristics (time of hospitalization). HFmrEF was intermediate regarding age, proportion with female sex, prevalence of hypertension, previous coronary revascularization and number of non-cardiac comorbidities. HFrEF and HFmrEF more commonly had underlying ischaemic aetiology of HF, while HFpEF and HFmrEF more often were overweight and had a history of atrial fibrillation (AF). AF was the most common precipitating reason for admission and more so in HFmrEF and HFpEF; myocardial ischaemia was more common in HFmrEF; infection, uncontrolled hypertension and bradyarrhythmia were more common in HFmrEF and HFpEF, whereas worsening renal function and ventricular arrhythmia were more common in HFrEF. Regarding primary clinical profile at presentation, the frequency of decompensated HF was higher, whereas that of hypertensive HF and right ventricular HF was lower with progressively lower EF. Pulmonary oedema was as frequent (13%) in all three groups. The prevalence of cardiogenic shock was low in all three groups (2.4% in HFrEF, 1.8% in HFmrEF and 1.6% in HFpEF, $p = 0.11$). New York Heart Association (NYHA) class, tricuspid regurgitation and peripheral oedema were worse in HFrEF, and the frequency of moderate-to-severe mitral regurgitation as well as concentrations of natriuretic peptides were higher with lower EF, although pulmonary rales (~70%) and pulmonary congestion on chest X-ray (~65%) were similar in all three groups. Systolic blood pressure was progressively 10 mmHg higher with each EF category, while heart rate was comparable between the three groups. *Figure 1* shows percent prevalence of select admission characteristics by EF category.

Hospital course

*Figure 2*A shows hospital interventions and outcomes. Median hospital stay was 7 days in all three groups (IQR 5–11 overall; 5–11 in HFrEF; 5–10 in HFmrEF and 4–11 in HFpEF). The proportion of patients with hospital stay >7 days was greater in HFrEF, but the mean hospital stay was shorter in HFrEF (10.3 ± 20.5 days) than in HFmrEF (11.2 ± 30.2 days) and HFpEF (11.5 ± 35.4 days; overall $p = 0.048$). Of 5951 patients, 169 (2.8%) died during hospitalization (3.4% of HFrEF patients, 2.1% of HFmrEF, 2.2% of HFpEF; $p = 0.01$). One patient had missing data on vital status at discharge, and 5781 patients survived to hospital discharge. All patients received some intravenous treatment (a criterion for enrolment in the registry with AHF), with similar use of diuretics and vasodilators in all three EF categories, but about three-fold more use of inotropes in HFrEF compared to HFmrEF and HFpEF.

During hospitalization, an improvement in symptoms of at least one NYHA class was more often achieved in HFpEF (77%) and HFmrEF (77%) than in HFrEF (71%, $p < 0.001$). *Figure 2*B shows in-hospital vital and laboratory changes in percent, with a greater absolute and relative weight loss in HFrEF [2.6 ± 3.7 kg (3.1%) vs. 2.1 ± 3.8 kg (2.5%) in HFpEF and 1.9 ± 4.6 kg (2.2%) in HFmrEF, $p = 0.003$ for absolute changes; $p = 0.008$ for percent changes]; an increase in serum sodium in HFpEF and HFmrEF but not HFrEF; more improvement in eGFR in HFrEF [an increase of 0.7 ± 14.9 ml/min/1.73 m^2 (15%) vs. 0.1 ± 13.7 ml/min/1.73 m^2 (5.1%) in HFmrEF vs. a reduction of 0.5 ± 13.7 ml/min/1.73 m^2 (an increase of 4.6%) in HFpEF, $p = 0.03$ for absolute changes; $p = 0.09$ for percent changes]; and more haemoconcentration (greatest increase in haemoglobin) in HFpEF. There was a similar reduction in absolute concentrations of NT-proBNP in all groups (1990 ± 3722 pg/ml in HFpEF, 1903 ± 5803 pg/ml in HFmrEF and 1926 ± 6718 pg/ml in HFrEF, $p = 0.69$), with a percent reduction from baseline twice as high in HFpEF (31%) as in HFmrEF (14%) and HFrEF (15%), although the difference did not reach statistical significance ($p = 0.44$) due to low number of paired data (92% of data missing for admission and/or discharge NT-proBNP). An absolute reduction in BNP was greater in HFrEF (541 ± 1578 pg/ml) than in HFmrEF (262 ± 601 pg/ml) and HFpEF (226 ± 637 pg/ml, $p < 0.001$), but percent reduction was comparable (23% in HFrEF, 19% in HFmrEF and 18% in HFpEF, $p = 0.12$; 95% of admission and/or discharge BNP missing). There were no changes in mean potassium concentrations during hospitalization in any of the three groups (values were missing for 23% of patients). Discharge characteristics of patients who survived are presented in online supplementary *Table S3*.

Post-discharge cause-specific outcomes

Data on 1-year follow-up were available for 4051 of the 5781 patients who survived to hospital discharge (70%). Median

Table 1 Baseline characteristics (time of hospital admission) of patients with acute heart failure in relation to ejection fraction category

Variable	HFpEF (n = 1729, 29%)	HFmrEF (n = 1082, 18%)	HFrEF (n = 3140, 53%)	p-value	Pairwise comparisons (P-HFpEF, M-HFmrEF, R-HFrEF)
Age, years, median [IQR]	74 [64–81]	71 [62–79]	66 [57–75]	<0.001	P > M > R
Age ≥65 years	75%	69%	54%	<0.001	P > M > R
Female sex	56%	40%	25%	<0.001	P > M > R
BMI ≥25 kg/m^2	75%	76%	72%	0.01	P, M > R
Weight, kg, median [IQR]	78 [68–90]	80 [70–90]	80 [71–90]	<0.001	P < M, R
Previous HF history	65%	69%	79%	<0.001	P < M < R
Previous HF hospitalization	33%	36%	43%	<0.001	P, M < R
Primary HF aetiology					
Ischaemic heart disease	31%	52%	54%	<0.001	P < M, R
Dilated cardiomyopathy	4.2%	11%	29%	<0.001	P < M < R
Valve disease	20%	14%	6.2%	<0.001	P > M > R
Hypertensive	22%	11%	4.0%	<0.001	P > M > R
Hypertension history	74%	68%	58%	<0.001	P > M > R
Prior PCI	9.1%	15%	22%	<0.001	P < M < R
Prior CABG	6.8%	11%	15%	<0.001	P < M < R
Pacemaker	7.7%	10%	5.7%	<0.001	R < P < M
ICD/CRT-D/CRT-P	1.8%	4.2%	19%	<0.001	P < M < R
Atrial fibrillation	58%	56%	44%	<0.001	P, M > R
Paroxysmal/persistent	21%	19%	16%	<0.001	P, M > R
Permanent	37%	36%	28%	<0.001	P, M > R
Previous stroke/TIA	13%	10%	9.4%	0.002	P > M, R
Peripheral vascular disease	12%	12%	14%	0.19	P, M, R
Diabetes	34%	38%	35%	0.14	P, M, R
Previous venous thromboembolism	5.3%	4.3%	3.7%	0.02	P > R
Chronic kidney disease	24%	23%	26%	0.06	M < R
COPD	20%	19%	18%	0.06	P > R
Sleep apnoea	4.4%	3.2%	2.4%	0.001	P > R
Hepatic dysfunction	6.8%	6.1%	7.8%	0.13	P, M, R
Thyroid dysfunction	11%	11%	10%	0.64	P, M, R
Cancer disease	6.3%	5.6%	3.8%	<0.001	P, M > R
Depression	8.4%	5.4%	5.9%	0.001	P > M, R
No. non-cardiac comorbidities, median [IQR]; mean ± SD	2 [1–3]; 2.0 ± 1.5	2 [1–3]; 1.9 ± 1.4	2 [1–3]; 1.8 ± 1.5	0.001	P > R
Current smoking	11%	15%	18%	<0.001	P < M < R
Clinical presentation at hospital admission					
Heart rate, bpm, median [IQR]	83 [70–104]	86 [71–109]	86 [72–102]	0.06	P < M, R
SBP, mmHg, median [IQR]	140 [120–160]	130 [120–150]	120 [110–140]	<0.001	P > M > R
Primary profile at presentation[a]					
Pulmonary oedema	13%	13%	13%	0.85	P, M, R
Cardiogenic shock	1.6%	1.8%	2.4%	0.11	P, M, R
Decompensated HF	65%	73%	81%	<0.001	P < M < R
Hypertensive HF	13%	7.3%	2.5%	<0.001	P > M > R
Right ventricular HF	7.4%	5.0%	1.5%	<0.001	P > M > R
NYHA class				<0.001	
II	24%	22%	14%		P, M > R
III	49%	52%	50%		P, M, R
IV	27%	26%	36%		P, M < R
Pulmonary rales	71%	72%	72%	0.57	P, M, R
Pulmonary congestion/alveolar oedema on chest X-ray[b]	64%	63%	66%	0.31	P, M, R
Peripheral oedema	56%	58%	61%	0.001	P < R

Table 1 (Continued)

Variable	HFpEF (n = 1729, 29%)	HFmrEF (n = 1082, 18%)	HFrEF (n = 3140, 53%)	p-value	Pairwise comparisons (P-HFpEF, M-HFmrEF, R-HFrEF)
Reason for index HF decompensation, precipitating factors[c]					
Atrial fibrillation	41%	42%	30%	<0.001	P, M > R
Myocardial ischemia	15%	26%	20%	<0.001	P < R < M
Infection	21%	20%	17%	0.001	P, M > R
Worsening renal function	16%	15%	18%	0.045	M < R
Uncontrolled hypertension	23%	19%	8.7%	<0.001	P > M > R
Anaemia	17%	14%	11%	<0.001	P > M, R
Ventricular arrhythmia	5.4%	5.4%	7.8%	0.002	P, M < R
Patient non-compliance	5.7%	7.0%	6.3%	0.39	P, M, R
Bradyarrhythmia	5.2%	4.5%	1.9%	<0.001	P, M > R
Iatrogenic	1.7%	1.1%	1.1%	0.18	P, M, R
Laboratory findings at hospital admission					
NT-proBNP[d], pg/ml, median [IQR]; mean ± SD	2590 [1206–5868]; 5348 ± 7799	3054 [1353–8044]; 6174 ± 7754	4524 [1964–9100]; 8105 ± 16 903	<0.001	P, M < R
BNP[d], pg/ml, median [IQR]; mean ± SD	331 [165–735]; 660 ± 1071	529 [286–1040]; 926 ± 1457	965 [532–1762]; 1623 ± 2208	<0.001	P < M < R
Sodium[d], mmol/L, median [IQR]	139 [136–142]	139 [136–142]	138 [135–141]	<0.001	P, M > R
Potassium[d], mmol/L, median [IQR]	4.3 [3.9–4.7]	4.3 [4.0–4.7]	4.3 [3.9–4.7]	0.08	P < R
Creatinine[d], mg/dl, median [IQR]	1.1 [0.9–1.4]	1.1 [0.9–1.5]	1.2 [1.0–1.6]	<0.001	P < M < R
eGFR[d], ml/min/1.73 m^2, median [IQR]	59 [42–78]	58 [41–78]	59 [41–79]	0.83	P, M, R
Urea[d], mg/dl, median [IQR]	33 [21–52]	30 [20–48]	36 [22–55]	<0.001	M < P < R
Bilirubin[d], mg/dl, median [IQR]	0.8 [0.5–1.1]	0.9 [0.6–1.3]	1.0 [0.7–1.5]	<0.001	P < M < R
Haemoglobin[d], g/dl, median [IQR]	12.5 [10.9–13.9]	12.7 [11.2–14.1]	13.1 [11.7–14.5]	<0.001	P < M < R
Electrocardiogram during hospitalization[e]					
Rhythm[a]					
Sinus	48%	48%	56%	<0.001	P, M < R
Atrial fibrillation/flutter	45%	42%	31%	<0.001	P, M > R
Paced	6.2%	9.3%	12%	<0.001	P < M < R
LBBB[f]	5.9%	12%	24%	<0.001	P < M < R
Echocardiography during hospitalization[e]					
EF, %, median [IQR]	56 [52–60]	44 [40–45]	28 [21–34]	<0.001	P > M > R
LVEDD[g], mm, median [IQR]	51 [45–56]	57 [51–61]	64 [59–70]	<0.001	P < M < R
LV hypertrophy[g]	50%	48%	33%	<0.001	P, M > R
LAVI[g], ml/m^2, median [IQR]; mean ± SD	34 [23–48]; 40 ± 25	27 [22–43]; 34 ± 19	32 [24–52]; 39 ± 20	0.02	P, R > M
LA diameter[g], mm, median [IQR]	46 [42–51]	46 [43–51]	49 [44–54]	<0.001	P, M < R
Aortic regurgitation (moderate–severe)[f]	10%	10%	8.4%	0.04	P > R
Mitral regurgitation (moderate–severe)[f]	38%	54%	64%	<0.001	P < M < R
Tricuspid regurgitation (moderate–severe)[f]	35%	38%	44%	<0.001	P, M < R

For pairwise comparisons, inequalities (> and <) show statistically significant ($p < 0.05$) differences between EF groups.

BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillation; IQR, interquartile range; LA, left atrial; LAVI, left atrial volume index; LBBB, left bundle branch block; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack.

[a]Mutually exclusive (only one option could be chosen for each patient).

[b]Data missing in 21% of patients.

[c]More than one reason could be chosen for each patient.

[d]Data missing for NT-proBNP or BNP: 64%; sodium and potassium: 9%; creatinine: 6%; eGFR: 8%; urea: 28%; bilirubin: 38%; haemoglobin: 6%.

[e]Performed at any time point during hospitalization.

[f]Data missing in 6% of patients.

[g]Data missing for LVEDD: 13%; LV hypertrophy: 8%, LAVI: 87%; LA diameter: 58% of patients.

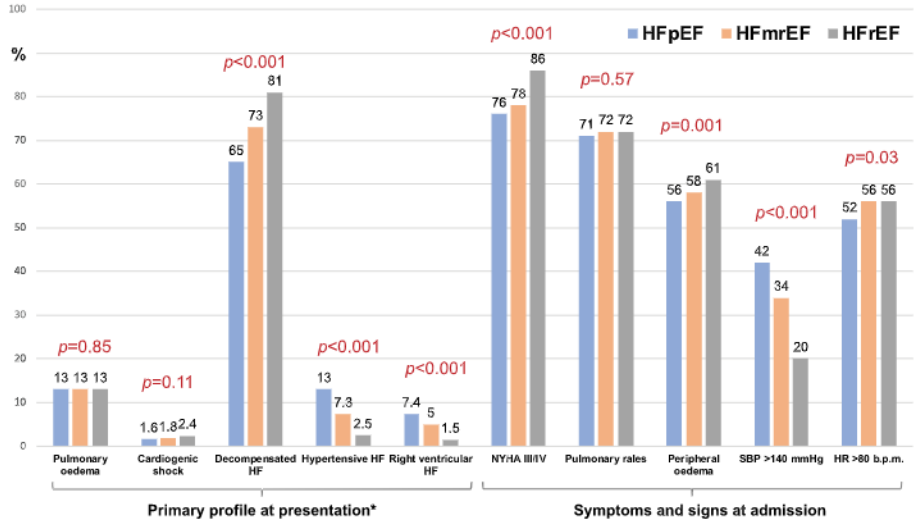


Figure 1 Select admission characteristics of patients with acute heart failure (HF) in relation to ejection fraction category. *Mutually exclusive (only one profile could be chosen for each patient). HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; NYHA, New York Heart Association; SBP, systolic blood pressure.

follow-up was 12 months (maximum 43 months), with a total of 4347 patient-years of follow-up. *Figure 3* presents cumulative incidence curves for CV and non-CV outcomes, as well as results of uni- and multivariable Cox proportional hazards regressions showing independent relationships between EF category and selected post-discharge outcomes. Patients with HFrEF had the greatest risk of all-cause death and CV outcomes, whereas patients with HFpEF had the highest risk of non-CV outcomes. All-cause mortality at 12 months was 16% for HFpEF (95% CI 14–18), 15% for HFmrEF (95% CI 13–18), and 20% for HFrEF (95% CI 18–22). First HF rehospitalization at 12-month follow-up was 16% for HFpEF (95% CI 13–18), 18% for HFmrEF (95% CI 15–21), and 25% for HFrEF (95% CI 23–27). All-cause death or first HF rehospitalization at 12 months was 27% for HFpEF (95% CI 24–30), 29% for HFmrEF (95% CI 25–32), and 39% for HFrEF (95% CI 37–41). All-cause hospitalization at 12 months was 35% for HFpEF (95% CI 32–37), 30% for HFmrEF (95% CI 27–34), and 37% for HFrEF (95% CI 35–39).

Figure 4 presents incidence rates per 100 patient-years. Death from any cause, HF and sudden cardiac death was greater in HFrEF and similar in HFmrEF and HFpEF. CV death was also greater in HFrEF but when excluding HF death from CV death, the CV death rates were similar. HF rehospitalization was greater in HFrEF and similar in HFmrEF and HFpEF. Non-CV death as well as non-CV hospitalization were greatest in HFpEF.

Predictors of post-discharge outcomes

Figure 5 and online supplementary *Tables S1* and *S2* show independent associations between select admission, in-hospital, and discharge characteristics and post-discharge all-cause death as well as first HF rehospitalization in patients with HFpEF, HFmrEF and HFrEF (*p*-values for interaction between EF categories are given in online supplementary *Tables S1* and *S2*). In general, infection and worsening renal function as reasons for HF decompensation were associated with higher risk of future events. Cancer disease and NYHA class III–IV at hospital discharge were associated with all-cause death in HFpEF and HFmrEF, but not HFrEF. History of AF and diabetes was associated with first HF rehospitalization in HFpEF and HFmrEF, but not HFrEF. Conversely, AF as a reason for HF decompensation was associated with lower risk of future HF rehospitalization in HFrEF, but not in HFpEF or HFmrEF. Moderate-to-severe mitral regurgitation was associated with higher risk of HF rehospitalization only in HFrEF, while NYHA class III–IV at hospital discharge only in HFmrEF. In summary, presence of comorbidities and worse discharge NYHA class were prognostic factors in HFpEF and HFmrEF, but not in HFrEF.

Pharmacotherapy at discharge and 1 year after hospitalization

Pharmacotherapy at hospital discharge is shown in online supplementary *Figure S2A*. The use of disease-modifying HF therapy and loop diuretics was progressively higher with lower EF. At 1-year follow-up, use of all drugs had declined in all EF categories (online supplementary *Figure S2B*). However, among HFrEF patients who remained on treatment, the proportion achieving target doses of ACEi and beta-blockers had somewhat increased (online supplementary *Figure S2C*).

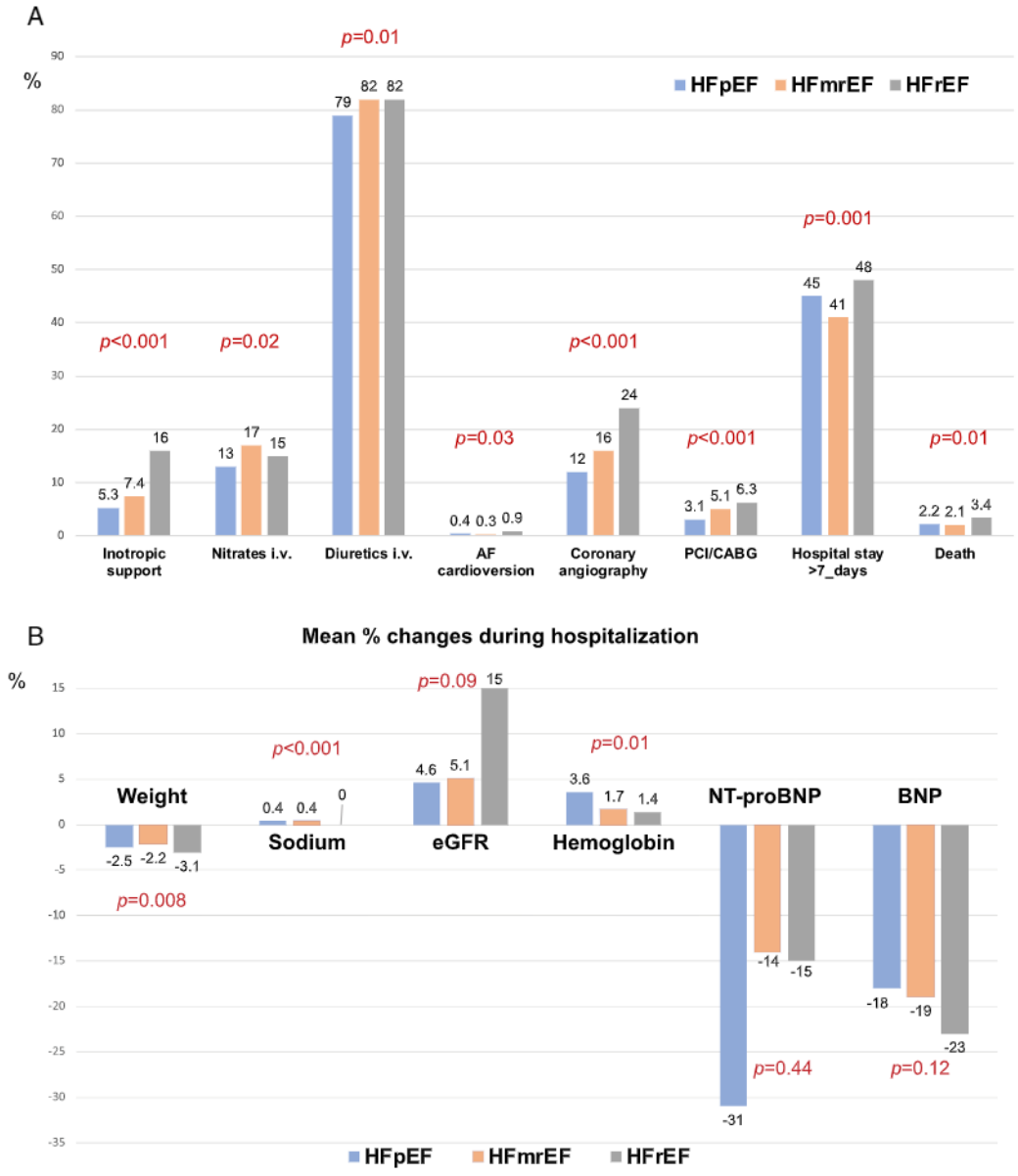
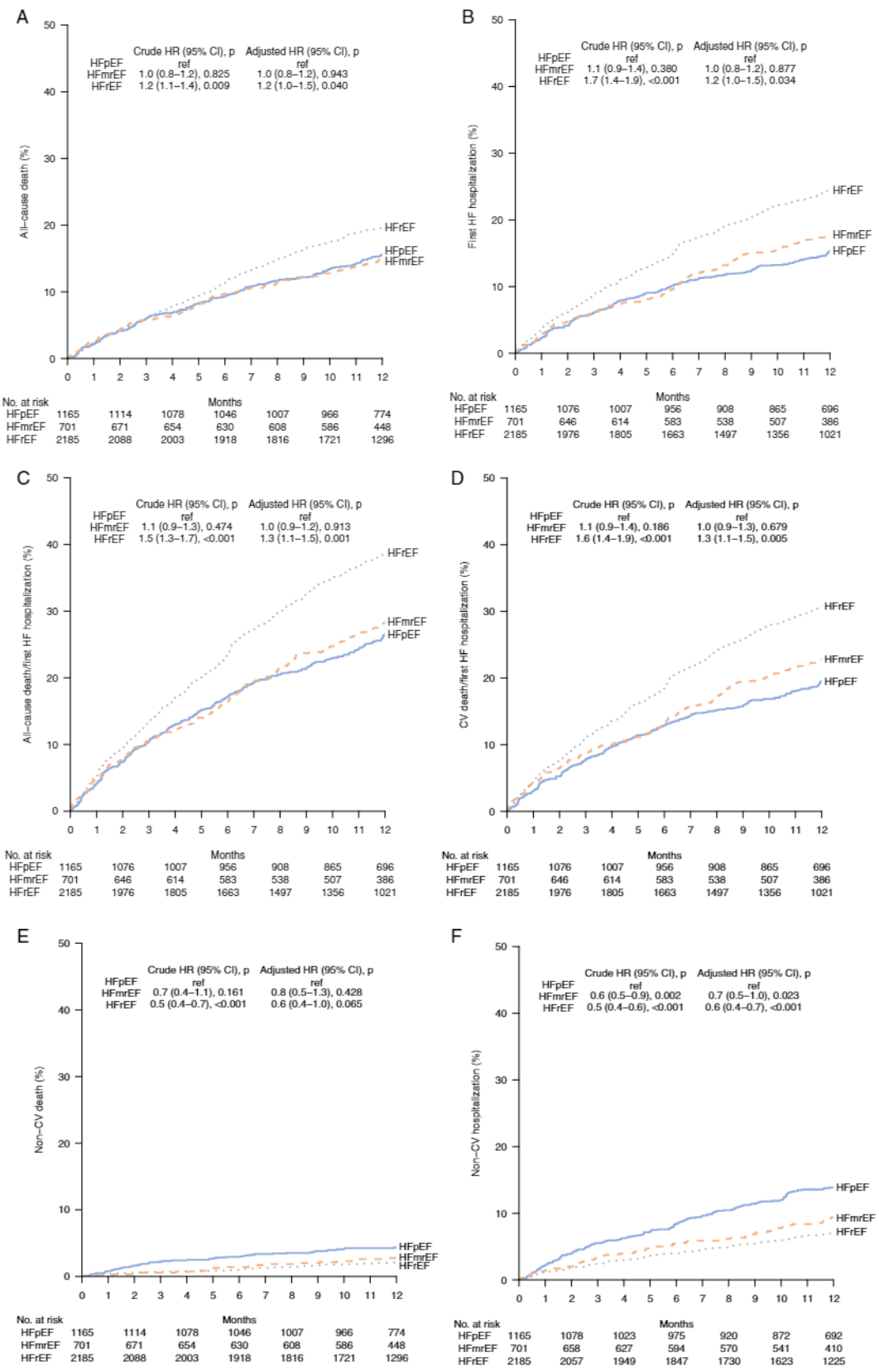


Figure 2 (*A*) In-hospital treatment and mortality. *p* for difference between heart failure with preserved (HFpEF), mildly reduced (HFmrEF) and reduced ejection fraction (HFrEF). Analysis included all patients hospitalized for acute heart failure ($n = 5951$). (*B*) Mean percent changes in weight and laboratory parameters during hospitalization. A negative value reflects a reduction, and a positive value reflects an increase during hospitalization. *p* is for difference between HFpEF, HFmrEF and HFrEF. Analysis included patients who survived to hospital discharge ($n = 5781$), and only those with both admission and discharge values available. For change in weight data were missing in 5%; sodium: 24%; estimated glomerular filtration rate (eGFR): 24%; haemoglobin: 28%; N-etrminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP): 88% of 5781 patients. Standard deviation (SD) for weight was 4.6%, 6.6% and 4.3% for HFpEF, HFmrEF and HFrEF, respectively; for sodium 3.3%, 3.4% and 3.4%, for eGFR 39%, 46% and 420%, for haemoglobin 42%, 14% and 28%, for NT-proBNP 55%, 111% and 114%, and for BNP 72%, 48% and 96% for HFpEF, HFmrEF and HFrEF, respectively. AF, atrial fibrillation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Discussion

We present a large, multinational and comprehensive analysis of AHF according to the three contemporary EF categories. The results present extensive clinical, laboratory, imaging and pharmacotherapy characteristics at admission, during hospitalization, at discharge, and at 1-year follow-up post-discharge. Furthermore, the results present in-hospital mortality rates and, for the first time, extensive cause-specific outcomes at 1-year post-discharge,



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including independent associations between admission, hospital, and discharge characteristics and post-discharge outcomes. Apart from presenting a comprehensive and up-to-date description of a large and representative AHF cohort, novel aspects include a detailed assessment of precipitating factors in AHF, changes in clinical and biochemical parameters during hospitalization, and, most importantly, in-hospital mortality and post-discharge cause-specific outcomes in acute HFpEF versus HFmrEF versus HFrEF. The main findings were that in AHF, HFrEF was more severe and had greater in-hospital mortality, and that post-discharge, HFrEF had greater CV risk, HFpEF greater non-CV risk, and HFmrEF lower overall risk (*Graphical Abstract*). In addition, this extensive characterization may serve as a reference document for clinicians and patients assessing and prioritizing therapy in AHF, for investigators designing AHF trials, and for health care organizations, administrators, payers, and other stakeholders assessing the impact of AHF.

Proportion of ejection fraction categories

The proportions of different EF categories were HFrEF 53%, HFmrEF 18%, and HFpEF 29%, consistent with previous AHF studies, with HFrEF proportions ranging from 36% to 66%, HFpEF from 17% to 43%, and HFmrEF from 13% to 25%.[15–22] In AHF diagnosed in emergency departments, HFpEF may be more common (64% in one study[23]). In chronic HF, there is considerable variability, but overall proportions appear similar. On the one hand, HFpEF has lower HF hospitalization risk and would be expected to be less common in AHF, but on the other hand, ambulatory HF clinics may be referral-based and thus encounter less HFpEF.[5,6,24] HFmrEF is typically the smallest group,[6,15–17,19–24] which may be due to HFmrEF patients being in transition.[25] HFmrEF is also a narrower range (40%–49% in the 2016 ESC guidelines[1] and this study, but 41%–49% in a recent global consensus statement,[4] which, given a common 5% digit preference in EF reporting, would likely mean an even lower proportion with HFmrEF).

Admission characteristics

Acute HF characteristics were similar to those available in previous AHF and chronic HF studies.[5,15–24] HFmrEF was intermediate between HFpEF and HFrEF with respect to age, sex, and non-cardiac comorbidities. Intermediate characteristics of HFmrEF patients may partially result from overlap with both reduced and preserved EF categories due to high intra- and interobserver variability in echocardiographic EF assessment (6%–13% and 8%–21%, respectively), as well as factual transition between EF categories.[26]

As in previous studies,[27] HFmrEF resembled HFrEF with respect to distinctly more common ischaemic aetiology and comorbidity, but resembled HFpEF with respect to some typical HFpEF characteristics, such as higher body mass index, more left ventricular hypertrophy and more AF. This may reflect a dichotomy within the HFmrEF group, with some HFmrEF patients sharing a common pathophysiological background with HFpEF (with a modest decline of EF from HFpEF) and some in whom coronary artery disease is the primary aetiology. The latter could represent either recovered HFrEF or a milder stage of HFrEF as a result of earlier and better treatment of ACS. The former represented precipitating factors common for HFmrEF and HFpEF: more AF, infection and uncontrolled hypertension, and less worsening renal function and ventricular arrhythmia compared to HFrEF. Most previous studies in AHF reported on primary HF aetiology, but not on precipitating factors, and those that did,[17,18] did not distinguish between AF and ventricular arrhythmias, showing similar proportions of arrhythmia as a reason for HF decompensation in the three EF categories.

At hospital admission, HFpEF and HFmrEF were less severe than HFrEF, with systolic blood pressure, symptoms of decompensated HF and concentrations of natriuretic peptides gradually worsening with decreasing EF category, which is consistent with previous observations.[15,18–21] Nevertheless, detailed analysis showed that the prevalence of pulmonary oedema and pulmonary congestion (both clinical and confirmed by chest X-ray) was the same in the three EF groups suggesting backward failure is equally common.

Hospital course

In-hospital mortality was higher in HFrEF (3.4%), with no difference between HFpEF (2.2%) and HFmrEF (2.1%). This is consistent with most previous registries, although single studies have suggested similar in-hospital or short-term mortality in all three EF categories.[15–23] Overall, in-hospital mortality in our mostly European cohort was low and comparable to previous large, American AHF registries (OPTIMIZE-HF, ADHERE, GWTG-HF).[15–17] Conversely, in three Asian AHF registries, in-hospital mortality was higher, especially in acute HFrEF.[19–21]

In the ESC-HF Long-Term Registry, intravenous therapy for HF (inotropes, vasodilators or diuretics) was an inclusion criterion for AHF patients. Intravenous diuretic treatment was frequent (~80%) in all three groups, while inotropic support was three times more frequent in HFrEF than in HFpEF and HFmrEF. These observations are consistent with previous reports,[15,16,18–21,23] although in the ALARM-HF and Korean AHF (KorAHF) registries the frequency of inotrope use was substantially higher (~45% in HFrEF and >25% in HFpEF) compared to our study (16% in HFrEF and 5.3% in HFpEF),

Figure 3 Kaplan–Meier curves for all-cause death, first heart failure (HF) rehospitalization, all-cause death or first HF rehospitalization, cardiovascular (CV) death or first HF rehospitalization, non-CV death, and non-CV hospitalizationin patients with acute HF. (*A*) All-cause death. (*B*) First rehospitalization for HF (HF). (*C*) All-cause death or first rehospitalization for HF. (*D*) CV death or first rehospitalization for HF. (*E*) Non-CV death. (*F*) Non-CV hospitalization. CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.

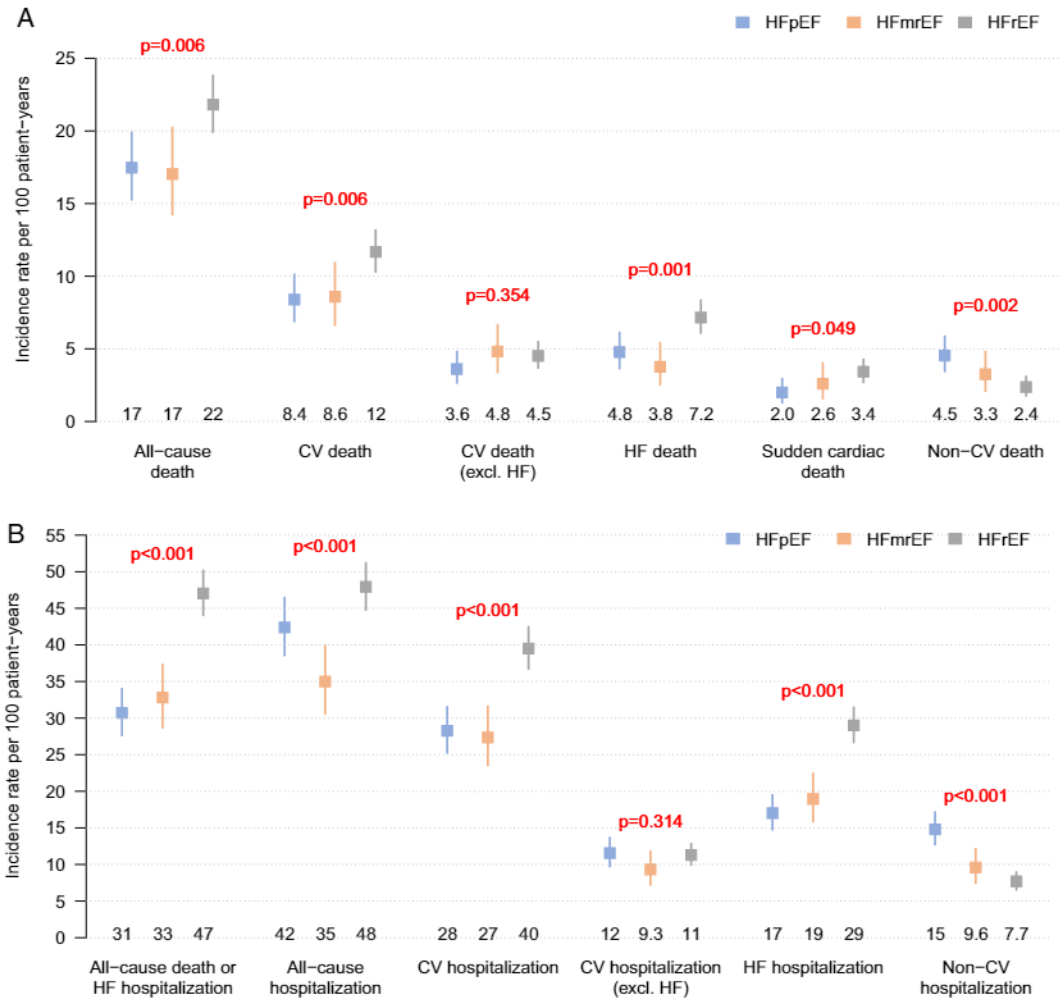


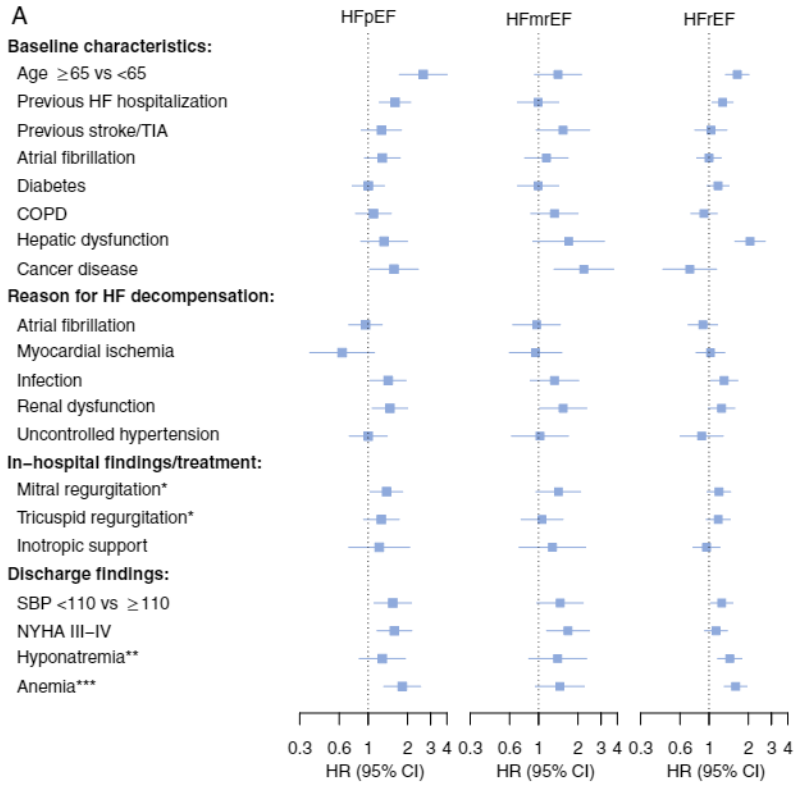
Figure 4 Post-discharge outcomes: incidence rates (per 100 patient-years) in relation to ejection fraction category. (*A*) 95% confidence intervals for heart failure (HF) with preserved (HFpEF), mildly reduced (HFmrEF) and reduced ejection fraction (HFrEF), respectively, are for all-cause death 15–20, 14–20 and 20–24; for cardiovascular (CV) death 6.9–10, 6.6–11 and 10–13; for CV death excluded. HF death 2.7–4.8, 3.4–6.6 and 3.7–5.5; for HF death 3.7–6.1, 2.5–5.4 and 6.1–8.3; for sudden cardiac death 1.3–2.9, 1.6–4.0 and 2.7–4.3; and for non-CV death 3.5–5.9, 2.1–4.8 and 1.8–3.1, respectively. (*B*) 95% confidence intervals for HFpEF, HFmrEF and HFrEF, respectively, are for all-cause death or HF hospitalization 28–34, 29–37 and 44–50; for all-cause hospitalization 39–46, 31–40 and 45–51; for CV hospitalization 25–32, 24–32 and 37–43; for CV hospitalization excluded. HF hospitalization 9.7–14, 7.2–12 and 9.9–13; for HF hospitalization 15–20, 16–22 and 27–32; and for non-CV hospitalization 13–17, 7.5–12 and 6.6–8.9. *p* is for difference between HFpEF, HFmrEF and HFrEF. Hospitalization refers to first hospitalization.

despite comparable admission blood pressure in the KorAHF registry.[18,20] The use of inotropes and intravenous vasodilators in our cohort was similar to in OPTIMIZE-HF and ADHERE.[15,16]

HFpEF and HFmrEF patients had less severe HF symptoms (better NYHA class) at hospital admission, and during hospitalization they improved more often compared to HFrEF. In the Kyoto Congestive Heart Failure (KCHF) registry, the frequency of worsening HF during hospitalization was higher with lower EF.[19] Conversely, in the OPTIMZE-HF registry changes in symptoms during hospitalization were in general similar between different EF categories.[15]

Natriuretic peptides were highest in HFrEF and lowest in HFpEF both at hospital admission and discharge (as in previous registries[15,19–21,28]); however, the relative reduction in natriuretic peptides during hospitalization was greater in HFpEF but statistically comparable between the three EF categories. This observation is unexpected given that patients with HFrEF had higher admission values, and novel, given that previous registries have reported absolute values of natriuretic peptides at admission and discharge, but have not analysed the magnitude of their reduction during hospitalization.[15,19–21,28]

Despite similar use of intravenous diuretics, comparable reductions in natriuretic peptides, and less symptomatic improvement, weight loss was higher in HFrEF. Weight reduction was also highest in HFrEF in the OPTIMIZE-HF and ADHERE registries, and was



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similar between the three EF categories in the KCHF registry.[15,16,19] Overall, weight reduction during hospitalization was ~2 kg in our study, similarly to what was observed in the OPTIMIZE-HF registry, while higher weight loss was reported in the ADHERE and KCHF registries, despite comparable use of intravenous diuretics.[15,16,19] Thus, in-patient treatment of HFrEF may result in greater fluid loss but not greater reductions in filling pressures, perhaps consistent with greater HF severity and/or neurohormonal activation.

Previous AHF registries have brought conflicting results regarding serum sodium concentrations, reflecting fluid status, in the three EF-stratified HF types, with some studies showing lower values in HFrEF,[15,18] and some showing no differences between the three EF categories.[17,19,21] In our study, admission and discharge sodium concentrations were lowest in HFrEF, with no improvement during hospitalization, contrary to HFmrEF and HFpEF, where a small increase in sodium concentration was observed. In contrast, improvement in eGFR during hospitalization was greatest in HFrEF, resulting in higher eGFR at discharge in those patients, despite more common renal dysfunction at hospital admission in HFrEF. This might be at least partly related to the fact that HFpEF patients are significantly older and thus, potentially more prone to worsening renal function with intensive diuretic treatment, and also commonly have right ventricular dysfunction. On the other hand, HFrEF patients were more often hypotensive on admission, more often required inotropic support, and thus most probably had more renal hypoperfusion at admission which might have resolved during hospital treatment. It should be noted, however, that emerging data suggest that worsening eGFR during hospitalization, if associated with effective diuresis, may not be harmful in the long-run but in contrast a marker of effective in-hospital diuresis.[29] Haemoglobin (both at admission and discharge) was lower with higher EF, similar to what was described in previous registries, which might be related to increasing age.[15,17,19–21] Haemoconcentration was greater in HFpEF which together with greater worsening renal function may reflect more effective diuresis and explain the greater reduction in natriuretic peptides.

Cause-specific post-discharge outcomes

In previous observational studies, all-cause mortality was comparable between the three EF categories, while in randomized clinical trials (generally enrolling younger patients with less competing comorbidities but more advanced HF for enrichment), mortality in HFrEF was considerably higher.[5–9,15,20,21,28] In ambulatory participants of the ESC HF Long-Term Registry, 1-year mortality in HFrEF (8.8%) was, from the clinical perspective, not that much higher than in HFmrEF (7.6%) and HFpEF (6.3%), although the difference was statistically significant due to the large number of observations.[5] In our analysis of the AHF cohort of the ESC HF Long-Term Registry, o1ne-year mortality in HFrEF (20%) was considerably higher than in HFmrEF (15%) and HFpEF (16%), and, not surprisingly, over twice as high as in ambulatory patients.

Data on post-discharge CV and non-CV risk in HFrEF versus HFmrEF versus HFpEF are lacking. Comparing only HFrEF versus HFpEF, there are reports of worse CV outcomes in HFrEF, and worse non-CV outcomes in HFpEF, but other studies demonstrated similar risk of CV and HF-related endpoints regardless of EF category.[5,26–28] In our analysis, post-discharge non-CV mortality and non-CV hospitalizations were higher in HFpEF, while CV mortality and CV hospitalizations were higher in HFrEF. However, the latter was driven by higher rates of HF death and HF rehospitalizations in HFrEF, whereas rates of CV death excluding HF death and of CV hospitalizations excluding HF hospitalizations were not significantly different between the three EF groups. Rates of sudden cardiac death were highest in HFrEF, but still quite low (3.4 per 100 patient-years). With similar rates of CV non-HF readmissions in the three groups, higher rates of HF readmissions in HFrEF and higher rates of non-CV readmissions in HFpEF, the risk of all-cause hospitalization was lowest in HFmrEF (and highest in HFrEF). In the GWTG-HF registry, the frequency of all-cause readmissions at 1 year was slightly higher for HFpEF (63%) and HFmrEF (63%) compared to HFrEF (60%). Conversely to our analysis, rates of CV readmissions in HFmrEF were closer to HFrEF than HFpEF.[28]

Limitations

In this observational registry, there were missing data on both admission, in-hospital, and post-discharge characteristics. To reduce bias due to data missing not at random and thus increase generalizability, we used multiple imputation. The EF captured in AHF was not adjudicated and may have been temporarily affected by co-existing conditions such as rapid AF. There was no information on the exact timing of echocardiography (including EF assessment) during hospitalization, and EF was obtained per local protocol and routine (there was no core laboratory). The

Figure 5 Independent associations between admission and discharge characteristics and post-discharge all-cause death, and first heart failure (HF) rehospitalization in patients with acute HF in relation to ejection fraction category. (*A*) All-cause death. Hazard ratios (HR) and 95% confidence intervals (CI) are shown. Results were adjusted for discharge treatment and other relevant variables. Only selected variables (those that were significant predictors in at least one ejection fraction group) are shown. A complete multivariate model is shown in online supplementary *Table S2*. (*B*) First rehospitalization for HF. HR and 95% CI are shown. Results were adjusted for discharge treatment and other relevant variables. Only selected variables (those that were significant predictors in at least one ejection fraction group) are shown. A complete multivariate model is shown in online supplementary *Table S3*. COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack. *Moderate to severe. **Sodium concentration <135 mmol/L. ***Haemoglobin concentration <12 g/dl in women and <13 g/dl in men.

presented analysis was based on a single EF assessment during hospitalization and was not repeated during follow-up. Still, despite its limitations (high intra- and interobserver variability; changes over time – in relation to heart rate, loading conditions, and treatment), echocardiographic EF assessment remains the most commonly used tool for the evaluation of left ventricular systolic function. Some patients had *de novo* HF and may have been more prone to EF increase after initiation of treatment. However, for many patients with *de novo* HF, the disease process has often been subclinical or even clinical well before initial presentation.[30]

Compared to previous registries, patients in our study were somewhat younger, which might represent selection bias related to the requirement to obtain signed informed consent from all patients (unless exempt by the local ethics committee), as well as the fact that the registry included only patients from cardiology departments or specialized HF units (and not internal medicine or geriatric departments). 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. Exclusion of such patients from the registry might have led to an underrepresentation of older and more diseased patients (mostly with HFpEF), with a possible impact on prognosis (mostly in the HFpEF group) and the observed differences in outcomes between HFpEF, HFmrEF and HFrEF. Thus, the extent to which the findings from this study can be generalized to other populations is unclear. In all studies, there is a balance between detailed and adjudicated data (e.g. adjudication lacking in the present analysis), such as in a trial (which provides internal validity) and sample size and generalizability to larger populations (e.g. general medicine and geriatrics lacking in this analysis) (which provides external validity). Nevertheless, the ESC HF Long-Term Registry offers 337 sites in 33 countries with quite extensive characterization including EF, many clinical parameters and biomarkers, allowing a combination of reasonable internal and external validity. In this pragmatic, observational registry, coexisting diagnoses (including precipitating factors), echocardiography protocol and outcomes were not adjudicated. The registry allowed enrolment of a patient with concomitant ACS and HF. The diagnosis of ACS as precipitating factor was judged by the investigator. In the present study, patients with ACS were excluded, because: (i) we aimed to select patients with a primary diagnosis of HF, (ii) in ACS patients, *de novo* HFrEF or HFmrEF may develop, which often significantly improves after revascularization in the acute phase, confounding EF classification for the present study. Thus, patients with ACS were excluded but patients with HF and ischaemia (including potentially type 2 myocardial infarction) were included. In the registry, there was no distinction between moderate versus severe valvular disease, nor between primary versus secondary mitral regurgitation. We excluded patients with moderate–severe aortic stenosis because this could confound the HF diagnosis, with increased left-sided pressures and symptoms attributable to an obstruction at the level of the aortic valve rather than left ventricular HF. We included patients with moderate-severe mitral regurgitation because this is commonly secondary to HF.

The limitations notwithstanding, our large comprehensive analysis contains extensive clinical, laboratory, imaging and treatment variables, as well as cause-specific outcomes, allowing for a nuanced and generalizable phenotyping of patients with AHF and HFpEF versus HFmrEF versus HFrEF.

Conclusions

In this detailed and comprehensive analysis of EF categories in AHF, we confirm previous findings in chronic HF and add new information suggesting that in AHF, HFrEF is more severe than HFmrEF and HFpEF, with similar congestion but more hypotension and need for inotropes, and considerably greater in-hospital mortality and post-discharge risk of HF death and HF hospitalization. HFmrEF appeared to be a milder form of HFrEF with the lowest overall risk. In contrast, HFpEF had more comorbidities and greater non-CV risk. These findings may explain why previous AHF trials including patients across the whole EF spectrum have been disappointing, and suggest that the impact of EF classification in AHF should be further evaluated in prospective studies. Also, this research provides important information for clinical and other stakeholder decision making and future AHF trial design.

Supplementary Information

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

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