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RESEARCH ARTICLE

Characteristics and clinical outcomes of patients with acute heart failure with a supranormal left ventricular ejection fraction

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Aim Recent data suggest that guideline-directed medical therapy of patients with heart failure (HF) with reduced ejection fraction (HFrEF) might improve clinical outcomes in patients with HF up to a left ventricular ejection fraction (LVEF) of 55–65%, whereas patients with higher LVEF do not seem to benefit. Recent data have shown that LVEF may have a U-shaped relation with outcome, with poorer outcome also in patients with supranormal values. This suggests that patients with supranormal LVEF may be a distinctive group of patients.

Methods and results RELAX-AHF-2 was a multicentre, placebo-controlled trial on the effects of serelaxin on 180-day cardiovascular (CV) mortality and worsening HF at day 5 in patients with acute HF. Echocardiograms were performed at hospital admission in 6128 patients: 155 (2.5%) patients were classified as HF with supranormal ejection fraction (HFsnEF; LVEF >65%), 1440 (23.5%) as HF with preserved ejection fraction (HFpEF; LVEF 50–65%), 1353 (22.1%) as HF with mildly reduced ejection fraction (HFmrEF; LVEF 41–49%) and 3180 (51.9%) as HFrEF (LVEF <40%). Patients with HFsnEF compared to HFpEF were more often women, had higher prevalence of non-ischaemic HF, had lower levels of natriuretic peptides, were less likely to be treated with beta-blockers and had higher blood urea nitrogen plasma levels. All-cause mortality was not statistically different between groups, although patients with HFsnEF had the highest numerical rate. A declining trend was seen in the proportion of 180-day deaths due to CV causes from HFrEF (290/359, 80.8%) to HFsnEF (14/24, 58.3%). The reverse was observed with death from non-CV causes. No treatment effect of serelaxin was observed in any of the subgroups.

Conclusions In this study, only 2.5% of patients were classified as HFsnEF. HFsnEF was primarily characterized by female sex, lower natriuretic peptides and a higher risk of non-CV death.

Keywords Acute heart failure • Heart failure with supranormal ejection fraction • Clinical outcome • Serelaxin

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Introduction

Traditionally, the cornerstone of treatment of heart failure (HF) with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <40%) has consisted of a beta-blocker (BB), an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and a mineralocorticoid receptor antagonist (MRA). More recently, an angiotensin receptor–neprilysin inhibitor (ARNI) and a sodium–glucose contransporter 2 inhibitor (SGLT2i) were added to the foundational treatment of HFrEF.[1] The beneficial effects of ARBs, BBs and MRAs seem to extend to HF with mildly reduced ejection fraction (HFmrEF; LVEF 40–49%).[2–4] However, in patients with HF and preserved ejection fraction (HFpEF; LVEF >50%) only SGLT2i is proven to be beneficial.[5] Within a subgroup of patients, however, with HF with a so-called 'supranormal' ejection fraction (HFsnEF; LVEF >65%) none of these therapies seem to reduce mortality and morbidity. Moreover, a U-shaped relationship between mortality and LVEF has been observed, showing an increased risk of mortality in patients with a low LVEF, but also in patients with a LVEF >65%.[6] There is therefore a growing interest in having a better understanding of the prevalence, characteristics and clinical outcome of patients with HFsnEF. Limited data are available on HFsnEF in the chronic setting and to our knowledge no data are available on HFsnEF in acute heart failure (AHF).

We therefore aimed to evaluate the prevalence, characteristics and clinical outcomes of patients with HFsnEF in a large randomized controlled trial of patients with AHF.

Methods

RELAXin in Acute Heart Failure 2 (RELAX-AHF-2) was a multicentre, placebo-controlled randomized clinical trial comparing the effects of serelaxin with matching placebo in AHF patients. The study design and rationale has been published previously.[7] In short, the RELAX-AHF-2 trial included 6545 patients ≥18 years of age that were admitted to the hospital for AHF, diagnosed with brain natriuretic peptide (BNP) ≥500 pg/ml or N-terminal proBNP (NT-proBNP) ≥2000 pg/ml (with the exception of BNP ≥750 pg/ml or NT-proBNP ≥3000 pg/ml for patients ≥75 years of age or with atrial fibrillation), combined with symptoms of dyspnoea and congestion on chest radiography. Other inclusion criteria included normal-to-elevated systolic blood pressure (≥125 mmHg) and mild-to-moderate renal impairment (estimated glomerular filtration rate [eGFR] >25 and <75 ml/min/1.73 m^2). Patients were eligible if symptoms persisted after receiving the first dose of at least 40 mg (or equivalent) of intravenous furosemide and were able to be randomized within 16 h of hospital admission. Patients were randomized to either 48 h of intravenous serelaxin (30 μg/kg per day) or a matching placebo. All patients were required to undergo echocardiography with LVEF measurement during index hospitalization. LVEF quantification method was left at discretion of the investigator. Written informed consent was obtained from all patients. Local ethic committees of the participating sites approved the study protocol.

Study outcomes

Time to cardiovascular (CV) mortality through day 180 (primary endpoint of the original RELAX-AHF-2 trial), in addition to time to first event of non-CV and all-cause mortality were the endpoints of interest for this *post-hoc* analysis. Worsening HF at day 5 (second primary endpoint of the original RELAX-AHF-2 trial) and time-to-event of the composite of rehospitalization for HF or renal failure (RF) or time-to-event of only rehospitalization for HF/RF were regarded as secondary endpoints for this analysis.

Statistical analysis

Patients lacking LVEF quantification during index hospitalization were excluded from the analysis leaving 6128 patients (94% of trial enrolment). Baseline characteristics of excluded patients can be found in online supplementary *Table Appendix S1*. Patients were then divided into four groups, HFrEF (LVEF <40%), HFmrEF (LVEF 40–49%), HFpEF (LVEF 50–65%) and HFsnEF (LVEF >65%).

Baseline characteristics are presented as mean and standard deviation (SD) for normally distributed continuous variables and as median and interquartile range (IQR) for non-normally distributed continuous variables and count and percentage for discrete data. Normality was assessed using QQ plots and the differences between HF subtypes were compared with analysis of variance (ANOVA), Kruskal–Wallis test, Student's *t*-test or the Chi-square test depending on the type of data and on its distribution.

Due to a low number of complete cases and due to the plausibility of data missing at random, multiple imputation was used to generate 50 imputed datasets. HFpEF and HFsnEF were compared using logistic regression identifying predictors for HFsnEF, for this analysis only the subset of HFpEF/HFsnEF patients was used (n = 1595). Laboratory values were log-transformed to reduce the impact of potential outliers and linearity was assessed by plotting the log odds of HFsnEF against continuous predictors. First, all variables were tested univariably in the imputed data in a logistic regression model, variables with a p-value of ≤0.10 were included in multivariable analysis. Second, backward stepwise variable selection was performed on the imputed data by excluding variables based on highest p-value until all variables in the model had a p-value of ≤0.05. This was all done on the pooled imputed data, generating pooled test statistics for all variables.

For analysis of clinical outcomes, Cox regression models were fit to the imputed data. Three models were built, one unadjusted model, one model adjusted for age and sex and one multivariable model based on previous work.[8] This model adjusted for creatinine, haemoglobin, sodium, blood urea nitrogen (BUN), asthma/bronchitis/chronic obstructive pulmonary disease, peripheral arterial occlusive disease, respiration rate, systolic blood pressure, body mass index (BMI), peripheral oedema, intravenous loop diuretics (total dose in furosemide units) at baseline, known history of diabetes mellitus, prior HF hospitalization, actual study treatment, composite of NT-proBNP or BNP Z-score, sex and age for all mortality outcomes.

For the composite endpoint and HF/RF rehospitalization outcomes, the following variables were added to the model: atrial fibrillation/flutter, pulse rate, geographical region and depression. BMI was left out.[8] Due to some patients having either BNP or NT-proBNP measurement, log transformation and Z-scaling was used to create a combined NT-proBNP/BNP Z-score.

Treatment effect was tested using Cox regression adding an interaction between treatment and the HF subtypes and comparing the model with the interaction to the model without interaction using a likelihood ratio test.

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A two-tailed p-value of $\leq$0.05 was considered statistically significant. All analyses were performed using R statistical software version 4.1.3. The mice package was used for multiple imputation.[9]

Results

A total of 6128 patients with LVEF measured at index hospitalization were included in this analysis. *Table 1* shows the clinical characteristics of patients divided into the following four groups: HFrEF, HFmrEF, HFpEF and HFsnEF with 3180 (51.9%), 1353 (22.1%), 1440 (23.5%) and 155 (2.5%) patients in each group, respectively. Median LVEF values were 30%, 43%, 55% and 70%, respectively. Per increasing LVEF category, age and the percentage of females increased. The proportion of ischaemic aetiology of HF, together with the proportion of patients that had a history of HF was higher in patients with HFrEF and HFmrEF compared to HFpEF and HFsnEF. Usage of MRAs was lower in the higher LVEF groups (37.6% in HFrEF compared with 15.1% in HFsnEF, p for trend <0.001), whereas haemoglobin, NT-proBNP and eGFR were lower in higher LVEF groups.

Predictors of HFsnEF compared with HFpEF

Multivariable logistic regression identified female sex (odds ratio [OR] 2.25, 95% confidence interval [CI] 1.54–3.29, $p < 0.001$), a lower log BNP Z-score (OR 2.90, 95% CI 1.18–7.14, $p = 0.02$), no baseline use of a beta-blocker (OR 1.50, 95% CI 1.03–2.17, $p = 0.03$), presence of non-ischaemic aetiology of HF (OR 1.58, 95% CI 1.02–2.43, $p = 0.04$) and a higher BUN (log2) (OR 1.68, 95% CI 1.27–2.23, $p < 0.001$) as independent predictors of HFsnEF versus HFpEF (*Figure 1*).

Clinical outcomes

Table 2 summarizes unadjusted event rates in patients with HFsnEF versus patients with HFpEF, HFmrEF and HFrEF. All-cause mortality was not significantly different between groups, although patients with HFsnEF had the highest numerical rate. Patients with HFsnEF showed a significantly higher proportion of non-CV mortality (6.4% vs. 2.17%, 2.14% and 3.82% of HFrEF, HFmrEF and HFpEF, respectively). No differences were seen in 180-day all-cause and CV mortality. Multivariable Cox regression analysis showed a significantly higher hazard of non-CV mortality in HFsnEF (HR 2.65, 95% CI 1.29–5.43, $p = 0.009$) and HFpEF (HR 1.58, 95% CI 1.05–2.37, $p = 0.03$) compared with HFrEF; this was not seen in HFmrEF (HR 0.92, 95% CI 0.58–1.2, $p = 0.71$). Compared with HFrEF, the HR for 180-day CV mortality was 0.97 (95% CI 0.77–1.22, $p = 0.77$) for HFmrEF, 0.93 (95% CI 0.73–1.20 $p = 0.60$) for HFpEF and 1.11 (95% CI 0.63–1.94, $p = 0.71$) for HFsnEF. The results for multivariable Cox regression for all outcomes of the RELAX-AHF-2 trial can be found in *Table 3*. Causes of death are summarized in *Table 4* and visualized in *Figure 2*. Death from non-CV causes increased per LVEF category, where patients with HFrEF (69/359, 19%) showed the lowest incidence and patients with HFsnEF the highest incidence (10/24, 41.7%). In addition, rehospitalization for RF/HF was significantly lower in all HF subgroups compared to HFrEF, with HFsnEF having the lowest risk of rehospitalization (HR 0.61, 95% CI 0.39–0.95, $p = 0.03$). No significant treatment effect was observed in any of the four subgroups.

Discussion

In the present study, we showed that in AHF patients the prevalence of HFsnEF was low and associated with a significantly higher non-CV mortality compared with all other subgroups, although CV and all-cause mortality was similar.

Choosing a cut-off to investigate the entity of HFsnEF is arbitrary. Few studies have looked at this group of patients, especially in AHF. We chose a cut-off of >65% for two reasons. First, treatment effect of empagliflozin in EMPEROR-Preserved was consistent throughout the whole range of LVEF but was attenuated in patients with a LVEF >65%.[10] Second, a large observational study including all patients that underwent echocardiography, showed that, regardless of age and sex, subjects with a LVEF >65% had an increased risk of mortality compared to patients with a LVEF between 55–65% and those with lower LVEF.[6] These findings were in line with other studies showing an increased risk of mortality when LVEF exceeded 65%.[11]

We found that patients with HFsnEF had the lowest risk of rehospitalization for HF/RF. This is also in line with other studies showing a lower risk of HF hospitalizations in patients in the higher LVEF subgroups.[10,12] These studies investigated the risk of HF hospitalization only, but did not include hospitalization for RF. This, in contrast to the combined secondary endpoint of RELAX-AHF-2 in which renal rehospitalizations were included. It is noteworthy that the rate of this combined endpoint was lowest in the HFsnEF group, implying that the risk of HF rehospitalizations as well as RF rehospitalizations is low in this group.

There are limited data on the prevalence and clinical characteristics of patients with HFsnEF. Our finding of an older patient population with a higher percentage of women is in line with the findings of the pooled analysis of the EMPEROR trials.[10] Another sub-analysis of a study assessing the relationship between all-cause mortality and a supranormal LVEF in the general population, showed that only 8.5% of HF patients had a LVEF $\geq$65%.[6] Furthermore, they also found that with increasing LVEF the percentage of women increased to 69% in the group with LVEF $\geq$65%.[6] After an acute coronary event in elderly women the proportion of patients with a LVEF >65% was around 13%, but as they included only women and not necessarily HF patients it is not surprising that they found a higher proportion.[6,13] A reason for the higher prevalence of HFsnEF in previous studies could be due to the fact that this *post-hoc* analysis was performed in an AHF cohort. Systemic congestion, neurohumoral activation and inflammation can negatively affect ventricular function and, therefore, the LVEF is expected to be somewhat lower than in the chronic stable situation.[14]

We were particularly interested to study the differences between HFsnEF and HFpEF, to evaluate whether within the

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Table 1 Baseline characteristics of the different subgroups of heart failure

	HFrEF (*n* = 3180)	HFmrEF (*n* = 1353)	HFpEF (*n* = 1440)	HFsnEF (*n* = 155)	*p* for trend
Age (years)	70.3 (11.6)	74.8 (10.0)	76.1 (9.9)	76.4 (10.3)	<0.01
Female sex	910 (28.6%)	619 (45.8%)	821 (57.0%)	114 (73.5%)	<0.01
Caucasian	2871 (90.7%)	1300 (96.3%)	1327 (92.9%)	142 (91.6%)	<0.01
HF characteristics					
NYHA class					<0.01
I	91 (3.7%)	43 (4.4%)	60 (6.3%)	5 (4.8%)	
II	871 (35.9%)	398 (40.6%)	423 (44.2%)	49 (47.1%)	
III	1186 (48.9%)	451 (46.0%)	388 (40.5%)	42 (40.4%)	
IV	276 (11.4%)	89 (9.1%)	87 (9.1%)	8 (7.7%)	
Previous HF hospitalization	1726 (57.6%)	664 (52.6%)	660 (49.7%)	63 (43.8%)	<0.01
Aetiology					<0.01
Ischaemic	1457 (59.3%)	584 (58.5%)	387 (39.4%)	28 (26.7%)	
Non-ischaemic	1002 (40.7%)	414 (41.5%)	594 (60.6%)	77 (73.3%)	
Index ejection fraction	30.0 [23.7–35.0]	43.0 [40.0–45.0]	55.0 [50.0–60.0]	70.0 [68.0–73.0]	<0.01
Last known ejection fraction in the previous 12 months	30.0 [25.0– 37.0]	45.0 [40.0–50.0]	55.0 [50.0–60.0]	64.5 [60.0–70.0]	<0.01
Comorbidities					
Hypertension	2741 (86.4%)	1255 (92.8%)	1366 (94.9%)	147 (94.8%)	<0.01
Diabetes mellitus	1422 (44.7%)	632 (46.7%)	681 (47.3%)	79 (51.0%)	0.04
COPD	714 (22.7%)	354 (26.3%)	372 (25.9%)	34 (21.9%)	0.03
Atrial fibrillation or flutter	1495 (47.2%)	766 (56.9%)	881 (61.3%)	87 (56.1%)	<0.01
Current smoker	434 (13.7%)	124 (9.2%)	111 (7.7%)	7 (4.6%)	<0.01
CABG	539 (17.0%)	168 (12.4%)	176 (12.2%)	11 (7.1%)	<0.01
PCI	831 (26.4%)	316 (23.5%)	291 (20.3%)	24 (15.6%)	<0.01
Myocardial infarction	1209 (38.6%)	470 (35.0%)	295 (20.6%)	32 (20.6%)	<0.01
CRT	187 (5.9%)	29 (2.1%)	15 (1.0%)	4 (2.6%)	<0.01
ICD	455 (14.3%)	56 (4.2%)	26 (1.8%)	2 (1.29%)	<0.01
Signs and symptoms					
Dyspnoea on exertion	2999 (99.7%)	1243 (99.8%)	1329 (99.5%)	143 (98.6%)	0.08
Elevated JVP	2079 (74.6%)	817 (71.4%)	855 (69.8%)	94 (71.2%)	<0.01
Rales	2841 (94.2%)	1185 (94.6%)	1268 (94.1%)	134 (92.4%)	0.66
Orthopnoea	2911 (96.5%)	1201 (95.8%)	1300 (96.5%)	140 (96.6%)	0.90
Peripheral oedema	2549 (84.5%)	1090 (86.9%)	1136 (84.3%)	124 (85.5%)	0.77
Physical examination					
Systolic blood pressure (mmHg)	139 (13.6)	143 (15.3)	147 (16.1)	148 (18.4)	<0.01
Diastolic blood pressure (mmHg)	81.5 (13.5)	79.0 (13.4)	77.1 (14.6)	74.8 (15.1)	<0.01
Heart rate (bpm)	83.5 (15.6)	80.6 (16.1)	78.1 (16.2)	76.8 (16.8)	<0.01
BMI (kg/m^2)	29.2 (6.0)	29.9 (6.2)	30.8 (6.9)	32.1 (7.8)	<0.01
Medications					
ACEi/ARB	2052 (69.3%)	899 (69.5%)	952 (68.6%)	109 (71.7%)	0.91
Beta-blocker	2216 (74.8%)	958 (74.0%)	1061 (76.4%)	104 (68.4%)	0.91
MRA	1112 (37.6%)	365 (28.2%)	256 (18.4%)	23 (15.1%)	<0.01
Serelaxin group	1561 (49.4%)	667 (49.6%)	747 (52.2%)	83 (53.9%)	0.06
Furosemide equivalent at baseline (mg)	60.0 [40.0–80.0]	60.0 [40.0–80.0]	60.0 [40.0–80.0]	40.0 [40.0–80.0]	0.79
Laboratory values					
Haemoglobin (g/L)	131 (18.8)	125 (19.2)	121 (19.6)	116 (18.5)	<0.01
Sodium (mEq/L)	140 [137–142]	140 [138–142]	140 [138–142]	139 [137–142]	<0.01
Potassium (mmol/L)	4.32 (0.6)	4.35 (0.6)	4.32 (0.6)	4.39 (0.7)	0.37
Creatinine (μmol/L)	122 (33.1)	119 (32.9)	119 (35.7)	119 (33.4)	<0.01
eGFR (ml/min/1.73 m^2)	53.0 [41.8–64.0]	50.3 [39.7–61.0]	49.0 [38.0–60.0]	45.0 [36.0–58.5]	<0.01
NT-proBNP at screening (pg/ml)	7312 [4242–13 509]	5786 [3507–9006]	4418 [2932–7822]	3997 [2781–7051]	<0.01
ALT (U/L)	24.5 [16.8–39.0]	22.0 [15.0–34.0]	21.0 [15.0–32.6]	22.0 [15.0–33.5]	<0.01
AST (U/L)	27.0 [20.0–37.8]	26.0 [19.2–36.0]	25.0 [19.0–34.7]	25.0 [19.0–34.8]	<0.01

Values are given as mean (standard deviation), or median [interquartile range], unless otherwise indicated.

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; 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; HFsnEF, heart failure with supranormal ejection fraction; ICD, implantable cardioverter-defibrillator; IV, intravenous; JVP, jugular venous pressure; MRA, mineralocorticoid receptor antagonist; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

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currently defined HFpEF population, those with a supranormal ejection fraction were distinctly different. Phenotyping the heterogeneous pool of HFpEF patients is important to get insight in different pathophysiological mechanisms, which could contribute to phenotype-specific treatment and improved clinical outcome.[15] We therefore studied predictors of HFsnEF compared to patients with HFpEF. The results from our logistic regression indeed suggest that HFpEF and HFsnEF are significantly different in certain aspects, suggesting that it might be a distinctive clinical entity. In our current study, we found that a higher proportion of female sex is associated with HFsnEF, in addition to lower natriuretic peptides, a higher prevalence of non-ischaemic HF aetiology and higher plasma levels of BUN. To strengthen the assumption that HFsnEF indeed is a separate entity, other methodological approaches could be considered. A multi-omics study investigating the differences between all the HF subtypes might be a very interesting option.[16]

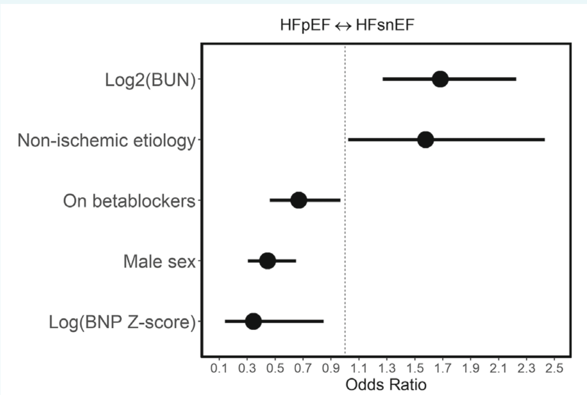

Figure 1 Multivariable predictors of heart failure with supranormal ejection fraction (HFsnEF) compared with heart failure with preserved ejection fraction (HFpEF) patients. Backward stepwise variable selection on multiple imputed ($n = 50$) datasets, variables with univariable p-value of <0.10 were included in the multivariable model. BNP, brain natriuretic peptide; BUN, blood urea nitrogen.

The pathophysiological mechanisms of patients with HFsnEF have yet to be elucidated. It has been found that women with a supranormal LVEF (but not HF) were at increased risk of major adverse cardiac events and had more microvascular dysfunction and increased sympathetic tone.[17] In another study where patients were evaluated for coronary artery disease using coronary computed tomography angiography, it was found that a LVEF >65% was associated with worse outcomes in women. Interestingly, they found that the prevalence of small hearts (defined according to an indexed left ventricular end-systolic volume <16 ml/m^2) was twice as high in women than in men.[11] Women tend to have smaller indexed left ventricular end-systolic volumes and smaller left ventricular end-diastolic volumes compared to men.[18] Small ventricles can only generate sufficient cardiac output by increasing ejection fraction or heart rate.[19] In addition, it has been shown that those low ventricular volumes and associated supranormal LVEFs are reducing pumping efficiency, meaning that every heartbeat consumes more oxygen.[20] Those mechanisms could contribute to increased adverse outcome, especially in women. Investigating this specific subgroup of patients (women with HF and low volumes) might be of special interest.

The relationship between all-cause mortality and LVEF, both in acute and chronic HF, after an acute coronary event or in the general population has been described earlier, where it was found that this relationship was U-shaped.[6,8,13,21,22] Another recent study found that genetic predisposition to and presence of a supranormal LVEF (LVEF >70%) was associated with decreased survival.[23] Multivariable-adjusted splines already demonstrated a U-shaped relationship between all-cause mortality and continuous LVEF in RELAX-AHF-2.[8] We did not find a statistically higher all-cause mortality in patients with HFsnEF, but as the group size was small and the number of events even smaller, we might not have had the statistical power to detect a significant difference. Although we did not find an increase in all-cause mortality, we did find an increase in the risk of non-CV mortality, which is consistent with previous study in the RELAX-AHF-2 of non-CV mortality being higher in HFpEF.[24] Little is known about cause of death in patients with HFsnEF, especially in AHF. It has been found that elderly patients with HFpEF (>75 years) had an increased risk of non-CV death after a hospitalization for AHF compared to

Table 2 Unadjusted event rates

	HFrEF (n = 3180)	HFmrEF (n = 1353)	HFpEF (n = 1440)	HFsnEF (n = 155)	p-value
180-day all-cause death	359 (11.3%)	139 (10.3%)	159 (11.0%)	24 (15.5%)	0.25
180-day CV death	290 (9.1%)	110 (8.1%)	104 (7.2%)	14 (9.0%)	0.18
180-day non-CV mortality	69 (2.2%)	29 (2.1%)	55 (3.8%)	10 (6.4%)	<0.01
WHF day 5	220 (6.9%)	96 (7.1%)	107 (7.4%)	15 (9.7%)	0.59
180-day rehospitalization for RF/HF	631 (19.8%)	219 (16.2%)	260 (18.1%)	22 (14.2%)	0.01
180-day composite	809 (25.4%)	286 (21.1%)	333 (23.1%)	34 (21.9%)	0.01

CV, cardiovascular; 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; HFsnEF, heart failure with supranormal ejection fraction; RF, renal failure; WHF, worsening heart failure.

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Table 3 Cox regression analysis of left ventricular ejection fraction subgroups and primary and secondary outcomes

	ACM[a] 180 days	Non-CVD[a] 180 days	CVD[a] 180 days	WHF[b] day 5	HF/RF hospitalization[b] 180 days	CVD + HF/RF hospitalization[b] 180 days
Univariable						
HFrEF	Ref	Ref	Ref	Ref	Ref	Ref
HFmrEF	0.91 (0.75–1.11), $p = 0.35$	0.99 (0.64–1.52), $p = 0.95$	0.89 (0.72–1.11), $p = 0.31$	1.03 (0.81–1.31), $p = 0.82$	0.79 (0.68–0.93), $p < 0.01$	0.81 (0.71–0.93), $p < 0.01$
HFpEF	0.97 (0.81–1.17), $p = 0.78$	1.75 (1.23–2.50), $p < 0.01$	0.79 (0.63–0.99), $p = 0.04$	1.08 (0.86–1.36), $p = 0.52$	0.90 (0.78–1.04), $p = 0.17$	0.90 (0.79–1.02), $p = 0.11$
HFsnEF	1.41 (0.93–2.13), $p = 0.10$	3.07 (1.58–5.95), $p < 0.01$	1.02 (0.60–1.74), $p = 0.95$	1.42 (0.84–2.40), $p = 0.19$	0.73 (0.47–1.11), $p = 0.14$	0.87 (0.62–1.23), $p = 0.45$
Age/sex						
HFrEF	Ref	Ref	Ref	Ref	Ref	Ref
HFmrEF	0.83 (0.68–1.01), $p = 0.06$	0.87 (0.56–1.36), $p = 0.55$	0.82 (0.65–1.02), $p = 0.08$	0.99 (0.78–1.27), $p = 0.99$	0.78 (0.67–0.92), $p < 0.01$	0.79 (0.69–0.90), $p < 0.01$
HFpEF	0.87 (0.71–1.05), $p = 0.15$	1.53 (1.05–2.21), $p = 0.03$	0.70 (0.56–0.89), $p < 0.01$	1.05 (0.82–1.33), $p = 0.70$	0.89 (0.77–1.04), $p = 0.13$	0.87 (0.76–0.99), $p = 0.04$
HFsnEF	1.27 (0.83–1.93), $p = 0.27$	2.79 (1.41–5.52), $p < 0.01$	0.91 (0.53–1.56), $p = 0.73$	1.41 (0.83–2.39), $p = 0.21$	0.72 (0.47–1.11), $p = 0.13$	0.84 (0.60–1.19), $p = 0.34$
Full model[a]						
HFrEF	Ref	Ref	Ref	Ref	Ref	Ref
HFmrEF	0.95 (0.77–1.16), $p = 0.61$	0.92 (0.58–1.45), $p = 0.71$	0.97 (0.77–1.22), $p = 0.77$	1.05 (0.81–1.35), $p = 0.71$	0.81 (0.69–0.95), $p = 0.01$	0.83 (0.72–0.96), $p = 0.01$
HFpEF	1.08 (0.87–1.33), $p = 0.48$	1.58 (1.05–2.37), $p = 0.03$	0.93 (0.73–1.20), $p = 0.60$	1.20 (0.93–1.55), $p = 0.17$	0.84 (0.71–0.99), $p = 0.03$	0.91 (0.78–1.05), $p = 0.19$
HFsnEF	1.45 (0.94–2.24), $p = 0.09$	2.65 (1.29–5.43), $p < 0.01$	1.11 (0.63–1.94), $p = 0.71$	1.60 (0.93–2.78), $p = 0.09$	0.61 (0.39–0.95), $p = 0.03$	0.81 (0.57–1.16), $p = 0.26$

Values are given as hazard ratio (95% confidence interval).

ACM, all-cause mortality; CVD, cardiovascular death; 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; HFsnEF, heart failure with supranormal ejection fraction; RF, renal failure; WHF, worsening heart failure.

[a]For CVD, non-CVD or ACM, the following variables were used for correction: creatinine (µmol/L), haemoglobin (g/L), sodium (mmol/L), blood urea nitrogen (mg/dl), history of cerebrovascular accident, asthma/bronchitis/chronic obstructive pulmonary disease, peripheral arterial occlusive disease, respiration rate (breaths/min), systolic blood pressure (mmHg), body mass index (kg/m^2), oedema, intravenous loop diuretics (total dose in furosemide units) at baseline, known history of diabetes mellitus, prior HF hospitalization, actual study treatment, composite of N-terminal pro-brain natriuretic peptide or brain natriuretic peptide Z-score; sex, age (years).

[b]For WHF at day 5, rehospitalization for RF or HF through day 180 or the composite of CVD and HF/RF hospitalization, the following variables were used to correct: creatinine (µmol/L), haemoglobin (g/L), sodium (mmol/L), blood urea nitrogen (mg/dl), history of cerebrovascular accident, depression, asthma/bronchitis/chronic obstructive pulmonary disease, atrial fibrillation/flutter, peripheral arterial occlusive disease, pulse (bpm), respiration rate (breaths/min), systolic blood pressure (mmHg), oedema, intravenous loop diuretics (total dose in furosemide units) at baseline, known history of diabetes mellitus, prior HF hospitalization, actual study treatment, grouped geographical region, composite of NT- N-terminal pro-brain natriuretic peptide or brain natriuretic peptide Z-score, sex, age (years).

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Table 4 Percentages of cardiovascular and non-cardiovascular mortality stratified per heart failure subgroup

	HFrEF (*n* = 359)	HFmrEF (*n* = 139)	HFpEF (*n* = 159)	HFsnEF (*n* = 24)	*p*-value
Adjudicated cause of death					<0.01
Cardiovascular	290 (80.8%)	110 (79.1%)	104 (65.4%)	14 (58.3%)	
Non-cardiovascular	69 (19.2%)	29 (20.9%)	55 (34.6%)	10 (41.7%)	

HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFsnEF, heart failure with supranormal ejection fraction.

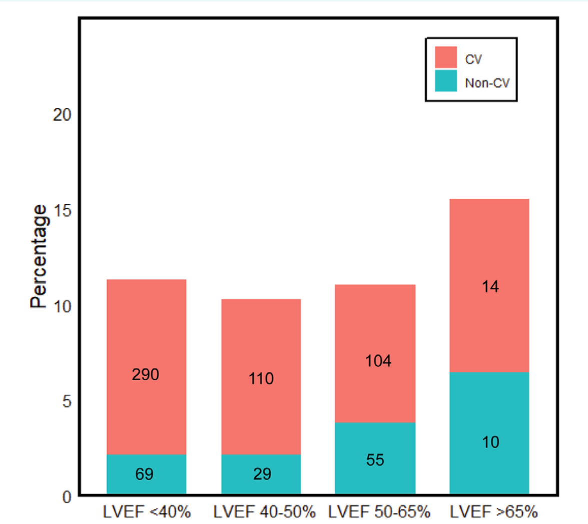

Figure 2 Proportion of 180-day all-cause, cardiovascular (CV) and non-CV mortality by heart failure subgroup. The numbers inside the bars reflect the absolute number of events per category. LVEF, left ventricular ejection fraction.

younger patients.[25] In our cohort, HFpEF and HFsnEF patients were generally older, which most likely have contributed to the higher risk of non-CV death. Secondly, in the predecessor of this study, RELAX-AHF, it was found that patients that died from non-CV causes had higher LVEF than patients who died from CV-causes.[26] To our knowledge this is the first study examining CV and non-CV mortality for patients with HFsnEF, showing a high proportion of non-CV death after AHF hospitalization.

Strengths and limitations

To our knowledge, we are the first to extensively describe the predictors, characteristics, and clinical outcome of patients with HFsnEF in AHF. For this *post-hoc* analysis, we have used a large well-defined cohort of AHF patients, where LVEF was assessed at baseline. A few limitations need to be addressed. First, as this was a *post-hoc* analysis, results from this study should only be hypothesis generating. Second, when assessing clinical outcome, it should be taken into account that only AHF patients with a systolic blood pressure >125 mmHg were included in this study. This might have excluded patients who were at higher risk of in-hospital and post-discharge adverse events, especially in the HFrEF group. Third, LVEF quantification and echocardiographic assessment was done at the discretion of the investigator and measurements were not supervised by a central core lab. Therefore, LVEF quantification, especially for patients with a higher LVEF, could come with a certain degree of uncertainty. Fourth, due to a low number of patients in the HFsnEF group, we had an even lower amount of events in this group, which might lead to an increased type II error risk. Fifth, RELAX-AHF-2 required patients to have elevated natriuretic peptide level. As NT-proBNP decreases with increasing LVEF, this might have caused a lower prevalence of patients with HFsnEF in our cohort. Finally, logistic regression analysis identifies predictors for HFsnEF and is capable of investigating correlations, but a more in-depth analysis might be more suitable to establish whether HFsnEF is a separate entity.

Conclusions

Relatively few patients with AHF have HFsnEF. These are more often female, have lower natriuretic peptides and show a higher non-CV mortality compared with the other HF subgroups. Our findings suggest that patients with HFsnEF have higher non-CV mortality and lower risk of recurrent HF hospitalization over the 180 days post-discharge than other cohorts of HF patients categorized according to LVEF. More research is needed to confirm these differences in risk and to elucidate the exact pathophysiology and sex-specific characteristics of this group.

Supplementary Information

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

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