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ORIGINAL RESEARCH ARTICLE

Predictors of long-term outcome in heart failure with preserved ejection fraction: a follow-up from the KaRen study

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Abstract

Aims Heart failure (HF) with preserved ejection fraction (HFpEF) has poor long-term prognosis. We assessed rates and predictors of outcome 10 years after an acute episode of HF.

Methods and results The Karolinska-Rennes (KaRen) study enrolled HFpEF patients with acute HF, ejection fraction ≥ 45%, and N-terminal pro-brain natriuretic peptide > 300 ng/L in 2007–11. Clinical data were collected at enrolment and after 4–8 weeks including detailed echocardiography. Follow-up data were collected 10 years after study initiation, starting from 6 months after enrolment until 2018 assessed by telephone. Independent predictors of primary (all-cause mortality or HF hospitalization) and secondary (all-cause mortality) outcomes were assessed by multivariable Cox regression. Of 539 patients, long-term follow-up data were available for 397 patients [52% female; median (interquartile range) age 79 (73, 84) years]. Over a follow-up of 5.44 (2.06–7.89) years, 1, 3, 5, and 10 year mortality rates were 15%, 31%, 47%, and 74%, respectively, with an incidence rate of 130/1000 patient-years. The primary outcome was met in 84% of the population, with an incidence rate of 227/1000 patient-years. The independent predictors of the primary outcome were tricuspid regurgitation peak velocity (m/s) [hazard ratio 1.87 (1.34–2.62)], diabetes mellitus [1.75 (1.11–2.74)], and cancer [1.75 (1.01–3.03)] while female sex was associated with reduced risk [0.64 (0.41–0.98)].

Conclusions In HFpEF, 1, 3, 5, and 10 year mortality was 15%, 31%, 47%, and 74% and mortality or first HF hospitalization was 35%, 54%, 67%, and 84%, respectively. Independent predictors of mortality or HF hospitalization were tricuspid regurgitation peak velocity, diabetes mellitus, cancer, and male sex. In clinical management of HFpEF, attention should be paid to both cardiac and non-cardiac conditions.

Keywords HFpEF; Diastolic heart failure; Predictors; Prognosis; Mortality

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Introduction

Heart failure (HF) accounts for a significant part of the global disease burden affecting 26 million people worldwide.[1] According to the European Society of Cardiology guidelines, HF is classified based on left ventricular ejection fraction (LVEF) into HF with preserved LVEF (≥50%; HFpEF), HF with reduced LVEF (<40%; HFrEF), and HF with mid-range LVEF (HFmrEF; LVEF 40–49%).[2] HFpEF patients represents almost half of all HF, but the population is highly heterogeneous and poorly characterized.[2] Further, HFpEF is associated with mortality rates similar to HFrEF, especially following a hospital admission for HF.[3,4] Unlike HFrEF, there are no proven therapies that reduce mortality or morbidity in HFpEF.[5–7]

Previous studies have suggested a variety of prognostic predictors in HFpEF, including non-cardiac co-morbidities such as

anaemia, diabetes mellitus, and obesity,[8] and echocardiographic measurements representing reduced left ventricular (LV) compliance and right ventricular remodelling.[9,10] However, their implication on long-term outcome have been inadequately investigated because in most studies the follow-up is limited to 5 years or less. Therefore, longer follow-up data are needed to improve the understanding of this syndrome and the prognostic impact of its different phenotypes.

The Karolinska-Rennes (KaRen) study was designed to enrol patients presenting with acute signs and symptoms of HFpEF, with the purpose of improving the understanding of the pathophysiology and prognostication in this syndrome.[11] The aim of the current analysis was to assess risk for and independent predictors of 10 year mortality and hospital admissions in the KaRen study.

Material and methods

Study design and data

The KaRen study was a prospective, observational, multicentre study aiming to characterize and identify prognostic factors for morbidity and mortality in HFpEF. Patients were included during an acute presentation of HF with signs and symptoms of HF according to Framingham criteria for HF,[11] LVEF $\geq$ 45% by echocardiography, and brain natriuretic peptide (BNP) $>$ 100 ng/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) $>$ 300 ng/mL within 72 h of presentation. In total, 539 patients were enrolled at baseline whereof 438 returned for a follow-up visit in stable state after 4–8 weeks, which included a detailed echocardiographic assessment, electrocardiogram, and clinical evaluation. The baseline data in the present analysis were collected at enrolment (clinical characteristics and medical history) and at the stable 4–8 week visit (laboratory assessments and detailed echocardiography). Echocardiography was assessed using ViVid 7 ultrasound systems (GE Healthcare, Horten, Norway) and analysed in the core lab in Rennes, France.[11,12] Hyponatraemia was defined as sodium $<$ 135 mmol/L, anaemia was defined as haemoglobin $<$ 12 g/dL in women and $<$13 g/dL in men (according to World Health Organization), and estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Follow-up and outcomes

Patients were followed by telephone call every 6 up to 18 months regarding potential hospitalizations and mortality until November 2012. For the purpose of the current study, long-term follow-up data were assessed in France and Sweden by a 10 year telephone contact with patients or medical institutions and patient charts, and in Sweden through the Swedish National Patient Register, which provided mortality and HF hospitalization data (through ICD-10 codes) for the time period between 30 September 2012 and 30 September 2018. Patients were followed until death or censored alive at the last follow-up visit or contact with medical institution (seven patients in France) where they were enrolled. Consistent with our previous prognostic analyses in the KaRen study,[13] the primary composite outcome was defined as time to all-cause mortality or first HF hospitalization. The secondary outcome was all-cause mortality.

Statistical analysis

Due to the known sex-based differences in patient characteristics in HFpEF, baseline characteristics were reported in the overall cohort and stratified by sex. Continuous variables were presented as median [interquartile range (IQR)] and compared in women vs. men using the Mann–Whitney test while categorical variables were reported as absolute frequencies (percentages) and compared using the χ^2 test. Missing values for baseline characteristics were presented as numbers (%). The Kaplan–Meier analysis was used to assess and log-rank test to compare the occurrence of the primary and secondary outcomes in women vs. men, across the distribution of tricuspid regurgitation peak velocity (TRV) [i.e. classified as low ($<$2.8 m/s), medium (2.8–3.1 m/s), or high ($>$3.1 m/s)] and diastolic dysfunction (with E/e′ ratio categorized as $>$13 or $\leq$13). The latter two were chosen because they have previously been shown to be important for shorter-term outcomes.[10,14] Information on TRV was missing in 46% of the patients, and these were excluded from the multivariable analyses. The incidence rate (IR) for each outcome was reported as events per 1000 patient-years.

Associations between clinical characteristics, echocardiographic variables, and the primary and secondary outcomes were analysed by unadjusted and adjusted Cox proportional hazard models and presented as hazard ratio (HR) and 95% confidence intervals (CIs). We conducted univariable analyses on selected clinically relevant characteristics, that is, sex, age, New York Heart Association (NYHA) class before admission, heart rate, body mass index (BMI), eGFR, NT-proBNP, hyponatraemia, ischaemic heart disease, hypertension, atrial fibrillation (AF) or flutter, stroke, diabetes mellitus, anaemia, syncope, pulmonary disease, cancer, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), beta-blockers, mineralocorticoid receptor antagonist (MRA), and loop diuretics. We also analysed echocardiographic measurements [LVEF $\geq$ 50%, TRV, interventricular septal thickness (IVST), E/e′ ratio $>$13 vs. $\leq$13, and systolic peak of mitral annulus velocity (LV s′)] to investigate their association with the outcomes. Heart rate, BMI, eGFR,

NT-proBNP, and LVEF were categorized to enhance interpretability, and number of parameters included in the multivariable model were restricted to below 10 events per variable to avoid overfitting. We included these clinical and echocardiographic parameters in a multivariable regression model to investigate the independent predictors of the primary and secondary outcomes. The complete unadjusted and adjusted Cox proportional hazard models for patients with LVEF $\geq$ 45% and $\geq$50%, respectively, are provided in Supporting Information, *Tables S1–S4*. For all the analyses, a *P*-value $\leq$ 0.05 indicated statistical significance. Statistical analyses were performed in Stata, StataCorp (2017), Stata Statistical Software: Release 15 (College Station, TX: StataCorp LLC).

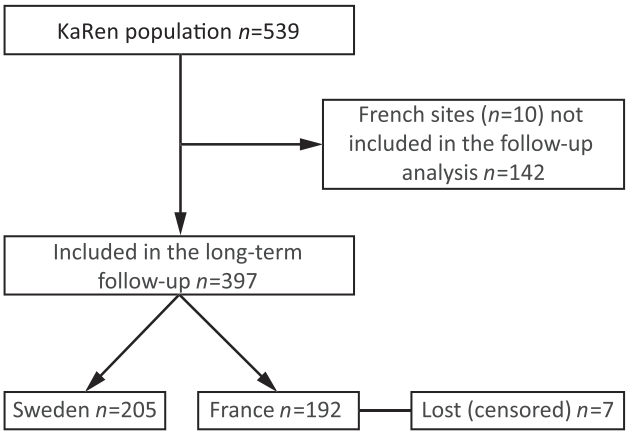
Ethical considerations

The KaRen study and the current analysis were reviewed and approved by the French and Swedish ethics committees and conformed to the Declaration of Helsinki. All patients provided written informed consent.

Results

Between 21 May 2007 and 29 December 2011, 539 patients were enrolled in three centres in Sweden and eleven centres in France (whereof one centre in France participated in the present follow-up analysis). Hence, 397 patients (205 in Sweden and 192 in France) were included in the current analysis (*Figure 1*).

Figure 1 Flow chart showing patient inclusion in the 10 year follow-up analysis of the Karolinska-Rennes (KaRen) study.



Baseline characteristics

In the overall population at enrolment, median (IQR) age was 78 (72, 84) years; 52% were female. Most patients were in NYHA class II prior to acute presentation (61%), NT-proBNP levels were 2469 (1319, 4860) (ng/L), and eGFR was 62 (46, 79) (mL/min/1.73 m^2). In total, 36% were obese, defined as BMI $\geq$ 30 kg/m^2, 78% had hypertension, 63% had AF or flutter, 26% had diabetes mellitus, and 45% had anaemia. Out of 291 patients with heart rate $\geq$ 70 b.p.m., 67% had AF (*Table 1*).

When compared with men, women were older, less likely to report history of ischaemic heart disease, cancer, anaemia, and renal disease, and more likely treated with digoxin (*Table 1*). Finally, there were differences in echocardiographic measurements between the sexes (*Table 2*). Women had higher E/e′ ratio and supine heart rate, but lower stroke volume, LV end-diastolic volume (LVED), LV end-systolic volume (LVES), LV s′, and smaller IVST and right atrial area (RA). The severity of TRV did not differ between the sexes.

Survival analysis

Median follow-up was 5.44 years (2.06–7.89). In the overall cohort, the rate of all-cause mortality or first HF hospitalization was 227 per 1000 patient-years, and the mortality rate was 130 events per 1000 patient-years. Event-free survival rate at 1, 3, 5, and 10 years for the primary outcome was 65%, 46%, 33%, and 16% and for the secondary outcome 85%, 69%, 53%, and 26%, respectively. The event-free survival rates were higher in women compared with men, that is, for the primary outcome 67% vs. 63% at 1 year, 50% vs. 42% at 3 years, 39% vs. 26% at 5 years, and 18% vs. 12% at 10 years and for the secondary outcome 85% vs. 83% at 1 year, 74% vs. 64% at 3 years, 61% vs. 44% at 5 years, and 30% vs. 21% at 10 years. Survival curves in the overall population and in the strata defined according to sex, TRV, and E/e′ ratio are depicted in *Figure 2* for all-cause mortality or first HF hospitalization and in *Figure 3* for all-cause mortality. Women reported lower crude risk of the primary and secondary outcomes compared with men (log-rank *P* = 0.023 and *P* = 0.015, respectively; *Figures 2B* and *3B*).

Predictors of prognosis

Figure 4 shows the patient characteristics independently associated with the primary outcome, that is, female sex (HR 0.64 [95% CI 0.41–0.98]; *P* = 0.040), diabetes mellitus (HR 1.75 [95% CI 1.11–2.74]; *P* = 0.016), cancer (HR 1.75 [95% CI 1.01–3.03]; *P* = 0.045), and TRV (HR 1.87 [95% CI 1.34–2.62]; *P* < 0.001). Patient characteristics independently associated with higher risk of all-cause death were higher age (HR 1.03

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Table 1 Clinical characteristics by sex

	Missing (%)	Total (n = 397)	Male (n = 191)	Female (n = 206)	P-value
Age (years)		78 (72, 84)	77 (70, 83)	79 (73, 84)	0.045
BMI (kg/m^2)	11 (2.8)	28 (24, 32)	28 (25, 32)	28 (24, 31)	0.254
Obese (≥30 kg/m^2)	11 (2.8)	144 (36)	74 (39)	70 (35)	0.461
Physical findings					
Systolic blood pressure (mmHg)	2 (0.5)	150 (130, 170)	150 (130, 164)	150 (130, 172)	0.210
Diastolic blood pressure (mmHg)	2 (0.5)	76 (65, 90)	75 (64, 90)	76 (67, 90)	0.178
Mean arterial blood pressure (mmHg)	2 (0.5)	100 (88, 114)	99 (87, 112)	103 (90, 117)	0.090
Supine heart rate (b.p.m.)	3 (0.8)	80 (68, 100)	80 (66, 92)	82 (70, 107)	0.007
Tachycardia (>100 b.p.m.)	1 (0.3)	127 (32)	40 (21)	87 (42)	<0.001
NYHA class in stable state before admission, *n* (%)	9 (2.3)				0.101
I		78 (20)	45 (24)	33 (16)	
II		241 (61)	111 (59)	130 (65)	
III		67 (17)	29 (16)	38 (19)	
IV		2 (0.5)	2 (1.1)	0 (0)	
Co-morbidities, *n* (%)					
Valve disease	1 (0.3)	93 (23)	40 (21)	53 (26)	0.288
Hypertension	1 (0.3)	310 (78)	154 (80)	156 (76)	0.223
Atrial fibrillation or flutter		251 (63)	119 (62)	132 (64)	0.755
Known heart failure prior to presentation		158 (40)	75 (39)	83 (40)	0.838
Ischaemic heart disease	3 (0.8)	130 (33)	74 (39)	56 (27)	0.013
History of myocardial infarction	65 (16.4)	66 (17)	39 (26)	27 (15)	0.019
History of brady syncope	8 (2.0)	10 (3)	7 (3.7)	3 (1.5)	0.208
History of tachy syncope		39 (10)	21 (11)	18 (8.7)	0.502
History of non-cardiac syncope		38 (9.6)	21 (11)	17 (8.3)	0.396
Diabetes mellitus	2 (0.5)	105 (26)	58 (31)	47 (23)	0.087
Stroke	1 (0.3)	43 (11)	22 (12)	21 (10)	0.747
Peripheral vascular disease	3 (0.8)	60 (15)	33 (18)	27 (13)	0.263
Conventional pacemaker		53 (13)	29 (15)	24 (12)	0.306
Implantable cardioverter defibrillator	2 (0.5)	1 (0.3)	0 (0)	1 (0.5)	1.000
Coronary artery bypass grafting		31 (8)	20 (11)	11 (5.3)	0.063
Any valve intervention	2 (0.5)	3 (0.8)	2 (1.1)	1 (0.5)	0.609
Pulmonary disease	2 (0.5)	36 (9)	23 (12)	13 (6.3)	0.054
Cancer	1 (0.3)	67 (17)	41 (22)	26 (13)	0.022
Liver disease		8 (2)	4 (2.1)	4 (1.9)	1.000
Smoking	14 (3.5)	175 (44)	118 (65)	57 (28)	<0.001
History of renal disease		123 (31)	73 (38)	50 (24)	0.003
Anaemia (<12 g/dL women, <13 g/dL men)	4 (1.0)	177 (45)	108 (57)	69 (34)	<0.001
Medications at discharge, *n* (%)					
ACEi or ARB	88 (22.2)	237 (60)	112 (76)	125 (78)	0.689
Beta-blocker	88 (22.2)	248 (63)	116 (78)	132 (82)	0.475
MRA	88 (22.2)	86 (22)	41 (28)	45 (28)	1.000
Loop diuretic	88 (22.2)	264 (67)	125 (85)	139 (86)	0.747
Thiazide diuretic	88 (22.2)	29 (7)	11 (7.4)	18 (11)	0.330
Calcium channel blocker	88 (22.2)	81 (20)	43 (29)	38 (24)	0.302
Digoxin	88 (22.2)	29 (7)	6 (4.1)	23 (14)	0.003
Nitrate	88 (22.2)	41 (10)	22 (15)	19 (12)	0.503
Anti-arrhythmic	88 (22.2)	40 (10)	18 (12)	22 (14)	0.737
Anticoagulant	88 (22.2)	178 (45)	80 (54)	98 (61)	0.250
Oral anticoagulant among patients with atrial fibrillation/flutter	88 (22.2)	163 (41)	77 (79)	86 (85)	0.352
Antiplatelets	88 (22.2)	95 (24)	53 (36)	42 (26)	0.084
Statins	88 (22.2)	141 (36)	70 (47)	71 (44)	0.648
Glucose-lowering medication	88 (22.2)	76 (19)	40 (27)	36 (22)	0.357
Whereof insulin	88 (22.2)	46 (12)	28 (70)	18 (50)	0.101
Laboratory data					
eGFR (mL/min/1.73 m^2)		62 (46, 79)	63 (46, 87)	61.5 (46, 76)	0.237
NT-proBNP (ng/L)	1 (0.3)	2469 (1319, 4860)	2371 (1419, 4900)	2600 (1310, 4790)	0.980
NT-proBNP among patients with atrial fibrillation/flutter		2605 (1469, 4941)	2359 (1419, 4900)	2878.5 (1485, 4969.5)	0.370
NT-proBNP among patients without atrial fibrillation/flutter		2292 (1120, 4630)	2394.5 (1360, 5018)	2394.5 (1360, 5018)	0.250
Haemoglobin (g/L)	4 (1.0)	12.3 (11, 13.8)	12.2 (11, 14)	12.3 (11.2, 13.6)	0.926
Sodium (mmol/L)					0.268
Low (<135)		59 (15)	31 (16)	28 (14)	
Normal (135–145)		335 (84)	160 (84)	175 (85)	

(*Continues*)

Table 1 (continued)

	Missing (%)	Total (n = 397)	Male (n = 191)	Female (n = 206)	P-value
High (>145)		3 (0.8)	0 (0)	3 (1.5)	
Potassium (mmol/L)	3 (0.8)				0.434
Low (<3.5)		34 (8.6)	13 (6.8)	21 (10)	
Normal (3.5–5.0)		324 (82)	158 (83)	166 (81)	
High (>5.0)		36 (9)	19 (10)	17 (8.3)	

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association.
Continuous variables are presented as median (interquartile range) and categorical variables as numbers (n) and percentages.

Table 2 Echocardiographic characteristics from 4–8 week clinical visit, by sex

Parameters	Missing (%)	Total (n = 397)	Male (n = 191)	Female (n = 206)	P-value
LV ejection fraction (%)	155 (39.0)	63 (56, 67)	62 (56, 66)	63 (57, 68)	0.151
Stroke volume (mL)	221 (56.0)	29.6 (25.6, 36.8)	31.4 (26.6, 41.9)	28.8 (25, 33.7)	0.012
LV end-diastolic volume (mL/m^2)	155 (39.0)	89 (74, 113)	104 (87, 129)	77 (65, 92)	<0.001
LV end-systolic volume (mL/m^2)	155 (39.0)	35 (25, 45)	40 (33, 49)	28 (21, 38)	<0.001
LV s′ (cm/s)	145 (36.5)	6.5 (5.5, 7.5)	7 (6, 8)	6 (5, 7)	<0.001
LA volume index (mL/m^2)	318 (80.1)	30.9 (21.1, 40.4)	27.1 (22.4, 34.7)	33.1 (21.2, 41.7)	0.298
LA volume index > 34	318 (80.1)	31 (8)	12 (32)	19 (45)	0.260
LV mass index (g/m^2)	350 (88.0)	115 (95, 141)	123 (102, 156)	109 (95, 133)	0.113
Men with LVMI > 115	371 (93.5)		15 (58)	—	
Women with LVMI > 95	376 (94.7)		—	14 (67)	
Interventricular septal thickness (mm)	156 (39.2)	11 (10, 13)	12 (11, 14)	11 (10, 12)	<0.001
LV longitudinal strain	317 (80.0)	15.5 (13.2, 18.4)	15.2 (12, 18)	16.1 (13.6, 18.6)	0.270
E/e′ ratio	163 (41.1)	10.8 (8.5, 15.1)	9.8 (8, 13.29)	11.7 (9.1, 16.6)	<0.001
Right atrial area (cm^2)	149 (38.0)	20 (17, 24.5)	22 (19, 27)	19 (16, 22)	<0.001
Tricuspid regurgitation (m/s)	182 (45.8)	2.9 (2.5, 3.3)	2.9 (2.4, 3.2)	2.9 (2.6, 3.3)	0.145
Mitral regurgitation: Grade	151 (38.0)				0.018
1		133 (34)	71 (61)	62 (48)	
2		45 (11)	15 (13)	30 (23)	
3		14 (4)	3 (2.5)	11 (8.6)	
Tricuspid annulus plan systolic excursion (mm)	148 (37.3)	17 (13, 20)	17 (13, 21)	16 (13, 20)	0.259
RV global longitudinal strain	317 (80.0)	−15.25 (−18, −12)	−15 (−17.5, −12.5)	−16 (−18, −11)	0.851

LA, left atrial; LV s′, systolic peak of mitral annulus velocity; LV, left ventricular; LVMI, LV mass index.
Continuous variables are presented as median (interquartile range) and categorical variables as numbers (n) and percentages.

per year [95% CI 1.00–1.06]; P = 0.032), heart rate ≥ 70 b.p.m. (HR 1.68 [95% CI 1.04–2.71]; P = 0.035), anaemia (HR 1.63 [95% CI 1.05–2.53]; P = 0.029), hyponatraemia (HR 2.69 [95% CI 1.58–4.59]; P < 0.001), and elevated TRV (HR 2.14 [95% CI 1.48–3.08]; P < 0.001), whereas female sex (HR 0.50 [95% CI 0.31–0.79]; P = 0.004), LV s′ (HR 0.83 [95% CI 0.71–0.96]; P = 0.015), and LVEF ≥ 50% vs. 45–49% (HR 0.23 [95% CI 0.08–0.63]; P = 0.004) were independently associated with a reduced mortality risk (*Figure 5*).

For the two pre-specified risk factor comparisons, the presence of medium and high vs. low TRV at the 4–8 week assessment was associated with higher risk of both outcomes (log-rank test; both P < 0.001; *Figures 2C* and *3C*). Similarly, elevated TRV was independently associated with both outcomes (*Figures 4* and *5*). An E/e′ ratio > 13 was associated with worse prognosis for both outcomes in the univariable analysis, but not after adjustments in the multivariable model, HR 1.19 [95% CI 0.78–1.80] (P = 0.421) for the primary outcome and HR 0.95 [95% CI 0.61–1.49] (P = 0.833) for the secondary outcome.

Discussion

In this long-term outcome analysis of the KaRen HFpEF study, the 1, 3, 5, and 10 year mortality was 15%, 31%, 47%, and 74% and mortality or first HF hospitalization was 35%, 54%, 67%, and 84%, respectively. TRV and female sex were independently associated with both outcomes. Diabetes and cancer were associated with increased risk of all-cause mortality or HF hospitalization whereas higher heart rate, anaemia, and hyponatraemia were independent predictors of all-cause mortality.

Prognosis in heart failure with preserved ejection fraction

Previous studies have reported inconsistent mortality rates in HFpEF, with lower rates in clinical trials compared with epidemiological studies.[15] Mortality rates in HFpEF are comparable

Figure 2 The Kaplan–Meier survival curves of the primary outcome (all-cause mortality or first heart failure hospitalization)—Survival curves for (A) all subjects and (B) sex and (C) subjects with tricuspid regurgitation peak velocity (TR) classified as low (<2.8 m/s), medium (2.8–3.1 m/s), or high (>3.1 m/s) and (D) E/e′ ratio classified as >13 or ≤13.

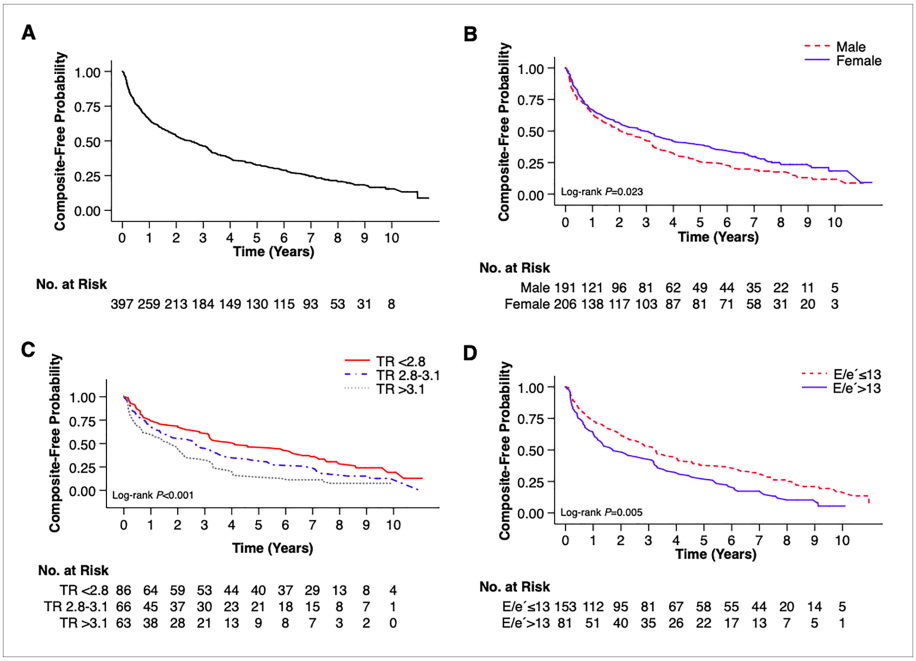


Figure 3 The Kaplan–Meier survival curves of the secondary outcome (all-cause mortality)—Survival curves for (A) all subjects and (B) sex and (C) subjects with tricuspid regurgitation peak velocity (TR) classified as low (<2.8 m/s), medium (2.8–3.1 m/s), or high (>3.1 m/s) and (D) E/e′ ratio classified as >13 or ≤13.

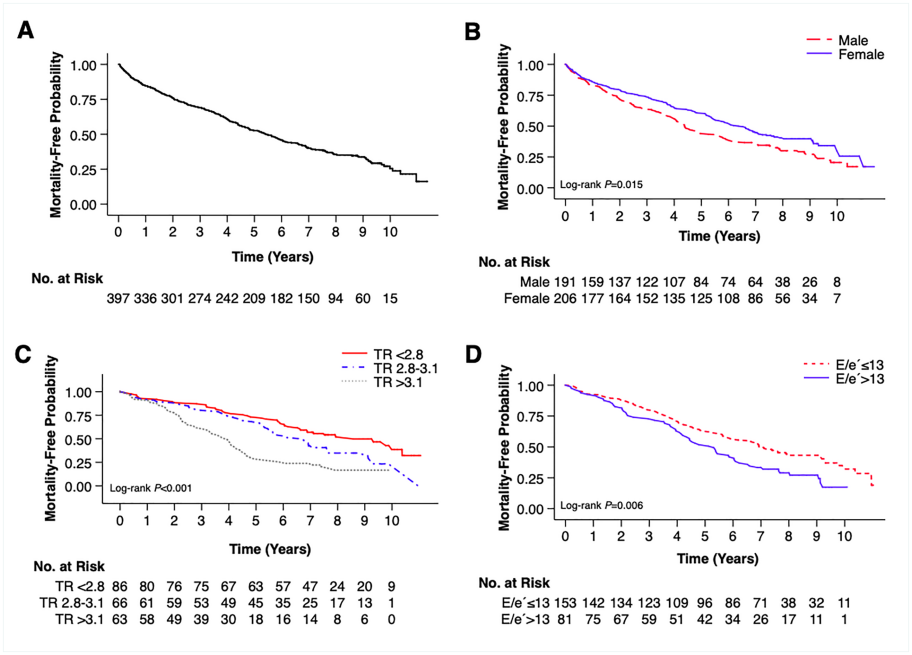
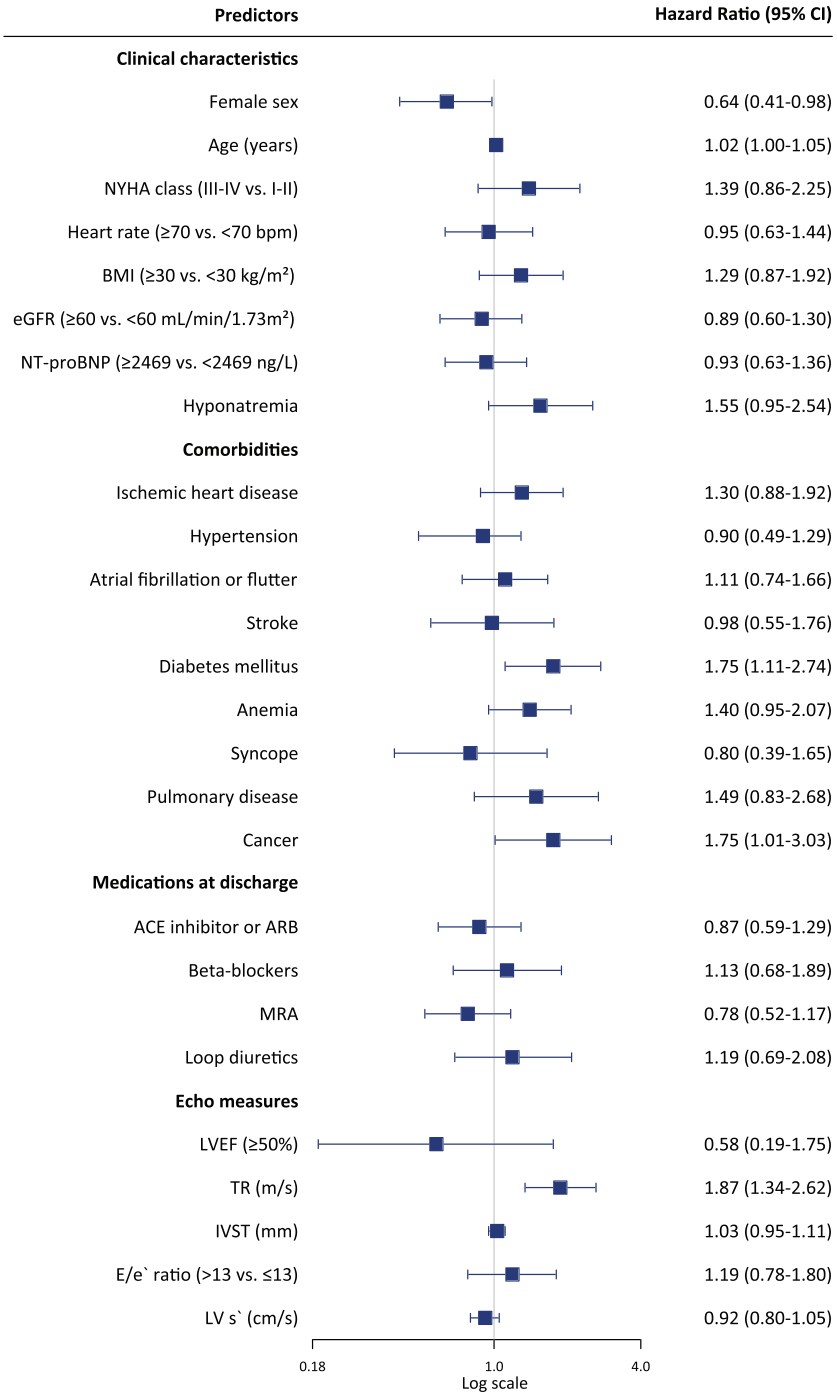


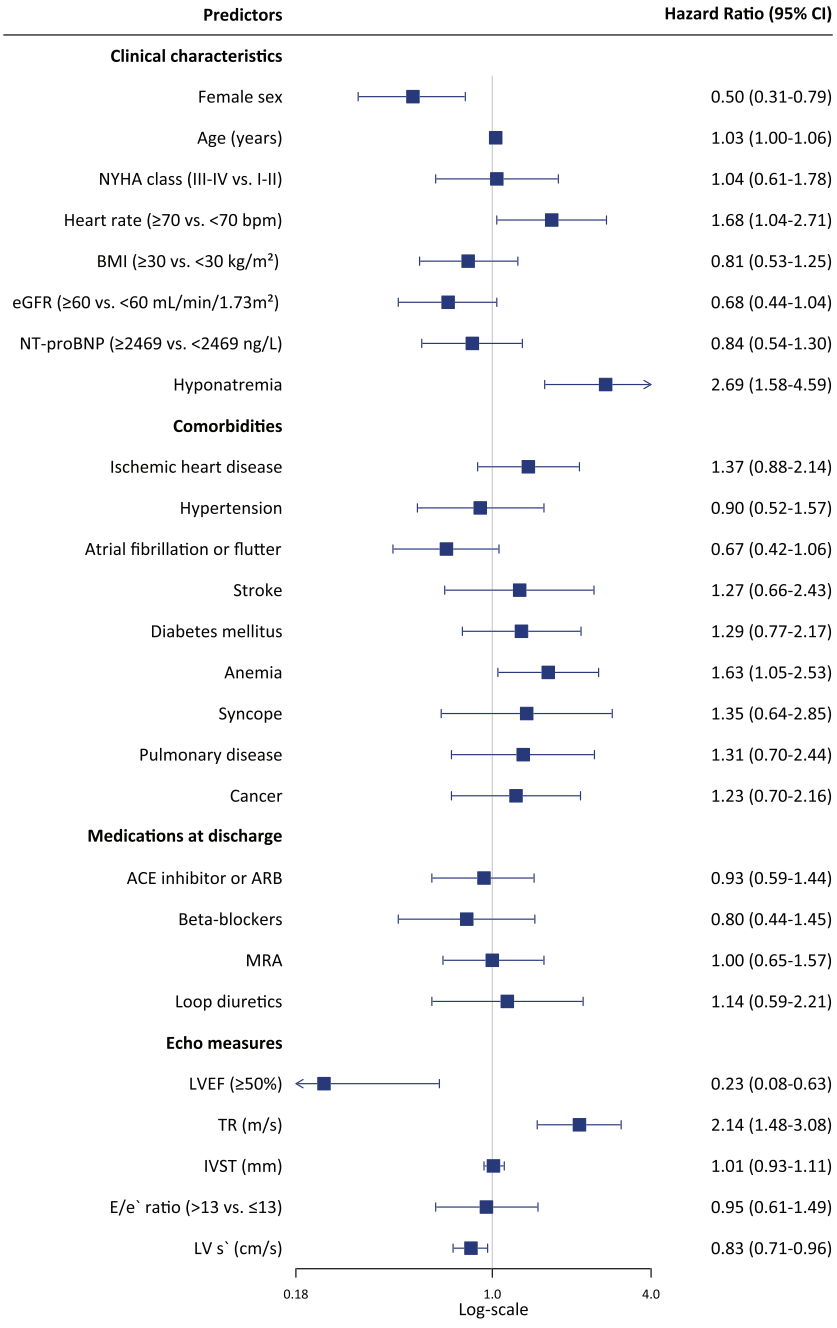
Figure 4 Predictors of all-cause mortality or first heart failure hospitalization—Forest plot depicting multivariable hazard ratios for the primary outcome (time to all-cause mortality or first heart failure hospitalization). ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IVST, interventricular septal thickness; LV s′, systolic peak of mitral annulus velocity; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TR, tricuspid regurgitation peak velocity.



with HFrEF, although survival seems to increase over time in HFrEF but not in HFpEF,[16] which could be a result of emerging effective treatment in HFrEF but not HFpEF.

In 2006, Bhatia *et al*. showed that 1 year following a hospital admission for HFpEF (defined as LVEF $>$ 50%), the mortality rate was 22% and composite outcome (all-cause

Figure 5 Predictors of all-cause mortality—Forest plot depicting multivariable hazard ratios for the secondary outcome (time to all-cause mortality). Abbreviations as in *Figure 4*.



mortality/HF hospitalization) rate was 31%,[3] which was in accordance with some studies[16,17] but lower than large registries.[4] Our study has a lower 1 year mortality rate of 15% but similar rate of the composite outcome of 35%. In longer follow-up studies on patients admitted for decompensated HF, 5 year mortality rates were reported between 45% and 65%.[16–18] In contrast, Shah *et al*. reported a higher 5 year mortality rate of 75% among patients with HFrEF, HFmrEF, and HFpEF with similar rate for HF readmission across the whole LVEF spectrum.[4] Our patients with decompensated HF included in 2007–11 had a slightly lower 5-year mortality rate of 47%.

We present novel insights in prognosis 10 years after an acute episode of decompensated HF, with a 10 year mortality rate of 74 and 10 year rate of mortality or HF hospitalization of 84%, implying that prognosis remains very poor over the

long term in HFpEF patients. To our knowledge, there are few studies with 10 year follow-up data; however, two observational studies have shown similar rates.[17,18] Due to differences in the study design, HFpEF diagnostic criteria, and year of enrolment, it is challenging to compare findings across HFpEF studies. The lower mortality rate in KaRen than previous studies[4] might to some extent be explained by the fact that only 40% of KaRen patients had previous HF diagnosis prior to enrolment and that de novo HFpEF may have better long-term prognosis. The nature of KaRen study design with regular, long-term follow-up mirrors that of clinical trials and could have contributed to lower outcome rates as well.

The female pattern

Our study adds and extends the current understanding of sex differences in HFpEF, demonstrating that women with HF have higher survival rates compared with men over a long study period across a wide range of LVEFs, even after adjusting for clinical characteristics.[19] Women had higher E/e′ ratio, which has also been shown in normal subjects,[20] but the absence of differences in estimated systolic pulmonary artery pressures implies that women do not have higher filling pressures than men. In accordance with the NORRE study, LA volume and right heart cavities were slightly smaller in women vs. men. As in healthy women and in HF studies, heart rate was higher in women than in men, independently of the rhythm.[21] Although AF prevalence was the same in women and men, women with AF had higher heart rate, which has also previously been demonstrated. The reason may be the smaller LV volumes in women, suboptimal rate control, or residual congestion at the 4–8 week follow-up. Reflecting longitudinal systolic dysfunction,[22] women in our study had lower LV s′ compared with men, further indicating a reduced risk for overall mortality. Altogether, our findings reflect the overall picture of women with HFpEF having worse diastolic function.

Co-morbidities and associated conditions

Earlier studies reveal that HFpEF patients are often older, women with mainly non-cardiac co-morbidities compared with HFrEF,[19] which is consistent with our findings. Non-cardiac co-morbidities such as anaemia, diabetes mellitus, hypertension, and overweight or obesity are highly prevalent in HFpEF and suggested as potential disease drivers of the myocardial remodelling and dysfunction.[23] The adjusted models for both the primary and secondary outcomes display a clear trend with increased risk of mortality or HF hospitalization and of mortality alone in the presence of co-morbidities and associated conditions.

We found that anaemia and hyponatraemia were both associated with all-cause mortality corroborating previous findings,[3] however not significantly associated with the primary outcome, reflecting a more general pattern of associated conditions in cardiovascular diseases. Anaemia in patients with HF and specifically HFpEF is associated with higher risk of mortality and/or HF hospitalization.[13] Several studies have shown that hyponatraemia is associated with adverse outcomes in HF but its role in HFpEF is more unclear. Park *et al*. found that hyponatraemia is a risk factor for adverse in-hospital outcomes but had no long-term prognostic value.[24] In our study, more than 80% of patients were on loop diuretics. Diuretic use may be associated with both dilutional and depletional hyponatraemia, which in turn may be a marker of worse HF status. Indeed, our study suggests that hyponatraemia is associated with higher risk of death and may call for tailoring of long-term diuretic dose in HFpEF patients. Natriuretic peptides and chronic kidney disease (CKD) have previously been demonstrated to predict outcome in HFpEF[25,26]; however, we did not observe any impact of NT-proBNP or CKD on our primary and secondary outcomes, maybe due to collinearity between the covariates in the multivariable models. Diabetes was in our study independently associated with the primary outcome including HF hospitalization but not all-cause mortality. In HFpEF, diabetes and metabolic stress in combination with mechanical stress such as hypertension (present in 78% of our patients) have been suggested as a major mechanism underpinning HFpEF pathophysiology.[23] Finally, cancer contributed to an increased risk of mortality in line with previous studies,[3] but there is a need to further investigate the pathophysiological role of cancer in HFpEF and the cardiotoxicity related to cancer therapy.

Echocardiographic predictors

In HFrEF, TRV is associated with LV systolic and diastolic dysfunctions as well as HF events and increased mortality.[27] TRV may better reflect LV impairment than global insensitive parameters like LVEF. TRV has previously been associated with right ventricular dysfunction, a common feature in HFpEF with elevated pulmonary arterial systolic pressure reflecting increased LV pressure.[28] In our multivariable analysis, TRV was the only echocardiographic measurement associated with increased risk for both outcomes. This confirms recent data from Japan showing in which high TRV was associated with mortality (HR 1.04, 1.00–1.07; P = 0.043; median follow-up 748 days).[14] Diastolic dysfunction as reflected by E/e′ ratio has been claimed to be an important prognostic marker,[29] and in the mean follow-up of 28 months of this cohort, we reported that E/e′ ratio was the only echocardiographic predictor associated with adverse outcome.[10] In this extended follow-up, E/e′ ratio $>$ 13 had worse prognosis compared with $\leq$13 and was significant in the univariable

analysis as a continuous variable, but not in the multivariable regression models adjusted for TRV.

Heart failure with preserved ejection fraction and AF are intertwined and share pathophysiology, risk factors, and co-morbidities. The presence of AF in patients with HF regardless of ejection fraction is associated with worse prognosis.[30] We did not find AF to be associated with outcomes, possibly due to study design limitations. Further, information on patients who underwent catheter ablation during the follow-up period were not available. However, a higher heart rate was associated with all-cause mortality. Interestingly, in a small retrospective report in HFpEF, maintenance of sinus rhythm does not seem to alter the risk of all-cause mortality but lower the risk of cardiovascular events.[31] HFpEF patients, regardless presence of AF, have so far not benefited from rate control drugs in randomized controlled trials.[2] There are evidence suggesting that AF patients with HF benefit from pulmonary vein isolation, and this is now studied in HFpEF in the RAFT cohort.[32]

Limitations

The KaRen study is a well-characterized cohort of HFpEF patients; however, the limitations are inherent in the observational nature of the study and thus residual confounding. In the present study, 10 centres (n = 142 patients) in France were excluded due to lack of direct access to patient data required for a telephone follow-up, and there were additional few patients lost to follow-up (n = 7). Complete and detailed echocardiography in patients with many co-morbidities in HFpEF is challenging, and therefore, there is a relatively large proportion of missing data. The relatively small sample size and lack of some echocardiographic measurements did not allow for sub-group analyses and may have contributed to loss of important associations while the use of large predictor models might result in arbitrary significance. However, we believe the predictors of outcomes in our adjusted models would most likely remain of importance in a larger patient material. In this analysis, we did not investigate specific therapies and their impact on outcome as treatment may have changed during the long period of follow-up. Diagnostic criteria for HFpEF have changed since patient enrolment in KaRen; therefore, patients with LVEF $\geq$ 45% were enrolled meaning that our analyses included a few patients (n = 6) with HFmrEF.

Conclusions

In HFpEF, 1, 3, 5, and 10 year mortality was 15%, 31%, 47%, and 74% and mortality or first HF hospitalization was 35%, 54%, 67%, and 84%, respectively. TRV and female sex were independently associated with both outcomes. Diabetes and cancer were associated with increased risk of all-cause mortality or HF hospitalization whereas higher heart rate, anaemia, and hyponatraemia were independent predictors of all-cause mortality. In addition to early prevention and treatment of co-morbidities, age, female sex, and echocardiographic abnormalities such as TRV, LVEF, and LV s′ are important for phenotyping HFpEF and to narrow selection criteria for future clinical intervention trials.

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Conflict of interest

C.H. receives consulting fees from Novartis and Roche Diagnostics and speaker honoraria from Novartis and MSD; E.D. receives research facilities from General Electric Healthcare and a grant from Novartis. He has also teaching facilities provided by Bristol-Myer-Squibb; C.L. receives research grants from Swedish Heart-Lung Foundation and Stockholm County Council and speaker honoraria from Medtronic, Abbot, Microport, Boston Scientific, Novartis, Vifor, Impulse Dynamics, and Bayer; G.S. reports grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, grants from MSD, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, personal fees from Cytokinetics, and personal fees from Medtronic, outside the submitted work; L.H.L. was funded by the Swedish Research Council, the Swedish Heart Lung Foundation, and the Stockholm County Council and receives research grants from AstraZeneca, Novartis, Boehringer Ingelheim, ViforPharma, and Boston Scientific and consulting or speaker's honoraria from AstraZeneca, Novartis, Boehringer Ingelheim, ViforPharma, Bayer, Sanofi, Fresenius, Merck, Myokardia, MedScape, Radcliffe Cardiology, and Lexicon. Other authors have no conflict of interest to declare.

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Supporting information

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

Table S1. Adjusted and Unadjusted Cox proportional hazard analyses to determine factors associated with primary outcome (all-cause mortality or first HF hospitalization) in 397 subjects with LVEF ≥45%.

Table S2. Adjusted and Unadjusted Cox proportional hazard analyses to determine factors associated with secondary outcome (all-cause mortality) in 397 subjects with LVEF ≥45%.

Table S3. Adjusted and Unadjusted Cox proportional hazard analyses to determine factors associated with primary outcome (all-cause mortality or first HF hospitalization) in 391 subjects with LVEF ≥50%.

Table S4. Adjusted and Unadjusted Cox proportional hazard analyses to determine factors associated with secondary outcome (all-cause mortality) in 391 subjects with LVEF ≥50%.

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