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ORIGINAL RESEARCH ARTICLE

Trends in cause-specific readmissions in heart failure with preserved vs. reduced and mid-range ejection fraction

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Abstract

Aims The aim of this study was to investigate whether the readmission of heart failure (HF) patients has decreased over time and how it differs among HF with preserved ejection fraction (EF) (HFpEF) vs. reduced EF (HFrEF) and mid-range EF (HFmrEF).
Methods and results We evaluated HF patients index hospitalized from January 2004 to December 2011 in the Swedish Heart Failure Registry with 1 year follow-up. Outcome measures were the first occurring all-cause, cardiovascular (CV), and HF readmissions. A total of 20 877 HF patients (11 064 HFrEF, 4215 HFmrEF, and 5562 HFpEF) were included in the study. All-cause readmission was the highest in patients with HFpEF, whereas CV and HF readmissions were the highest in HFrEF. From 2004 to 2011, HF readmission rates within 6 months (from 22.3% to 17.3%, $P = 0.003$) and 1 year (from 27.7% to 23.4%, $P = 0.019$) in HFpEF declined, and the risk for 1 year HF readmission in HFpEF was reduced by 7% after adjusting for age and sex ($P = 0.022$). Likewise, risk factors for HF readmission in HFpEF changed. However, no significant changes were observed in all-cause or CV readmission rates in HFpEF, and no significant changes in cause-specific readmissions were observed in HFrEF. Time to the first readmission did not change significantly from 2004 to 2011, regardless of EF subgroup (all *P*-values > 0.05).
Conclusions Declining temporal trend in HF readmission rates was found in HFpEF, but all-cause readmission still remained the highest in HFpEF vs. HFrEF and HFmrEF. More efforts are needed to reduce the non-HF-related readmission in patients with HFpEF.

Keywords Heart failure; Readmission; Trends; Prognosis

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Introduction

The burden of readmission in heart failure (HF) remains challenging. Whether and how readmissions differ among different phenotypes of HF, namely, HF with reduced, mid-range, and preserved ejection fraction (EF) (HFrEF, HFmrEF, and HFpEF, respectively), have not been satisfactorily evaluated. Although the prevalence and incidence are similar and both high,[1] there is still no evidence-based therapy that could reduce mortality in HFpEF compared with HFrEF.[2–7] In this context, to improve well-being and quality of life may be a viable alternative in the treatment of HFpEF patients.[8,9] In particular, hospital readmissions should be paid careful attention given that they exert considerable influence on patients' quality of life in terms of financial cost and physical suffering.

The community population-based Olmsted County study reported that patients with HFpEF were hospitalized an average of 1.39 times per year after diagnosis and that the hospitalization rates did not change significantly over a 10 year study period.[10] Other studies found that in patients hospitalized with HFpEF, 20% were readmitted within 1 month and >50% were readmitted within 1 year after discharge.[11–13]

However, whether the hospital readmission rates and risks change over time in HFpEF patients was scarcely studied. Data from the GWTG-HF (Get With The Guidelines—Heart Failure) registry showed neither significant interaction between time and EF groups for the risk of readmission nor a significant temporal relationship between calendar year of hospitalization and readmission.[14] However, the GWTG-HF study did not focus on trend, and these partial results were presented incompletely. In this study, we aimed to determine whether there were temporal changes in cause-specific readmission rates in HFpEF vs. HFrEF and HFmrEF patients using data from the Swedish Heart Failure Registry (SwedeHF).

Methods

Study protocol

The SwedeHF (www.swedehf.se) has been described previously.[15,16] The registry was established in 2003 as a nationwide HF registry in Sweden. A total of 101 303 registrations from 70 of 80 hospitals in Sweden and 100 of 1000 outpatient primary care clinics were enrolled until December 2014. Approximately 80 variables were recorded after outpatient clinic visits or at discharge. Socio-economic data and follow-up information on patients in the SwedeHF were obtained by linkage to the national database of the Swedish Tax Agency, the Swedish Board of Health, and Welfare and Statistics Sweden. The SwedeHF and linkage to other Swedish governmental health and statistical registries were approved by a multisite ethics committee. Both SwedeHF and the study protocol complied with the Declaration of Helsinki.

Study population

The criterion for entry in SwedeHF is clinician-judged HF in inpatient or outpatient departments. In the present study, if a patient reported more than one registration in different calendar years, only the first registration was included in the study and considered as the index registration. In all, 51 060 unique patients from SwedeHF were eligible for evaluation. Because the current study focused on readmission, those who were registered in outpatient clinics (n = 20 385) and who died before index discharge (n = 1180) were excluded. Patients without EF data (n = 4767) were also excluded. Moreover, patients registered before 1 January 2004 (n = 488) and after 31 December 2011 (n = 3363) were excluded because of a limited sample size and lack of 1 year follow-up information, respectively. Thus, the final sample included 20 887 HF patients registered from 2004 to 2011. Individual consent was not required in SwedeHF, but patients were informed of entry into the registry and allowed to opt out.

Disease definition

EF in the SwedeHF is recorded as $<$30%, 30–39%, 40–49%, and $\geq$50%. HF was classified as HFrEF (EF $<$ 40%), HFmrEF (EF = 40–49%), and HFpEF (EF $\geq$ 50%). Diagnosis of co-morbidities followed the clinical judgement except anaemia, which was re-defined as haemoglobin $<$ 130 g/L in men and $<$120 g/L in women or with a history of the condition.[17] Both current and previous smokers were included as smokers. Revascularization included percutaneous coronary intervention and coronary artery bypass grafting. Device therapy was defined in patients with implantation of a pacemaker, cardiac resynchronization therapy, or an implantable cardioverter-defibrillator. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Outcome and follow-up

Outcomes were the first occurring cause-specific readmissions: all-cause readmission, cardiovascular (CV) readmission, and HF readmission. All-cause readmission was defined as rehospitalization for any reason; CV readmission was defined as rehospitalization for any CV disease, including HF; and HF readmission was defined as subsequent admission for a primary diagnosis of HF. If a patient was readmitted more than once, only the first readmission was collected as the outcome measure. Follow-up time was defined as the date of index hospital discharge to the date of the outcome or maximum 1 year after index discharge.

Statistical analysis

Baseline characteristics were presented as frequencies and percentages for categorical variables and means ± standard deviations or medians with 25th and 75th percentiles for continuous variables. Patients were divided into three HF subgroups: HFrEF, HFmrEF, and HFpEF. Comparisons among groups were performed by the Kruskal–Wallis rank test for continuous variables and one-way ordered categorical variables, Spearman's rank-order correlation test for two-way ordered categorical variables, and Pearson's χ^2 test for unordered categorical variables. The overall cumulative incidence of 1 year cause-specific readmission in patients with HFpEF vs. HFrEF and HFmrEF was presented using Kaplan–Meier curves and compared by the log-rank test. Crude rates of short-term (1 and 3 months) and long-term (6 months and 1 year) cause-specific readmissions were reported by index year category (2004–2005, 2006–2007, 2008–2009, and 2010–2011) in HFrEF, HFmrEF, and HFpEF. The Kruskal–Wallis rank test was done to analyse the temporal trends of readmission rates. Time to the first cause-specific readmissions

was also compared over the index year categories with the same method.

Then the analysis focused on HFpEF patients by showing the readmission risk using the Kaplan–Meier method. A Cox proportional hazards model adjusted for age and sex was performed to calculate the hazard ratio (HR) of 1 year HF readmission of patients enrolled in 2010–2011 vs. 2004–2005. Because a decreasing trend was found in long-term HF readmission in HFpEF patients, we continued to explore whether risk factors for 1 year HF readmission changed over time (2004–2007 vs. 2008–2011) in HFpEF patients. All variables shown in the baseline characteristics table (*Table 1*) underwent a univariable Cox regression analysis, except for smokers, New York Heart Association (NYHA) function class, and N-terminal pro-brain natriuretic peptide (NT-proBNP) because of a large amount of missing data (>20%). Variables with a *P*-value _x0003C; 0.1 in the univariable analysis were simultaneously entered into the Cox proportional hazards models for the multivariable analysis and graphically depicted in forest plots showing HRs with 95% confidence intervals (CIs). Age and sex were forced into all multivariable Cox models regardless of the *P*-values. After that, the use rate of drugs in HFpEF patients were also compared between 2004–2007 and 2008–2011 by using the Pearson χ^2 test. Statistical significance was set to $P < 0.05$ (two-tailed). All statistical analyses were performed by Stata 16.0 (StataCorp LLC, College Station, Texas, USA).

Results

From 1 January 2004 to 31 December 2011, there were 20 877 registered HF inpatients eligible for analysis: 11 064 patients (53.0%) with HFrEF, 4251 (20.4%) with HFmrEF, and 5562 (26.6%) with HFpEF.

Baseline characteristics

Baseline characteristics are summarized in *Table 1*. Compared with HFrEF patients, HFpEF patients were older, more likely to be female, and had a higher level of education. Patients with HFrEF had a higher proportion of smokers and a higher level of income than patients with HFpEF. Diastolic blood pressure, heart rate, and weight were higher in HFrEF patients, whereas systolic blood pressure was higher in HFpEF patients. The proportion of patients with NYHA III or IV functional class was higher in HFrEF than in HFpEF, while the proportion of HF duration ≥ 6 months was similar in the two subgroups.

Patients with HFpEF more frequently had hypertension, atrial fibrillation (AF), valvular disease, lung disease, renal dysfunction, anaemia, stroke or transient ischaemic attack, sleep apnoea, history of cancer, and connective tissue disease. While patients with HFrEF had more ischaemic heart disease, history of revascularization and device therapy, and mental disorder, HFrEF patients also had higher levels of NT-proBNP, haemoglobin, and eGFR than HFpEF patients.

HFrEF patients were more likely to be treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), beta-blockers, aldosterone antagonists, statins, and platelet inhibitors at index discharge. While HFpEF patients received more diuretics and nitrates, HFrEF patients had more planned follow-ups at specialty care clinics and with HF nurse and more follow-up visits at cardiology clinics than had HFpEF patients. The length of index hospital stay was slightly longer in HFrEF than in HFpEF.

The proportion of patients with NYHA class III or IV or using diuretics was the lowest in the HFmrEF patient subgroup. Other baseline characteristics of HFmrEF patients were more likely to lie in between HFrEF and HFpEF.

Overall readmission burden in heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, and heart failure with preserved ejection fraction patients

Within the 1 year follow-up, 13 597 (65.1%) patients experienced all-cause readmission in the whole study cohort, with 9702 (46.5%) experiencing CV readmissions and 5944 (28.5%) experiencing HF readmissions. In general, the 1 year all-cause readmission risk was the highest in HFpEF patients, while the 1 year CV and HF readmissions were the highest in HFrEF patients. As depicted in *Figure 1* and *Table S1*, all-cause readmissions occurred in 3767 (67.7%) of the HFpEF patients, higher than in both HFrEF (7061, 63.8%, $P < 0.001$) and HFmrEF (2769, 65.1%, $P = 0.007$). CV readmissions occurred in 5355 (48.4%) HFrEF patients, higher than patients with HFpEF (2456, 44.2%, $P < 0.001$) or HFmrEF (1891, 44.5%, $P < 0.001$). Moreover, HF readmissions occurred in 3538 HFrEF (32.0%) patients, higher than in HFpEF (1359, 24.4%, $P < 0.001$) and HFmrEF (1047, 24.6%, $P < 0.001$) patients. Crude readmission rates are shown in *Table S1*.

Trends in cause-specific readmission rates

Temporal trends in short-term (1 and 3 months) and long-term (6 months and 1 year) cause-specific readmission rates throughout the study period (2004–2011) in HFrEF, HFmrEF, and HFpEF patients are presented in *Figure 2*. For HFpEF patients, both the 6 month (from 22.3% to 17.3%, $P = 0.003$) and 1 year (from 27.7% to 23.4%, $P = 0.019$) HF readmission rates significantly decreased, whereas no significant changes were observed in all-cause or CV readmission rates in this patient subgroup. For HFmrEF patients, the

Table 1 Baseline characteristics of patients with heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, and heart failure with preserved ejection fraction

Variables	Missing (%)	Overall *n* = 20 877	HFrEF *n* = 11 064	HFmrEF *n* = 4251	HFpEF *n* = 5562	*P*-value
Demographics						
Age, years	0	75.7 ± 11.6	73.6 ± 12.3	77.1 ± 10.6	78.9 ± 9.9	<0.001
Female sex	0	8520 (40.8)	3425 (31.0)	1884 (44.3)	3211 (57.7)	<0.001
Smokers	28.0	8517 (56.7)	4895 (59.9)	1692 (55.4)	1930 (50.7)	<0.001
Income, SEK	0.2	1293 (1078–1662)	1320 (1095–1729)	1287 (1076–1643)	1248 (1050–1548)	<0.001
Education	1.6					
Compulsory school		10 719 (52.2)	5472 (50.2)	2209 (52.7)	3038 (55.6)	
Secondary/university		9829 (47.8)	5421 (48.8)	1983 (47.3)	2425 (44.4)	<0.001
SBP, mmHg	1.4	127.9 ± 21.6	123.7 ± 20.6	131.4 ± 21.1	133.8 ± 22.3	<0.001
DBP, mmHg	1.4	73.1 ± 12.6	73.2 ± 12.6	73.5 ± 12.5	72.7 ± 12.7	0.001
Heart rate, b.p.m.	8.2	76.2 ± 16.1	77.0 ± 16.2	75.4 ± 16.0	75.3 ± 15.9	<0.001
Weight, kg	4.9	77.3 ± 18.5	77.5 ± 18.0	77.5 ± 18.7	76.7 ± 19.4	<0.001
HF evaluation						
NYHA III or IV	37.3	6130 (46.8)	3866 (53.7)	933 (35.5)	1331 (40.7)	<0.001
Duration of HF ≥ 6 months	0.8	9986 (48.2)	5278 (48.1)	2047 (48.4)	2661 (48.2)	0.896
Co-morbidities						
Hypertension	0	12 844 (61.5)	6099 (55.1)	2796 (65.8)	3949 (71.0)	<0.001
Diabetes	0	6237 (29.9)	3274 (29.6)	1297 (30.5)	1666 (30.0)	0.533
Ischaemic heart disease	1.2	11 646 (56.4)	6584 (60.3)	2479 (58.8)	2583 (47.0)	<0.001
AF	0	12 185 (58.4)	5886 (53.2)	2656 (62.5)	3643 (65.5)	<0.001
Valvular disease	0	5342 (25.6)	2712 (24.5)	1019 (24.0)	1611 (29.0)	<0.001
Lung disease	0	6605 (31.6)	3178 (28.7)	1378 (32.4)	2049 (36.8)	<0.001
Renal dysfunction	0	11 505 (55.3)	5830 (52.8)	2353 (55.5)	3322 (60.0)	<0.001
Anaemia	0	9666 (46.3)	4685 (42.3)	2029 (47.7)	2952 (53.1)	<0.001
Gout	0	1055 (5.1)	572 (5.2)	191 (4.5)	292 (5.3)	0.170
Stroke/TIA	0	3916 (18.8)	1934 (17.5)	790 (18.6)	1192 (21.4)	<0.001
Peripheral arterial disease	0	2329 (11.2)	1200 (10.9)	501 (11.8)	628 (11.3)	0.238
Sleep apnoea	0	602 (2.9)	273 (2.5)	127 (3.0)	202 (3.6)	<0.001
Cancer	0	2895 (13.9)	1445 (13.1)	589 (13.9)	861 (15.5)	<0.001
Connective tissue disease	0	6065 (29.1)	2784 (25.2)	1312 (30.9)	1969 (35.4)	<0.001
Mental disorder	0	2787 (13.4)	1541 (13.9)	516 (12.1)	730 (13.1)	0.012
Revascularization	0	5537 (26.5)	3253 (29.4)	1205 (28.4)	1079 (19.4)	<0.001
Device therapy	1.0	2736 (13.2)	1604 (14.7)	499 (11.8)	633 (11.5)	<0.001
Laboratory tests						
NT-proBNP, pg/mL	77.3	3835 (1780–8130)	4906 (2320–10 100)	3500 (1573–7084)	2639 (1291–5290)	<0.001
Haemoglobin, g/L	0	129.5 ± 17.7	132.0 ± 17.7	128.4 ± 17.5	125.5 ± 17.0	<0.001
eGFR, mL/min/1.73 m^2	0.3	57.9 ± 22.7	59.4 ± 23.2	57.5 ± 22.4	55.5 ± 21.8	<0.001
Management						
ACEIs/ARBs	0.4	16 340 (78.6)	9460 (85.8)	3243 (76.5)	3637 (65.8)	<0.001
Beta-blockers	0.7	17 747 (85.7)	9859 (89.7)	3579 (84.8)	4309 (78.3)	<0.001
Aldosterone antagonists	0.9	6165 (29.8)	3573 (32.6)	1081 (25.6)	1511 (27.5)	<0.001
Diuretics	0.5	17 922 (86.3)	9401 (85.4)	3550 (83.9)	4971 (89.9)	<0.001
Digoxin	0.7	3999 (19.3)	2104 (19.2)	784 (18.6)	1111 (20.2)	0.123
Statins	0.7	8918 (43.0)	5048 (45.9)	1883 (44.5)	1987 (36.0)	<0.001
Nitrates	0.9	4140 (20.0)	2118 (19.3)	881 (20.9)	1141 (20.7)	0.026
Platelet inhibitors	0.7	11 392 (55.0)	6258 (57.0)	2389 (56.6)	2745 (49.8)	<0.001
Oral anticoagulants	0.8	7509 (36.3)	3974 (36.2)	1541 (36.6)	1994 (36.2)	0.908
Length of hospital stay, days	0	6 (4, 9)	7 (4, 10)	6 (4, 9)	6 (4, 9)	<0.001
PFU level	9.4					
Primary care		9029 (47.7)	4074 (40.3)	1963 (50.6)	2992 (60.6)	
Specialty care		9891 (52.3)	6029 (59.7)	1915 (49.4)	1947 (39.4)	<0.001
PFU with HF nurse	8.9	5906 (31.1)	3989 (39.4)	1028 (26.4)	889 (17.8)	<0.001
Type of clinic	0					
Cardiology		11 523 (55.2)	6435 (58.2)	2306 (54.2)	2782 (50.0)	
IM/GM		9354 (44.8)	4629 (41.8)	1945 (45.8)	2780 (50.0)	<0.001

Values are given as *n* (%), mean ± standard deviation, or median (25th–75th percentile).
ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GM, geriatric medicine; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IM, internal medicine; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFU, planned follow-up; SBP, systolic blood pressure; SEK, Swedish Krona; TIA, transient ischaemic attack.

FIGURE 1 Cumulative incidence of cause-specific readmission in HFpEF patients vs. HFrEF and HFmrEF patients. Kaplan–Meier curves for all-cause (A), CV (B), and HF readmission (C) were compared among patients with HFrEF, HFmrEF, and HFpEF. CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

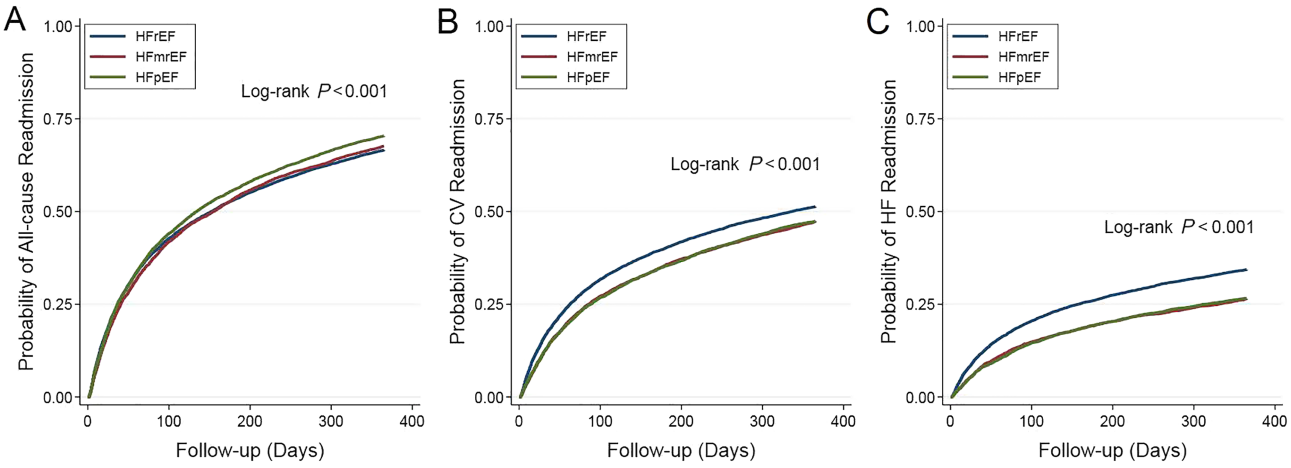
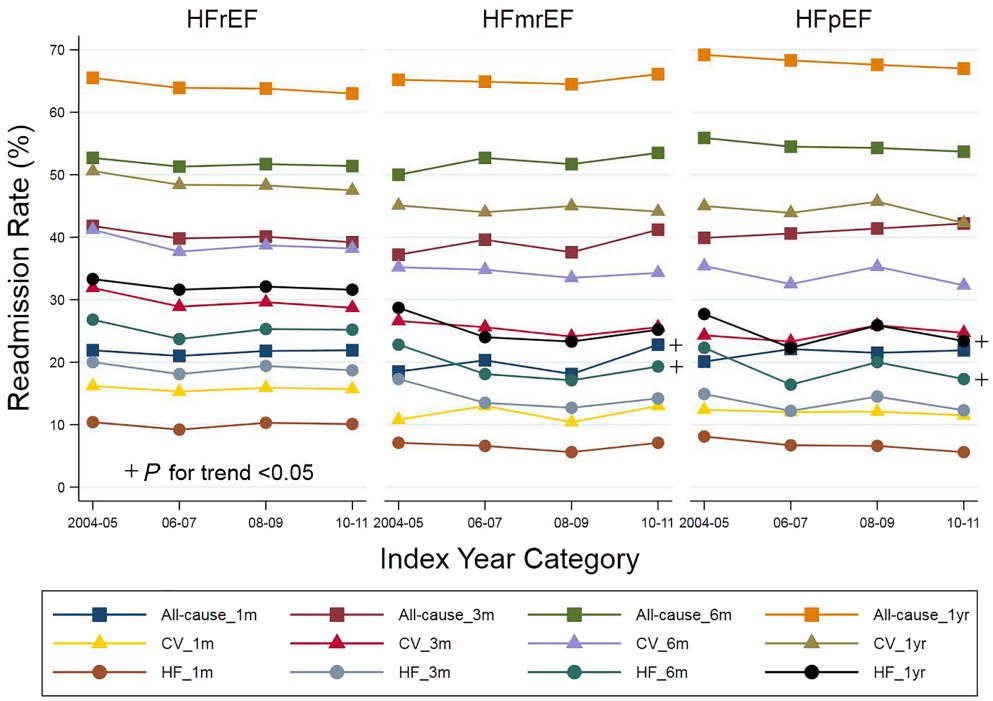


FIGURE 2 Trends in cause-specific readmission rates in HFpEF patients vs. HFrEF and HFmrEF patients. The 6 month HF readmission rates in both HFpEF and HFmrEF and 1 year HF readmission rates in HFpEF decreased significantly from 2004 to 2011. CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; 1m, 1 month; 3m, 3 months; 6m, 6 months; 1yr, 1 year.



1 month all-cause readmission rate slightly increased (from 18.5% to 22.8%, P = 0.018) and the 6 month HF readmission rate decreased (from 22.8% to 19.3%, P = 0.037). No significant changes in short-term or long-term cause-specific readmissions occurred in HFrEF patients.

Trends in time to the first cause-specific readmission

The median time to the first all-cause readmission was 57 days in HFrEF, 65 in HFmrEF, and 63 in HFpEF

(P = 0.002); for CV readmission, it was 62 days in HFrEF, 73 in HFmrEF, and 74 in HFpEF ($P < 0.001$); and for HF readmission, it was 66 days in HFrEF, 75 in HFmrEF, and 80 in HFpEF ($P < 0.001$). *Figure 3* shows that the time to the first all-cause, CV, and HF readmission did not change significantly from 2004 to 2011, regardless of EF subgroup (all P-values > 0.05).

Changes in readmission risk over time in heart failure with preserved ejection fraction patients

As shown in *Figure 4*, the cumulative probability of all-cause readmission did not change throughout the study period in HFpEF patients (P = 0.798). For CV readmission risk, Kaplan–Meier curves showed a decreasing trend that failed to reach statistical significance (P = 0.287). Consistent with the analysis in crude readmission rates, the HF readmission risk in HFpEF patients significantly decreased from 2004 to 2011 (P = 0.031). Compared with 2004–2005, the risk for 1 year HF readmission in HFpEF patients hospitalized in 2010–2011 declined by 7% after adjusting for age and sex (HR: 0.93, 95% CI: 0.87–0.99, P = 0.022).

Changes in risk factors for 1 year heart failure readmission in heart failure with preserved ejection fraction patients

Because only risk of HF readmission in HFpEF patients decreased during the study period, we further investigated changes in the risk factor profile for 1 year HF readmission in HFpEF patients by comparing 2004–2007 with 2008–2011 (*Figure 5*). Cox multivariable regression analysis revealed that longer duration of HF, lower level of haemoglobin or eGFR, AF, valvular disease, and use of aldosterone antagonists were all independent risk factors for HF readmission in HFpEF patients in 2004–2007. For the last 4 years of the study period (2008–2011), predictors for HF readmission in HFpEF changed to follow-up in the cardiology clinic, higher heart rate, longer duration of HF, lower level of haemoglobin or eGFR, diabetes, lung disease, use of diuretics or nitrates, and less use of statins.

FIGURE 3 Trends in time to the first cause-specific readmission in patients with HFrEF, HFmrEF, and HFpEF. No significant differences were found in time to the first any cause-specific readmission in patients registered in different calendar years, regardless of ejection fraction (EF) subgroups. CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

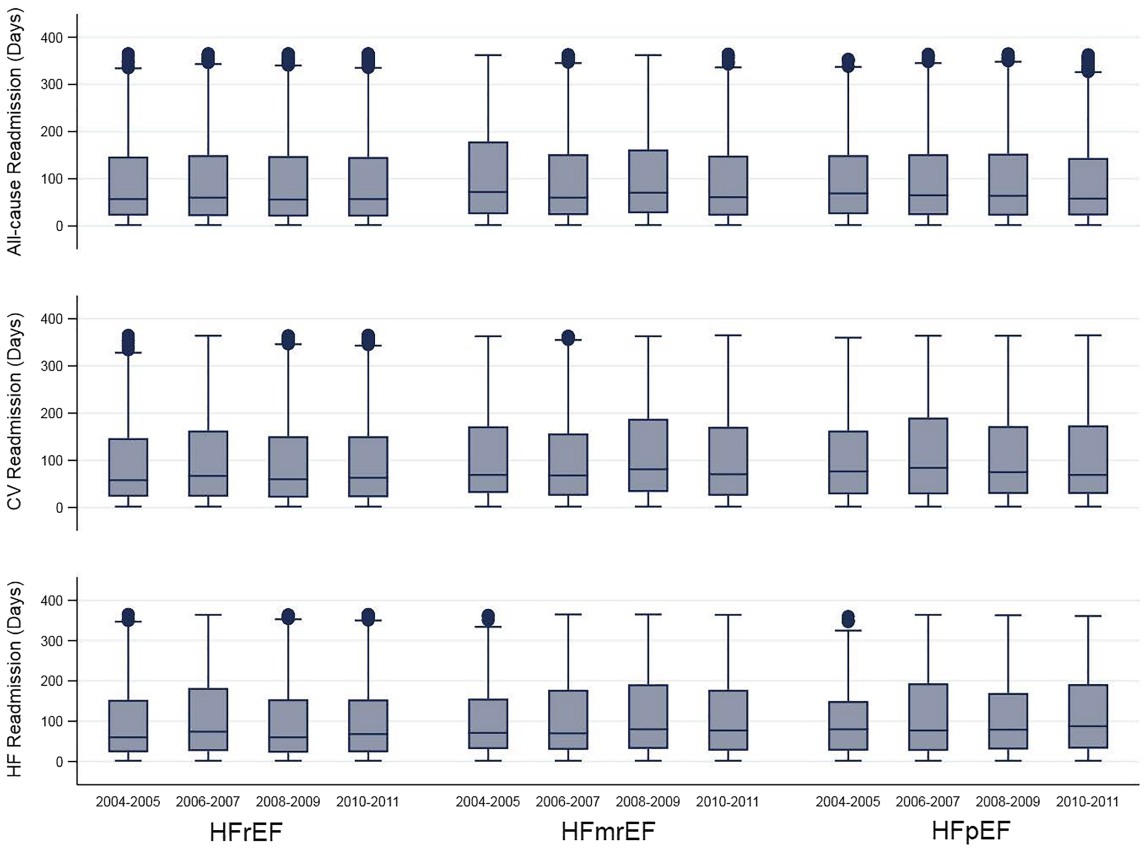


FIGURE 4 Trends in the cumulative incidence of cause-specific readmission in HFpEF patients. Incidence probabilities of all-cause (A), CV (B), and HF readmission (C) were compared by index year category in HFpEF patients. CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

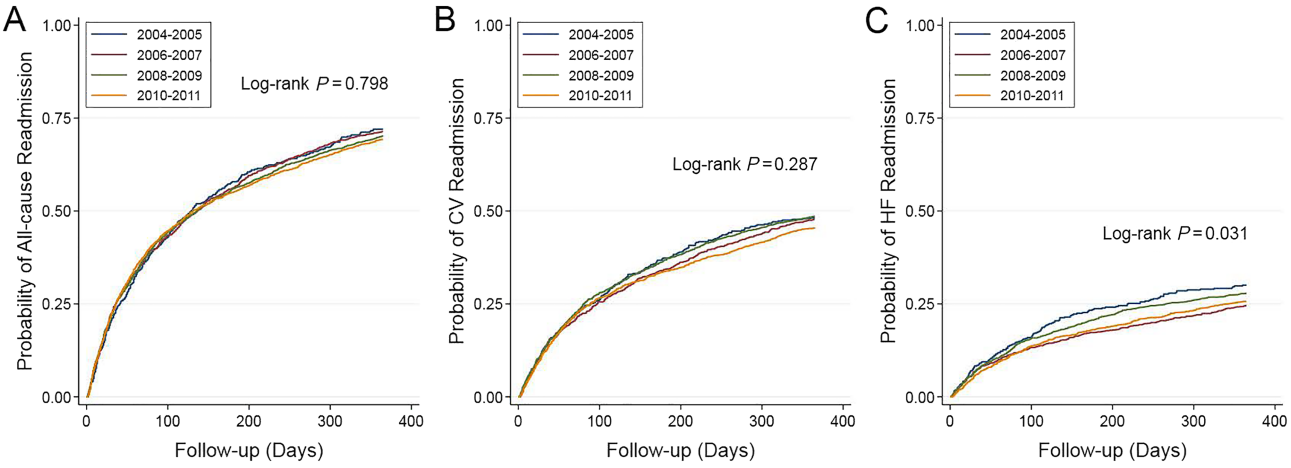
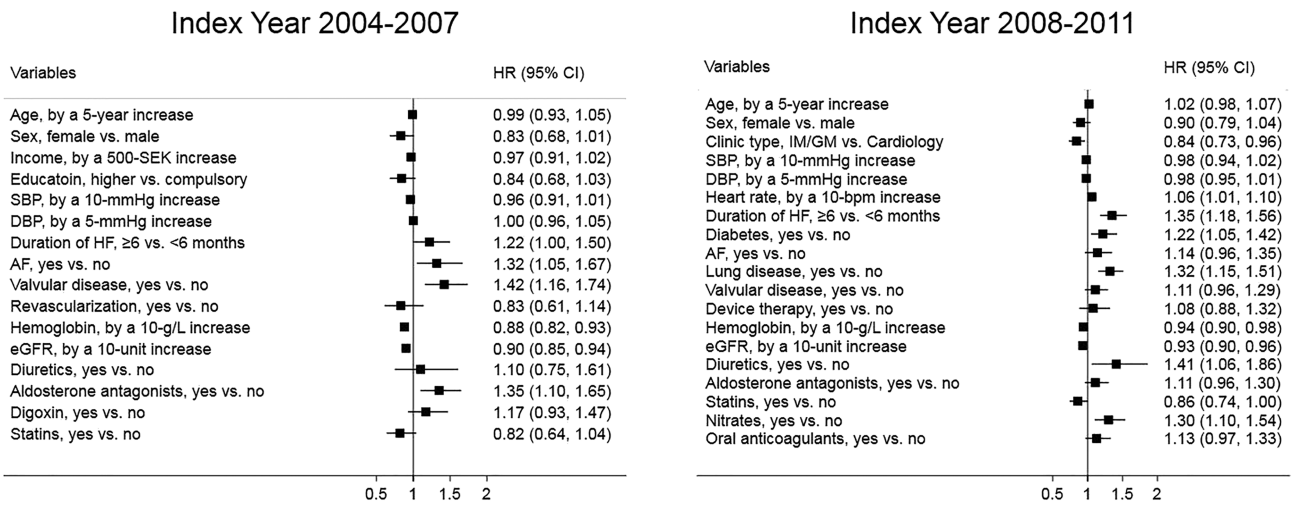


FIGURE 5 Comparison of predictors for HF readmission between HFpEF patients enrolled in 2004–2007 and 2008–2011. AF, atrial fibrillation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GM, geriatric medicine; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IM, internal medicine; SBP, systolic blood pressure; and SEK, Swedish Krona.



Discussion

As some drug treatments were showed related to readmission and no evidence confirmed prognosis improving drugs exist in HFpEF, we further explored drug changes in the study period in HFpEF patients. The prescription of ACEIs/ARBs, beta-blockers, statins, and oral anticoagulants at discharge was increased while the use of aldosterone antagonists, digoxin, nitrates, and platelet inhibitors was decreased in 2008–2011 compared with 2004–2007. The use rate of diuretics was kept unchanged (*Table S2*).

The present study demonstrates a heavy readmission burden in hospitalized HF patients, with the highest all-cause readmission rate in HFpEF patients and the highest CV or HF readmission rate in HFrEF patients. Declining trends in 6 month HF readmission rates in both HFpEF and HFmrEF and 1 year HF readmission rates in HFpEF were found from 2004 to 2011, while no significant changes in any cause-specific readmission risk were detected in patients with HFrEF.

HF patients, irrespective of EF subgroup, were all at high readmission risk. The GWTG-HF registry reported that the 1 year all-cause readmission rate was 59.6% in HFrEF, 63.2% in HFmrEF, and 62.5% in HFpEF; corresponding 1 year CV readmission rates were 42.4%, 41.6%, and 37.4%, and 1 year HF readmission rates were 30.9%, 28.4%, and 24.3%.[11] The all-cause and CV readmission rates in our cohort were slightly higher than in the GWTG-HF study, whereas the HF readmission rates were similar in the two studies. Moreover, we found that patients with HFpEF had higher all-cause readmission rate than patients with HFrEF, whereas CV and HF readmission rates were higher in HFrEF compared with HFpEF, which is also consistent with findings from the GWTG-HF,[11] although dissimilar from the study of Nichols *et al*. who found that patients with HFrEF and HFpEF experienced similar adjusted incidence rates of 1 year rehospitalization.[12] The higher all-cause readmission burden in HFpEF patients could be explained by the evidence that they had more non-CV co-morbidities than HFrEF patients. Therefore, the management of HFpEF patients should focus more on non-CV conditions, which is important given that no evidence-based therapy has been shown to improve the prognosis in these patients.[9]

Our findings in patients with HFmrEF differ from other studies.[11,14] We observed that patients with HFmrEF had an all-cause readmission risk similar to HFrEF patients and CV or HF readmission risk similar to HFpEF patients. Conversely, in the GWTG-HF registry HFmrEF patients showed a similar risk of all-cause readmission as HFpEF patients; their CV readmission risk was close to HFrEF and HF readmission risk was in between that of patients with HFrEF and HFpEF.[11] Yet the 5 year follow-up in GWTG-HF revealed that patients with HFmrEF had a higher all-cause readmission rate than HFpEF and HFrEF patients; CV and HF readmission rates were higher in patients with HFrEF and HFmrEF than in those with HFpEF.[14] Taken together, HFmrEF patients showed a distinct readmission risk compared with HFrEF and HFpEF patients, with discrepancies varying among regions and over time. The lower readmission risk in HFmrEF patients in our study may be beneficial out of their better NYHA functional class and in-between baseline characteristics. The complex relationship between HFmrEF and HFrEF or HFpEF warrants further investigation.

The trend of readmissions in HF patients remains controversial.[18–21] Studies from the Veterans Affairs Healthcare System and the Medicare system in the US both showed increased rates of 30 day readmission after hospitalization for HF over time,[18,19] while later the Hospital Readmissions Reduction Program reported modest decreasing trends in 30 day and 1 year adjusted readmission rates after discharge for HF.[20,21] In Europe, Gabet *et al*. found an increasing trend of HF-related readmission in HF patients from 2000 to 2012 in France.[22] However, none of the above studies performed an analysis of EF subgroups. Only study from the GWTG-HF registry once briefly reported no significant interaction between time and EF groups for the risk of readmission.[14] Our study presented temporal trends in short-term and long-term cause-specific readmissions by EF subgroups exhaustively. The declining trends in 6 month and 1 year HF readmissions in patients with HFpEF in our study may be related to enhanced symptom management by treatment with diuretics, which was used more frequently than in HFrEF despite that the NYHA functional class was better and the NT-proBNP value was lower in HFpEF patients. All-cause and CV readmissions in HFpEF patients remained constant during the study period, suggesting suboptimal multidisciplinary management of co-morbidities. Our findings imply that, in addition to focusing on HF therapy, we also need to target and optimize the control of non-HF-related co-morbidities in HFpEF, which might be a promising approach in reducing all-cause and CV readmission.

Along with the decrease of HF readmission rates from 2004 to 2011, risk factors for HF readmission in patients with HFpEF also changed over time. Duration of HF, haemoglobin, and eGFR were the three constant predictors of HF readmission throughout the study period, indicating that early diagnosis and treatment of HFpEF combined with optimal management of co-morbidities such as anaemia and renal dysfunction might be beneficial to reduce HF readmission. In HFpEF patients who were registered in 2004–2007, treatment with aldosterone antagonists was found a risk factor for 1 year HF readmission. This tendency still existed in 2008–2011, which might be due to suboptimal monitoring or lack of regular follow-up. Of note, HFpEF patients in our study were much older (78.9 vs. 68.7 years) and had worse renal function (eGFR 55.5 vs. 65.5 mL/min/1.73 m^2) than those in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.[6] Adverse effects (e.g. hyperkalaemia and worsening renal function) observed in the TOPCAT trial caused by aldosterone antagonists might appear with higher probability in our patients, where these adverse effects would conversely lead to worsened prognosis for HFpEF patients as confirmed by both TOPCAT and our study.[6,23] These findings suggest that physicians should be cautious when prescribing aldosterone antagonists to very old patients ($\geq$75 years) with HFpEF and reduced renal function. From subsequent analyses, we can see that aldosterone antagonists were prescribed less in 2008–2011 than the first 4 years of the study period. For heart rate, of which the impact to HFpEF is debatable,[24] the present study supports the relationship of a faster heart rate in patients with HFpEF with poor prognosis as it does in HFrEF.[25] Patients with planned follow-up at cardiology clinics instead of internal or geriatric medicine and those treated with diuretics or nitrates were more likely to be readmitted for HF because they presented with more severe HF. Besides, that HFpEF patients followed up in internal or geriatric medicine had less readmission may also be attributed to

better awareness and action of multidisciplinary control for co-morbidities than cardiology clinics.

Time to the first all-cause, CV, or HF readmission was all within 3 months after discharge in any EF subgroup, suggesting that physicians should emphasize and improve the post-discharge management of HF patients to reduce rehospitalization during this vulnerable period, because 75% of these early readmissions may be preventable.[26,27]

Limitations

This study has limitations, which are inherent in most registry studies. First, some data were missing, especially from three variables: smokers, 28%; NYHA class, 37.3%; and NT-proBNP, 77.3%. Because these variables were not included in the Cox multivariable regression analysis, we should treat the results and conclusions of this part more cautiously. Second, SwedeHF covers only ~54% of HF patients in Sweden. However, because 70 of 80 hospitals throughout the country contribute to the registry, we believe the present study could reflect the real-world HF patients in Sweden. Third, because we could not compensate for all variables in a registry study, unmeasured confounders could have affected the results. Finally, although we have used as much data as we can get from the SwedeHF registry, the current project could only cover a period of 2004–2011, while this would instead make our findings comparable with those of previous studies carried in the same period.

Conclusions

Hospitalized HF patients were still carrying considerable readmission burden, with the highest all-cause readmission rate in HFpEF patients and the highest CV or HF readmission rate in HFrEF patients. A declining temporal trend was found in 6 month and 1 year HF readmission rates in patients with HFpEF. In contrast, no significant changes in any cause-specific readmission rates were detected in patients with HFrEF. Management for HFrEF should still be mainly focused on the heart itself, while more efforts are needed to reduce the non-HF-related readmission in HFpEF.

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Conflict of interest

Dr Ulf Dahlström declares no conflicts of interest related to the present manuscript; outside the present manuscript, he receives a research grant from AstraZeneca and consultancies/honoraria from AstraZeneca, Novartis, and Amgen. The other authors report no conflicts.

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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. Crude readmission rates in patients with HFrEF, HFmrEF and HFpEF.
Table S2. Drug use comparison between 2004–2007 and 2008–2011 in HFpEF patients.

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