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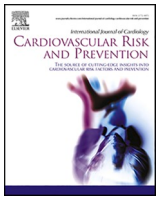

# Clinical characteristics at hospital discharge that predict cardiovascular readmission within 100 days in heart failure patients – An observational study

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ABSTRACT

*Background:* After a heart failure (HF) hospital discharge, the risk of a cardiovascular (CV) related event is highest in the following 100 days. It is important to identify factors associated with increased risk of readmission.
*Method:* This retrospective, population-based study examined HF patients in Region Halland (RH), Sweden, hospitalized with a HF diagnosis between 2017 and 2019. Data regarding patient clinical characteristics were retrieved from the Regional healthcare Information Platform from admission until 100 days post-discharge. Primary outcome was readmission due to a CV related event within 100 days.
*Results:* There were 5029 included patients being admitted for HF and discharged and 1966 (39%) were newly diagnosed. Echocardiography was available for 3034 (60%) patients and 1644 (33%) had their first echocardiography while admitted. The distribution of HF-phenotypes was 33% HF with reduced ejection fraction (EF), 29% HF with mildly reduced EF and 38% HF with preserved EF. Within 100 days, 1586 (33%) patients were readmitted, and 614 (12%) died. A Cox regression model showed that advanced age, longer hospital length of stay, renal impairment, high heart rate and elevated NT-proBNP were associated with an increased risk of readmission regardless of HF-phenotype. Women and increased blood pressure are associated with a reduced risk of readmission.
*Conclusions:* One third had a CV-readmission within 100 days. This study found clinical factors already present at discharge that are associated with increased risk of readmission which should be considered at discharge.

## 1. Introduction

The prevalence of heart failure (HF) in Sweden is approximately 2%, which is consistent with other Western countries [1–3]. HF affects mainly the elderly with nearly 75% of all patients being 75 years or older. A previous study of a HF population noted that the condition had a marked impact on health care utilization and costs [2]. There is a yearly all-cause mortality of 14% and a five-year survival of 48% [2,4].

Distribution of HF phenotypes is based principally on ejection fraction (EF) as determined by echocardiography [5]. Based on guidelines current during the study period, HF patients were further defined as either HF with reduced EF (HFrEF), in which the EF is <40%, or HF with mildly reduced EF (HFmrEF), in which the EF is between 40 and 49%. Individuals that present clinically as HF patients but have an EF >50% are classified as heart failure with preserved ejection fraction (HFpEF). Previous studies have shown the distribution of HF phenotypes to be 53–65% with HFrEF, 20% with HFmrEF and 27–35% with HFpEF [1,6].

HF hospitalization places a heavy burden on healthcare both in terms of resource utilization and high costs [2]. The subsequent 30–90 days after hospital discharge for HF is the most vulnerable period for HF patients and during this period, there is an increased risk of readmission [7–9]. In Sweden, approximately 44% of patients with HF are admitted to the internal medicine department at least once a year with an average hospital stay of 6–7 days [2,10,11]. The onset and first diagnosis of HF is in 53–80% of cases during hospitalization, which is likely due to the fact that HF begins with an acute deterioration of the health condition [1]. An American study of HF patients reported a 30-day readmission of 24% [6,11]. There were 61% of these readmissions that occurred within 16

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days after discharge. In previous studies on HF populations, it was found that hospital readmission within 30 days was 15%–18%. Hospital readmission within 90 days occurred in 31%–36% and after 6 months it occurred 47% [4,6,12]. After the initial diagnosis, HF patients are hospitalized on average once every year [13]. Since hospitalization should be avoided from a health economic and quality of life perspective, it is reasonable to investigate factors that increase the risk of readmission in HF patients [2,5,14].

Poor compliance to medication was another independent risk factor for HF readmission [12]. Recommended pharmacotherapies according to HF guidelines are underused even though there is convincing evidence that they have a positive effect on HF regarding mortality and the need of hospitalization [2,15,16].

The objective of the present study was to examine possible risk factors associated with readmission in patients hospitalized for HF within 100 days after hospital discharge. The risk factors investigated were particularly focused on distinguishing HF subgroups, age, sex, diabetes, chronic obstructive pulmonary disease, length of stay (LoS) at hospital, heart rate, systolic blood pressure, renal function, natriuretic peptides and recommended pharmacological HF treatment follow-up.

## 2. Method

Region Halland (RH) which is located in south-western Sweden and has an estimated population of 320,000 inhabitants. Within RH, there are three acute care hospitals, 40 inpatient wards, two emergency departments, 30 outpatient specialized clinics and 48 primary health care (PHC) facilities.

### 2.1. Data sources

This is a retrospective, population-based study of HF patients with different HF phenotypes in RH. Data were obtained from the Regional Healthcare Information Platform (RHIP) provided by RH, which includes data from both primary (both private- and public healthcare providers)- and secondary healthcare levels, including all prescribed medications, clinical investigation results (i.e., laboratory assessments, radiological examinations) and care delivery resources [17]. Data concerning pharmacotherapy were obtained through RHIP via two sources, the Swedish Prescribed Drugs Register and the pharmacy's dose dispensing unit (Apodos).

### 2.2. Study population

The study included all adult patients with HF hospitalized in RH from 2017 to 2020 which was 7436 individuals. Among these, 5494 were admitted with a HF diagnosis and 465 patients deceased before discharge. Consequently, 5029 patients hospitalized due to HF and discharged with a diagnosis of HF were included in the study. Individuals were defined as HF patients if they received an ICD-10 diagnosis of HF (Appendix-Table A) at some point during the period 2013 to 2020. The requirement was that all patients included were inhabitants of RH at the time of hospitalization according to the Swedish National Population Registry. A patient could only be included once in the study. For those patients admitted to hospital on more than one occasion during the study period, only the first hospitalization was included.

### 2.3. Study procedure

Age and sex was registered at the time of initial HF diagnosis, henceforth referred to as index. Comorbidities were retrieved in the lookback period from 2013 to 2020. The HF diagnoses applied are outlined in Appendix-Table A. For patients that died during the study period of any cause, the number of days from index to date of death was recorded. Deaths were defined as all-cause mortality. There was a registration of readmission during the 100-day study period and only the readmission having a CVD diagnosis was registered. The number of patients having readmission was retrieved and not the number of readmissions for each patient.

The recorded NT-proBNP values were based on the values that were current at the time of hospitalization and the highest values during the period 7 days before the index and throughout the hospitalization. NT-proBNP levels were assessed based on new onset or acute worsening of HF symptoms and further divided into three groups to describe the likeliness that the elevated age-dependent levels were associated with HF [18]. A NT-proBNP value $<$ 300 ng/l was considered normal and defined as HF unlikely. Elevated values were defined based on patient age as grey-zone or HF likely which displayed in Appendix-Table B. Renal function was assessed with the available eGFR (ml/min/1.73 $m^2$) and P-creatinine values closest to index [19]. Based on eGFR, renal function was defined as either normal with eGFR $\geq$60 ml/min, lowered with GFR 30–59 ml/min or impaired with GFR $<$30 ml/min. Heart rate values were collected from the electronic medical records registered upon admission and were further divided into those with heart rates $\geq$70 beats per minute (bpm). Data regarding systolic blood pressure upon admission was registered and grouped into three categories based on the blood pressure levels $<$100, 100–139 and $\geq$ 140 mm Hg.

The LoS at index was registered. LoS is defined as the number of days a patient was hospitalized from initial admission at index to discharge.

The medications registered were beta-blockers (C07), RAAS-inhibitors (ACEI, ARB and ARNI) (C09), MRA (C03DA) and loop-diuretics (C03C). All registered beta-blockers, RAAS-inhibitors, ARNI and MRAs have a HF treatment indication (listed in the Appendix-Table C) [6]. Data regarding HF treatments dispensed at the pharmacy were extracted 120 days prior to hospital admission as well as at the time of readmission. Dosages were not taken into consideration.

The study was approved by the Swedish Ethical Review Board, Stockholm Department 2 Medicine, with the registration number 2020–00455. An informed consent was waived, and this study procedure was granted by the Swedish Ethical Review Board. All the methods in this study were carried out in accordance with relevant guideline and regulations.

### 2.4. Statistical analyses

Continuous variables were described as means $\pm$ standard deviation (SD) or median and interquartile range (IQR), when applicable. Kruskal-Wallis tests were used for comparison of groups regarding LoS at index hospitalization and NT-proBNP since these were not normally distributed. These variables are also presented with median and IQR. One-way ANOVA was used for analysis of the continuous variables age, heart rate, systolic blood pressure and eGFR. Categorical variables were analysed using Chi-squared tests and summarized using frequency and percentages. A two-sided P-value $<$0.05 was considered as statistically significant. There was a separation into age-groups, those $>$75 years and those $\leq$75 years of age. The patients with LoS at index hospitalization $>$6 hospital days were registered. Missing values were most common for data related to renal function and NT-proBNP levels. As missing value of eGFR did not exceed the threshold of 10%, imputation was not performed. There were 16% missing values at index for NT-proBNP and an imputation was performed to account for these missing values. NT-proBNP is not normally distributed data and therefore it was not possible to use mean values. The patients were grouped according to HF subgroup, age and renal function. The cohort was categorized by age as $<$50, 50–75 and $\geq$ 75 years since this age distribution is used clinically [18]. Furthermore, renal function was categorized according to $\geq$60, 30–59 and $<$ 30 ml/min [19]. The median value of NT-proBNP was applied. Since it did not affect the outcome in the Cox regression for readmission, the imputation is not presented.

Treatment was separated into those having basic HF treatment with BB combined with RAASi and those which did not have this treatment, according to guidelines at the time of the study [6].

When comparing variables, two separate analyses were conducted. The first analysis included patients with a defined HF phenotype as determined by echocardiography, and the second included both patients with a defined HF-phenotype and patients with HF-NDP. Significance was determined through p-values for the separate analyses.

A Spearman rank correlation analysis was performed in order to clarify the relations between NT-proBNP and renal function and was allocated into three separate renal function levels, eGFR>60 ml/min, 30–60 ml/min and <30 ml/min.

A Cox regression model was applied to examine time to readmission within the first 100 days of discharge. The variables adjusted were HF subgroups, age, sex, diabetes, chronic obstructive pulmonary disease, LoS at hospital, heart rate, systolic blood pressure, renal function, NT-proBNP level and basal HF treatment according to guidelines. The variables age, LoS at hospital and systolic blood pressure were analysed as continuous variables. In the Cox regression model, heart rate, eGFR and NT-proBNP levels were entered as categorical variables. Since the HF phenotypes are based primarily on ejection fraction, there is a linear association across the HF phenotypes. The HF subgroups are considered having a clinical association as well and as ejection fraction is considered a rough measure, this variable is categorized. All analyses were performed with IBM SPSS Statistics 27.0.

## 3. Results

A total of 5029 patients were discharged with a HF diagnosis based on ICD-10 coding during the study period of 2017–2020 in RH. Among these, there were 2293 (46%) women and 2736 (54%) men. Echocardiography data were accessible for 3034 (60%) of the admitted patients, with 1644 (33%) having undergone a first-time echocardiography during the admission at index. A total of 1966 (39%) patients were newly diagnosed with HF during their hospital stay. Among the 3034 patients with echocardiography for diagnosing HF, there were 33% defined as HFrEF, 29% as HFmrEF and 38% as HFpEF. The distribution of the HF cohort is presented in Table 1.

The mean age for the total cohort was 80.0 years and 3541 (70%) patients were older than 75 years. Within the respective HF subgroups, the mean ages were 76.4 years for HFrEF, 77.2 years for HFmrEF 79.5 years for HFpEF, and 83.3 years for the HF-NDP-group. The distribution of comorbidities prior to hospital admission was evaluated both for the entire cohort, as well as for the various HF phenotypes and those patients defined as HF-NDP were available and are summarized in Table 1.

The mean eGFR for the total cohort was 51.4 ml/min (19.7) and there was significant difference amongst the subgroups (p-value <0.001). Renal function and NT-proBNP are presented in Table 1. The mean NT-proBNP for the total cohort was 5439 ng/l (8503) and was highest amongst HFrEF patients (p-value <0.001).

The distribution of the medication is presented in Table 2. The

**Table 1**
Clinical characteristics of the respective heart failure subgroups. Comorbidities were recorded upon admission and all other variables were recorded at discharge.

| Variable | Total | HF-Phenotype | | | | HF-NDP | p-value[b] |
|---|---|---|---|---|---|---|---|
| | | HFrEF | HFmrEF | HFpEF | p-value[a] | | |
| Total cohort, n (%) | 5029 (100) | 1010 (20) | 898 [18] | 1147 (23) | | 1974 (39) | |
| Women, n (%) | 2279 (45) | 298 (30) | 334 (37) | 594 (52) | <0.001[1] | 1053 (53) | <0.001[1] |
| Age, mean (SD) | 79.6 (11.5) | 79.1 (10.3) | 77.0 (11.3) | 76.0 (12.7) | <0.001[3] | 82.9 (10.7) | <0.001[3] |
| Age ≥75 years | 3653 (73) | 609 (60) | 575 (64) | 840 (73) | <0.001[1] | 1629 (82) | <0.001[1] |
| ***Disease categories*** | | | | | | | |
| Hypertension, n (%) | 3760 (75) | 662 (66) | 637 (71) | 928 (81) | <0.001[1] | 1553 (78) | <0.001[1] |
| IHD, n (%) | 2306 (46) | 581 (58) | 528 (59) | 475 (41) | <0.001[1] | 722 (37) | <0.001[1] |
| Previous AMI, n (%) | 963 [19] | 273 (27) | 289 (33) | 200 [17] | <0.001[1] | 201 [10] | <0.001[1] |
| PAD, n (%) | 248 [5] | 58 [6] | 45 [5] | 56 [5] | 0.64[1] | 89 [4] | 0.46[1] |
| CVI, n (%) | 800 [16] | 132 [13] | 140 [16] | 165 [14] | <0.001[1] | 363 [18] | 0.001[1] |
| VHD, n (%) | 1045 [21] | 217 [22] | 193 [22] | 369 (32) | <0.001[1] | 266 [14] | <0.001[1] |
| CKD, n (%) | 1166 (23) | 239 (24) | 205 (23) | 290 (26) | 0.41[1] | 432 [22] | <0.001[1] |
| Atrial fibrillation, n (%) | 2899 (58) | 542 (54) | 487 (54) | 705 (62) | <0.001[1] | 1165 (59) | <0.001[1] |
| Diabetes mellitus, n (%) | 1330 (26) | 292 (29) | 243 (27) | 304 (26) | 0.44[1] | 491 (25) | 0.12[1] |
| COPD, n (%) | 908 [18] | 133 [13] | 142 [16] | 238 [21] | <0.001[1] | 395 [20] | <0.001[1] |
| ***Clinical findings*** | | | | | | | |
| HR, mean (SD) | 82.4 (20.9) | 82.0 (20.7) | 82.2 (21.1) | 85.4 (23.3) | <0.001[3] | 81.3 (20.9) | <0.001[3] |
| HR ≥ 70 bmp, n (%) | 3178 (73) | 630 (74) | 556 (73) | 774 (74) | 0.95[1] | 1218 (73) | 0.91[1] |
| BP, mean (SD) | 139.7 (25.9) | 140.1 (25.1) | 137.6 (24.2) | 132.7 (23.2) | <0.001[2] | 139.7 (25.9) | <0.001[2] |
| BP < 100 mm Hg, n (%) | 199 [4] | 58 [6] | 32 [4] | 40 [4] | <0.001[1] | 69 [4] | <0.001[1] |
| BP 100–139 mm Hg, n (%) | 2342 (49) | 524 (55) | 429 (50) | 513 (46) | | 876 (47) | |
| BP ≥ 140 mm Hg, n (%) | 2232 (47) | 373 (39) | 397 (46) | 553 (50) | | 909 (49) | |
| ***Grouping of eGFR*** | | | | | | | |
| eGFR, mean (SD) | 51.4 (19.7) | 52.4 (20.1) | 53.3 (20.0) | 52.4 (20.0) | 0.32[2] | 50.4 (19.4) | <0.001[3] |
| ≥60, n (%) | 1826 (36) | 372 (36) | 371 (37) | 435 (41) | <0.001[1] | 648 (32) | <0.001[1] |
| 30-59, n (%) | 2437 (49) | 490 (49) | 408 (46) | 533 (46) | | 1006 (51) | |
| <30, n (%) | 753 [15] | 148 [15] | 115 [13] | 176 [15] | | 314 [16] | |
| Missing, n (%) | 11 (0) | 0 (0) | 4 (0) | 2 (0) | | 5 (0) | |
| ***Grouping of NT-proBNP*** [1] | | | | | | | |
| NT-proBNP, median (IQR) | 2704 (1148–5946) | 3804 (1443–9635) | 2640 (1113–5543) | 2391 (1100–4739) | <0.001[2] | 2550 (1051–5407) | <0.001[2] |
| HF not likely, n (%) | 273 [6] | 30 [3] | 59 [6] | 82 [8] | <0.001[1] | 102 [7] | <0.001[1] |
| Grey zone, n (%) | 1055 (25) | 174 [19] | 173 (23) | 283 (27) | | 429 [22] | |
| HF likely, n (%) | 2899 (69) | 714 (78) | 514 (69) | 690 (65) | | 981 (65) | |
| Missing, n (%) | 805 [16] | 92 [9] | 152 [15] | 91 [8] | | 466 (23) | |

Note; HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HF-NDP = heart failure with no defined phenotype, IHD= Ischemic heart disease, AMI = acute myocardial infarction, PAD= Peripheral artery disease, CVI = cerebrovascular insult, VHD = valvular heart disease, CKD = chronic renal disease, COPD = chronic obstructive pulmonary disease, HR = heart rate, eGFR = estimated glomerular filtration rate (ml/min), NT-proBNP = natriuretic terminal pro brain natriuretic peptide, HF=Heart failure.
1Chi-2 test, 2 Kruskal-Wallis test, 3 One-way ANOVA.
[a] Represents the p-value for patients with a defined HF-phenotype.
[b] Represents the p-value for the total group, including HF-NDP.

**Table 2**
Distribution of pharmacotherapy among HF subgroups at discharge and hospital utilization.

| | Total | HF-Phenotype | | | P-value[a] | HF-NDP | P-value[b] |
|---|---|---|---|---|---|---|---|
| | | HFrEF | HFmrEF | HFpEF | | | |
| Total cohort | 5029 (100) | 1010 (20) | 898 [(18) | 1147 (23) | | 1974 (39) | |
| *Medication* | | | | | | | |
| BB, n (%) | 4037 (80) | 915 (91) | 767 (85) | 902 (79) | <0.001[a] | 1453 (74) | <0.001[a] |
| ACEi, n (%) | 2269 (45) | 581 (58) | 460 (51) | 471 (41) | <0.001[a] | 757 (38) | <0.001[a] |
| ARB, n (%) | 1395 (28) | 304 (30) | 274 (30) | 344 (30) | <0.001[a] | 473 (24) | <0.001[a] |
| ARNI, n (%) | 183 (4) | 129 (13) | 20 (2) | 4 (0) | 0.97[a] | 30 (2) | <0.001[a] |
| RAASi, n (%) | 3539 (70) | 869 (86) | 698 (78) | 774 (68) | <0.001[a] | 1198 (39) | <0.001[a] |
| MRA, n (%) | 2349 (47) | 681 (67) | 409 (46) | 567 (49) | <0.001[a] | 692 (35) | <0.001[a] |
| SGLT2-antagonist, n (%) | 109 (2) | 26 (3) | 23 (3) | 27 (2) | 0.93[a] | 33 (2) | <0.001[a] |
| Diuretics, n (%) | 3965 (79) | 835 (83) | 615 (68) | 919 (80) | <0.001[a] | 1596 (81) | <0.001[a] |
| BB and RAASi, n (%) | 3028 (60) | 802 (79) | 627 (70) | 640 (56) | <0.001[a] | 58,959 (49) | <0.001[a] |
| BB-RAASi-MRA, n (%) | 1558 (31) | 575 (57) | 298 (33) | 314 (27) | <0.001[a] | 371 (19) | <0.001[a] |
| *Healthcare utilization* | | | | | | | |
| LoS at index, median (IQR) | 5 (3-9) | 6 (3-10) | 5 (3-9) | 5 (3-9) | 0.05[b] | 5 (2-8) | <0.001[2] |
| LoS >6 days, n (%) | 1950 (39) | 454 (45) | 322 (36) | 488 (42) | <0.001[a] | 686 (35) | <0.001[a] |
| Readmission, n (%) | 1638 (33) | 349 (35) | 255 (28) | 411 (36) | <0.001[a] | 623 (32) | <0.001[a] |
| Deceased, n (%) | 603 (12) | 101 (10) | 71 (8) | 116 (10) | 0.18[a] | 315 (16) | <0.001[a] |

Note; BB = betablockers, ACEi = Angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blockers, ARNI = angiotensin receptor neprilysin inhibitors, RAASi = renin-angiotensin-aldosterone-system inhibition (includes ACEi, ARNI and ARB), MRA = mineralocorticoid receptor antagonists, SGLT-2-antagonists = Sodium glucose cotransporter-2 antagonists, LoS = length of stay of hospital admission, SD = standard deviation, n = number.
1 = Chi-2 test, 2 = Kruskal-Wallis test.
[a] Represents the p-value for patients with a defined HF-phenotype. Exclusive.
[b] Represents the p-value for the total group, including HF-NDP. Overall.

highest occurrence of double therapy with BB and RAASi amongst the subgroups was within the HFrEF group at 78% (p-value <0.001). HFrEF patients also showed the highest percentage of triple therapy, with the addition of MRA. There was no significant difference in the percentage of patients with double and triple therapy at discharge.

The median LoS at the first admission is displayed in Table 2 and distributed for HF-phenotype. The LoS during hospitalization at index, it was on average 7.3 days (SD 7.7) in the total cohort. Patients with HFrEF had a mean LoS of 8.3 (SD 8.5), HFmrEF 7.4 (SD 7.9), HFpEF 8.1 (SD 9.1) and for HF-NDP 6.2 days (SD5.8) ($p < 0.001$). The patients <75 years of age had LoS of 7.9 (SD 8.9) days in average compared to patients ≥75 years of age that had 7.0 (SD 7.1) ($p < 0.001$). There was no difference in number of patients staying >6 days at first admission regarding age groups, 553 (40%) for the age-group <75 years and 1397 (38%) for those ≥75 years of age ($p = 0.21$).

A total of 1641 (33%) patients were readmitted at some point during the 100-day follow-up period which is displayed in Table 2). During this time, 614 (12%) patients died, and these deaths were considered as all-cause mortality. The CVD related readmission rates were 1267 (35%) amongst patients ≥75 years and 371 (27%) for the patients. The all-cause mortality rates were 545 (15%) patients at the age ≥75 years and 58 (4%) patients<75 years. The all-cause mortality by subgroup was 10% for both HFrEF and HFpEF, 8% for HFmrEF and 16% for the HF-NDP-group ($p < 0.001$).

A Spearman rank correlation analysis comparing NT-proBNP and renal function showed a correlation of 37%. There was a Spearman rank correlation analysis for each separate level of renal function as well that showed a correlation of 18% for those with eGFR >60 ml/min, 15% for those with eGFR 30–60 ml/min and 30% for those with eGFR <30 ml/min.

The risk of readmission after hospital discharge was analysed using the Cox regression model, which was adjusted for HF-subgroups, age, sex, diabetes, chronic obstructive pulmonary disease, LoS at hospital, echocardiogram at admission, heart rate, systolic blood pressure, renal function, NT-proBNP levels and basal HF treatment. This is presented in Table 3.

**Table 3**
Cox regression model applied to assess associated risk of readmission within 100 days of discharge.

| | HR | 95.0% CI for HR | | p-value |
|---|---|---|---|---|
| | | Lower | Upper | |
| *HF subgroup* | | | | |
| HFpEF | Reference | | | 0.06 |
| HFmrEF | 0.86 | 0.72 | 1.03 | |
| HFrEF | 0.99 | 0.84 | 1.16 | |
| HF-NDP | 0.82 | 0.70 | 0.97 | |
| *Basic of characteristics* | | | | |
| Age | 1.01 | 1.01 | 1.02 | <0.001 |
| Women | 0.86 | 0.76 | 0.97 | 0.03 |
| Hospital LoS | 1.01 | 1.01 | 1.02 | <0.001 |
| Echo at admission | 0.90 | 0.78 | 1.03 | 0.13 |
| *Comorbidities* | | | | |
| Diabetes | 1.10 | 0.97 | 1.25 | 0.14 |
| COPD | 1.17 | 1.01 | 1.34 | 0.03 |
| *Clinical findings* | | | | |
| Heart rate ≥70 bpm | 1.17 | 1.02 | 1.33 | 0.02 |
| SBP | 0.997 | 0.997 | 0.999 | 0.03 |
| *Renal function* | | | | |
| eGFR ≥60 | Reference | | | 0.005 |
| eGFR 30-59 | 1.12 | 0.97 | 1.29 | |
| eGFR <30 | 1.35 | 1.13 | 1.62 | |
| *NT-proBNP levels* | | | | |
| HF unlikely | Reference | | | <0.001 |
| Grey zone | 1.29 | 0.94 | 1.77 | |
| HF likely | 1.69 | 1.25 | 2.28 | |
| *HF treatment* | | | | |
| BB and RAASi | 0.92 | 0.82 | 1.04 | 0.19 |

Note; HR=Hazard ratio, CI = confidence interval, HF=Heart failure, HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HF-NDP = heart failure with no defined phenotype, LoS = length of stay, Echo = echocardiogram, COPD = chronic obstructive pulmonary disease, SBP = systolic blood pressure, eGFR = estimated glomerular filtration rate, NT-proBNP = natriuretic terminal pro brain natriuretic peptide, NT-proBNP levels for acute or new-onset HF based on age which is displayed in Appendix-Table 2, BB = beta-blockers, RAASi = renin-angiotensin-aldosterone-system inhibition (includes ACEi, ARNI and ARB).

## 4. Discussion

In this study where patients were followed for 100 days after being

hospitalized for HF, less than two thirds of the patients in the total cohort had an echocardiography at discharge and of these, one third performed their first diagnostic echocardiography during the hospitalization. During the study, 12% deceased and one third of the total population was readmitted due to a cardiovascular event. The factors that were associated with an increased risk of readmission was patients with HFrEF, old age, longer hospitalization, high heart rate, and reduced kidney function and high NT-proBNP values. Factors associated with reduced risk are women and increased systolic blood pressure.

The readmission rate with a cardiovascular diagnosis was 33% within 100 days in this study which is in line with another Swedish study showing 36,6% during a 3-month follow up [20]. In addition, another study showed 46% readmission rate within one year [6]. However, as the risk is highest during the initial period, the results are in line with expectations. The mortality is highest among the patients that have not performed echocardiogram and the mortality was equal regarding HFpEF and HFrEF and lowest among HFmrEF patients.

In the present study, 60% had performed echocardiography at any time which is a higher number compared with previous Swedish study that had a corresponding number of 36% [1]. However, there is a difference in the present cohort that only consists of patients that have been discharged with a HF diagnosis and a higher number of echocardiography would be expected. There were still 39% of the patients with their first HF diagnosis during the hospitalization and there were 33% among those that performed an echocardiography at that time of hospitalization. When patients are admitted to hospital due to HF, it would commonly be a deterioration in HF causing it. The hospitalization of HF is most often due to a deterioration and an updated echocardiogram would then be expected. Echocardiography performed during hospitalization was not shown to be associated with a lower risk of CV readmission. The severity of the patient's illness likely affects the risk of readmission, and the severity may likely vary in the patients who underwent an echocardiogram upon admission. Consequently, other markers are more important, which is evident from the results in the present study. A serial echocardiography is not regarded as necessary, although an echocardiogram should be repeated when there has been a deterioration in clinical status [16]. In addition, 80% receive their first HF diagnosis when hospitalized [1].

Already before hospital discharge with a diagnosis of HF, there are factors such as length of hospital stay constituting a risk of readmission and this also applies to patients with a higher burden of comorbidities. Regarding NT-proBNP during hospitalization, 58% of patients in the total cohort had a level likely associated with HF, which increased to 71% when considered only patients in the HFrEF subgroup [18]. NT-proBNP levels were obtained for 84% of the patients during the index hospitalization, which is consistent with comparable studies [1, 20]. An even higher number could be expected since it is not a complicated laboratory test and is useful for risk stratification at admission. A Spearman rank correlation analysis comparing NT-proBNP and renal function showed a correlation of 35%. The correlation became stronger as the severity of renal impairment increased. As renal impairment progresses, the kidneys are not able to excrete NT-proBNP. As such, the presence of highly elevated NT-proBNP levels alone is associated with an increased risk of readmission for HF patients with normally functioning kidneys, but do not infer the same risk for those with more severe renal impairment.

The recommended treatment for HFrEF and HFmrEF is beta-blockers, RAASi, MRA, ARNI as well as SGLT-2i according to current guidelines [16]. However, these guidelines were not available at the time that present study investigated and therefore it cannot be expected that SGLT-2i were fully used. After discharge, there were 80% treated with beta-blockers and 70% with RAASi which can be considered as high proportions. These results are similar to a comparable Swedish study in which treatment with beta-blockers was 88% and RAASi 76% [20]. Among the patients with HFrEF, all patients are in theory expected to have at least beta-blockers and RAASi [16]. The combination with beta-blockers and RAASi appeared in 60% after discharge in the total cohort and in the HFrEF group, it was as high as 78%. The combination with beta-blockers, RAASi and MRA only appeared in less than one third of the total cohort. In comparison, MRA was used in 30% of the patients in a similar study but did not include any data regarding the use of combination therapy for HF [20]. The treatment with BB and RAASi was not associated with lower risk for readmission for the HF cohort in present study. The dosage of BB and RAASi was not established in present study and the proportion of treated patients was already high at discharge. Therefore, the result is not surprising even if it is unequivocal that HF patients, with impaired left ventricular function have a good effect of such treatment.*4.1 Strengths and limitations.*

In the present study, there were only first hospitalizations and not subsequent events included. Since a few patients with probably higher morbidity would affect the overall results would most likely to give rise to the majority of admissions, it was preferred that the patient would be included only once.

Differences regarding readmission and HF phenotypes could not be demonstrated, which is puzzling as HFrEF is perceived as more severe and more demanding heart condition. All HF phenotypes consist of sick individuals where multi-disease is common. Since this study did not include detailed diagnoses at admission, it is difficult to determine how similar the cause for hospital admissions were between the groups. Measurement of EF during echocardiography is also a relatively rough measure, which means that the determination of HF phenotype is not exact. In reality, patients with HF are examined with echocardiography in different phases of HF and that some patients may have received initial treatment for HF before echocardiography is performed, which may affect the result of the examination. The determination of HF phenotypes was based solely on ejection fraction. This is possible in HFrEF and HFmrEF but more imprecise in HFpEF since wall thickness, relaxation pattern or filling pressure have not been evaluated. HFpEF has been relevant when echocardiography is performed in combination with a clinical assessment in connection with the diagnosis [22].

Even though the patients had a HF hospitalization at index, there was 16% missing NT-proBNP. An explanation could be that the NT-proBNP collected are those from hospital admission and have not been routine test for the complete study period. Additionally, some patients have not been hospitalized through the emergency department and are admitted to non-cardiac hospital wards where NT-proBNP is not used as a routine laboratory test.

Lastly, as this is a retrospective observational study, the results shown are purely associative and do not infer causality.

## 5. Conclusion

Among the patients hospitalized for HF, one third were readmitted and 12% deceased within 100 days after discharged. Echocardiogram prior or at initial hospitalization is underused and at the index hospitalization even though 39% got their first HF diagnose. It is undeniably important that measures should be taken at discharge after a patient has HF hospitalization to reduce the risk of readmission. Among patients with advanced age, longer LoS, COPD, high heart rate >70 bpm, impaired renal function and high levels of NT-proBNP values, it is essential to initiate adequate treatment and to establish follow-up strategies. In contrast, women and increased blood pressure are associated with a reduced risk of readmission.

## Credit author statement

**Jason Davidge**: Conceptualization, Methodology, Formal analysis, Writing- Reviewing and Editing. **Anders Halling**: Conceptualization, Methodology, Formal analysis, Writing- Reviewing. **Awais Ashfaq**: Data extraction, Software, Validation, Reviewing. **Kobra Etminani**: Conceptualization, Data extraction, Software, Validation, Reviewing. **Björn Agvall**: Conceptualization, Methodology, Formal analysis,

Writing- Reviewing, Supervision.

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## Data availability

The datasets generated and analysed in the current study are not publicly available due to the Swedish Health and Medical Services Act's regarding the Secrecy Act but could be available RH upon a reasonable request made to the corresponding author and followed by a specific review by the Regional Consultative Committee for data collection in RH.

## Declaration of competing interest

BA has received personal fees from AstraZeneca and Boehringer Ingelheim. JD, AH, KE and AA declare that there is no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200176.

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