Journal of the American Heart Association

ORIGINAL RESEARCH

Temporal Trends in Mortality and Hospitalization Risk in Patients With Heart Failure According to the Hospital Frailty Risk Score

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BACKGROUND: Heart failure (HF) and frailty often coexist. However, it is unknown how the interplay between HF and frailty at HF onset impacts prognosis of frail patients with HF and how this has evolved over time.

METHODS AND RESULTS: We identified 131 235 patients with new-onset HF (median age 74 years, 39.7% women) from Danish nationwide registers in 1999 to 2017. Stratification according to the Hospital Frailty Risk Score resulted in (1) 102 635 (78%) nonfrail, (2) 26 054 (20%) moderately frail, and (3) 2609 (2%) severely frail patients. The proportion of moderately frail patients increased from 13.2% to 24.9%. Five-year absolute risks of all-cause mortality, HF hospitalization, and non-HF hospitalization were calculated using the Kaplan-Meier and Aalen-Johansen estimators. From 1999 to 2002 to 2003 to 2017, all-cause mortality risk (95% CI) declined from 56.4% (55.8%–57.0%) to 33.3% (32.6%–34.1%), 79.8% (78.5%–81.0%) to 58.6% (57.2%–60.1%), and 90.8% (85.6%–96.0%) to 79.8% (76.4%–83.2%) in nonfrail, moderately frail, and severely frail patients, respectively. HF hospitalization risk remained almost constant over the study period. Non-HF hospitalization risk declined from 74.0% (73.5%–74.5%) to 65.8% (65.0%–66.5%) in nonfrail patients and remained stable overall in moderately frail and severely frail patients over the study period.

CONCLUSIONS: We observed an increase in frail patients. Mortality decreased for all frailty groups but remained high for severely frail patients. These findings indicate the need for further evidence on the optimization of care for frail patients with HF, and future research should address the development of comprehensive management strategies, integrating frailty assessment into standard clinical care and focused care for older patients with HF.

Key Words: all-cause death ■ frailty ■ heart failure ■ hospitalization risk ■ time trend

Heart failure (HF) remains a leading cause of morbidity, hospitalization, and mortality in older individuals.[1,2] Simultaneously, frailty, an aging-related syndrome marked by reduced physiological reserve and decreased resilience to stress, is emerging as a global health concern.[3] HF and frailty often coincide, with current data estimating the overall prevalence of frailty in HF to be ≈45%.[3–5] The presence of HF contributes to frailty by reducing cardiac output, leading to diminished physical capacity, muscle wasting, and overall decreased resilience. Conversely, frailty increases vulnerability to developing HF by impairing

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This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.037973

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We found an increase in the prevalence of frail patients and a decline in mortality across the frailty spectrum from 1999 to 2017, with mortality risk being consistently higher among frail patients compared with nonfrail counterparts, suggesting improvements in overall survival, even among frail patients.

What Are the Clinical Implications?

- Despite prescription of neurohormonal blockade, relatively, frail patients were associated with higher mortality rates than nonfrail patients, underscoring the need for reevaluating management strategies for frail patients with heart failure, potentially integrating tailored care according to frailty. Additionally, the high non-heart failure hospitalization risk warrants closer attention to managing comorbidities in this patient group.
- Moderately frail patients with heart failure who had high risks of mortality, but less frequent initiation on guideline-recommended heart failure pharmacotherapy, warrant specific attention on optimization of medication and rehabilitation to enhance life expectancy. Conversely, severely frail patients may benefit more from careful evaluation in choice between quality of life and palliative care as opposed to initiation of pharmacological intervention.

Nonstandard Abbreviations and Acronyms

ATC	*Anatomical Therapeutic Chemical*
BB	β-blockers
HFrEF	heart failure with reduced ejection fraction
HFRS	Hospital Frailty Risk Score
MRA	mineralocorticoid receptor antagonists
RASi	renin-angiotensin system inhibitors

the physiological reserve and ability to compensate for cardiac stressors.[6] Nevertheless, it remains unknown how the interplay between HF and frailty at HF onset has affected the prognosis of frail patients with HF throughout the past 20 years.

Despite the proven benefits of initiating guideline-recommended therapy for HF, real-world data have shown that frail patients with HF are less likely to receive therapy than their nonfrail counterparts.[7–10] Moreover, different frailty measures have demonstrated that frailty in patients with HF is associated with an increased risk of adverse outcomes such as death and hospitalization compared with nonfrail patients with HF.[11,12] However, registering frailty-related data in a real-world setting often presents a challenge due to the time-consuming and equipment-dependent nature of the tools currently available. As a result, there is no single reliable variable for frailty available in the registers. Nonetheless, the Hospital Frailty Risk Score (HFRS) offers a contemporary tool widely applied for assessing frailty through available register data.[13–16] Given these findings, and the ongoing uncertainty on the prognosis of patients with HF and frailty over time, there is a growing relevance to evaluate frailty in patients with HF and potentially establish management guidelines targeting frail patients with HF.[17]

To our knowledge, no previous studies have investigated the temporal trends of outcomes in patients with HF according to the HFRS using nationwide complete data spanning ≈20 years. Thus, we aimed to evaluate the 5-year risk of all-cause mortality, HF hospitalization, and non-HF hospitalization stratified by the HFRS at HF onset in this largescale observational study of patients with HF between 1999 and 2017.

METHODS

The data used in this study were provided by Statistics Denmark under specific permissions and licensing and are not publicly accessible due to restrictions. Requests for access to the data may be directed to the third-party provider, Statistics Denmark, upon reasonable justification and subject to their approval.

Data Sources

This study used the Danish nationwide health registers, interlinked through the distinctive personal identification number assigned to Danish citizens upon birth or immigration. The Danish Civil Registration system was used to acquire date of birth, sex, and immigration and emigration status.[18,19] To gather data on hospital contacts, including diagnoses classified according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) system, we used the Danish National Patient Registry.[20] Dates of all redeemed prescriptions were obtained from the Danish Registry of Medicinal Product Statistics, encoded using the *Anatomical Therapeutic Chemical* (*ATC*) classification system.[21] Information on death date was provided by the Danish Register of Causes of Death.[22] Data on personal income were obtained from the Danish Income Statistics Register, which contains information on income and transfer payments.[23]

Ethical Approval

Register-based retrospective observational studies do not require ethical approval by law in Denmark, and consent was therefore not obtained in this study.

Study Population

All patients between January 1, 1999 and December 31, 2017, aged 18 to 90 years, diagnosed with new-onset HF (*ICD-10* codes I50 and I42) as the primary diagnosis, inpatient or outpatient, were included in this study (Figure 1). The index date for each patient was defined as the date of the first HF diagnosis registered. The study period was divided into 4-year groups: 1999 to 2002, 2003 to 2007, 2008 to 2012, and 2013 to 2017, categorizing patients according to their index date. The accuracy of the *ICD-10* codes used for HF as the primary diagnosis have formerly been validated with a positive predictive value of 88% (95% CI, 84.4%–91.0%).[24] Patients with missing information, patients diagnosed with new-onset HF after December 31, 2017, or patients who emigrated before the index date were excluded.

Baseline Characteristics

Age, sex, comorbidities including atrial fibrillation/flutter, cancer, cerebrovascular disease, chronic obstructive pulmonary disease, ischemic heart disease, renal disease, peripheral vascular disease, and diabetes, as well as concordant pharmacotherapy including renin-angiotensin system inhibitors (RASi), β-blockers (BB), mineralocorticoid receptor antagonists, sodium-glucose transporter uptake inhibitors (SGLT2i), anticoagulants, antiplatelets, loop diuretics, potassium supplements, statins, thiazides, antidiabetics, and digoxin at index, were stratified by year group. Inpatient and outpatient contacts were used to define baseline comorbidities, from both primary and secondary diagnoses, using the *ICD-10* codes registered within 5 years before the index date. Two criteria were used to define patients with diabetes: an *ICD-10* code for diabetes (E10-14) or an *ATC* code (A10) indicating a prescription for antidiabetic medication.[25] Use of specific cardiovascular and antidiabetic medications were ascertained through *ATC* codes registered within 180 days before the index date. Charlson Comorbidity Index score >3 was computed for all patients. Income was calculated for all patients. Average household income was determined 5 years before the onset of HF and was categorized into quartiles, resulting in 4 groups. To ensure comparability between the income of individuals living alone and the income of a household with many members, the income was assessed from equivalized disposable income, which was determined by dividing the total household income by the weighted number of household members, according to the Organization for Economic Cooperation and Development modified scale.[26]

Definition of Frailty

Frailty was assessed with the HFRS, an established method for stratifying frailty status. The HFRS is based on *ICD-10* codes related to frailty-relevant comorbidities systematically assigned specific points. These comorbidities mostly consist of *ICD-10* codes for chronic diseases, but the HFRS also captures a range of frailty-related factors through the inclusion

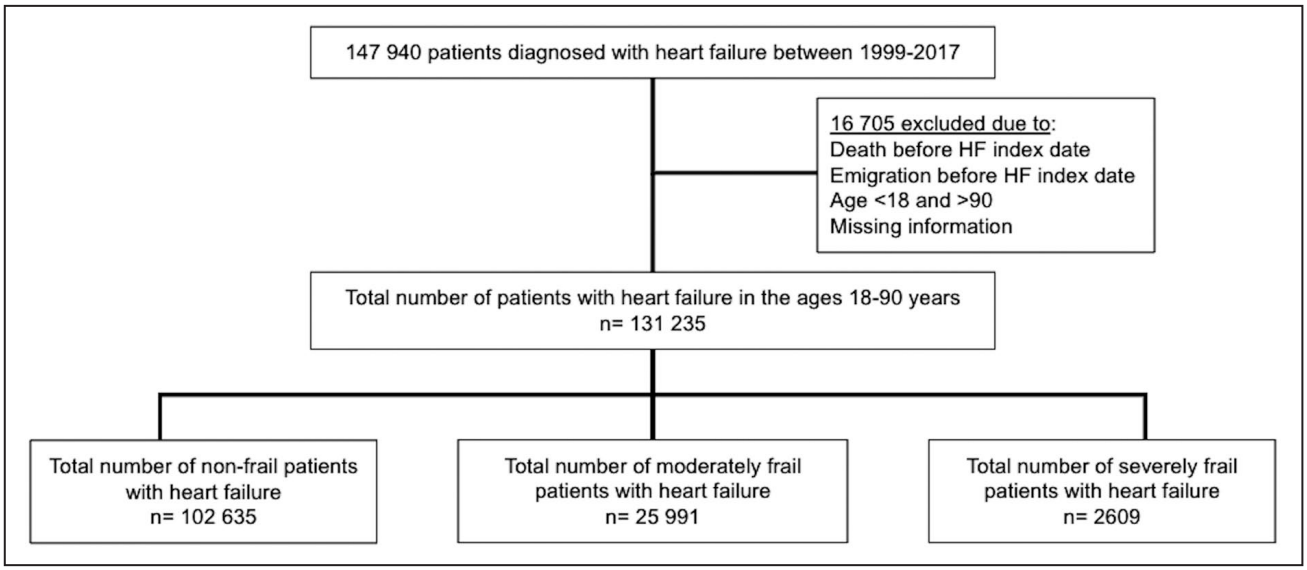


Figure 1. Flowchart of study cohort.
Flowchart depicting the study population selection. Patients with new-onset HF in 1999 to 2017 were included and stratified by frailty and year group. HF indicates heart failure.

of *ICD-10* codes on mobility restrictions, cognitive impairment, and emotional disturbances that extend beyond traditional comorbidity measure, rendering it a valuable instrument for identifying high-risk patients. In contrast to tools focusing solely on the presence of chronic disease, the HFRS therefore offers a practical population-based approach for risk stratification, facilitating efficient identification of vulnerable patients in real-world clinical settings, with the potential to guide tailored interventions and mitigate adverse outcomes.[13] Patients were categorized into 3 HFRS groups: (1) nonfrail (0–4 points), (2) moderately frail (5–15 points), and (3) severely frail (>15 points). Moderately and severely frail patients (HFRS ≥5) were classified as frail. The total HFRS was calculated based on comorbidities from within 5 years before the index date.

Statistical Analysis

Categorical variables were presented as total number of patients and percentage, whereas continuous variables were presented as median with interquartile range (IQR). *P* values were calculated using the Kruskal-Wallis test for continuous values and the χ^2 test for categorical values. The Kaplan-Meier and Aalen-Johansen estimators were used to estimate the 5-year absolute risk of (1) all-cause mortality (primary outcome), (2) HF hospitalization (secondary outcome), and (3) non-HF hospitalization (tertiary outcome), respectively, according to year and frailty group. For both inpatients and outpatients, HF hospitalization was defined as the first overnight hospitalization with HF as the primary diagnosis after new-onset HF. Likewise, non-HF hospitalization was defined as the first overnight hospitalization with specific primary diagnoses (detailed in Table S1) other than HF after the index date. Death was accounted for as a competing risk in the cumulative incidence of HF hospitalization and non-HF hospitalization. The outcomes were further examined in multivariable Cox proportional hazard models adjusted for year group, age, sex, and inpatient or outpatient diagnosis. Age was included as a categorical variable in the model, categorizing patients into 3 age groups: 18 to 69 years (reference), 70 to 79 years, and ≥80 years. The first year group (1999–2002) was used as the reference, and results were reported as adjusted hazard ratio and absolute risk with 95% CI. Patients were followed from index date to earliest event of either emigration, death, conclusion of the 5-year follow-up period, or the end-of-study date (December 31, 2018) (Figure S1). Moreover, a sensitivity analysis was performed, using a multivariable Cox proportional hazard model, investigating the interaction between year group and frailty status for all-cause mortality, comparing frail patients with nonfrail patients. Moderately and severely frail patients comprised the frail patient group. The analysis was adjusted for the same covariates as in the aforementioned Cox models. In addition, the proportion of patients initiated on neurohormonal blockade: BB, mineralocorticoid receptor antagonists (MRA), and RASi, as well as loop diuretics within 180 days before and 90 days after new-onset HF, was calculated, excluding patients who died before 90 days after the index date. Data management, statistical analyses, and illustration creation were performed using R (version 4.2.1 for Windows; R Foundation for Statistical Computing).

Supplemental Analyses

Last, we repeated calculations for baseline characteristics and the main analyses, including the 5-year absolute risk of all-cause mortality, HF hospitalization, and non-HF hospitalization, for a cohort of patients with HF with reduced ejection fraction (HFrEF) defined using a register-based definition validated in the Danish National Patient Registers with a positive predictive value of 95% as well as a sensitivity and specificity of 85%. Patients were categorized as having HFrEF if a prescription for RASi and BB within 90 days and 120 days, respectively, was redeemed. Patients not alive 120 days after index were excluded.[27]

RESULTS

Patient Characteristics

A comprehensive list of *ICD-10* and *ATC* codes for comorbidities and concordant pharmacotherapy used in this study can be found in Tables S1 and S2. These were further stratified by frailty in Table S3. Overall, 131 235 patients with new-onset HF between 1999 and 2017 were included. Of these, 102 635 (78%) were identified as nonfrail, 26 054 (20%) as moderately frail, and 2609 (2%) as severely frail (Table S3). For all patients enrolled, the median age was 74 (IQR, 64–81) years, and the age decreased from 76 (IQR, 66–82) years in 1999 to 2002 to 73 (IQR, 64–81) years in 2013 to 2017 ($P<0.001$) (Table). Age also decreased in all frailty groups throughout the study period, from 75 to 71 years for nonfrail patients ($P<0.001$), from 79 to 77 years for moderately frail patients ($P<0.001$), and from 80 to 78 years for severely frail patients ($P>0.05$) (Table S3). The proportion of female patients decreased significantly from 44.0% to 37.5% ($P<0.001$). The proportion of patients with HF with atrial fibrillation/flutter, cancer, renal disease, and diabetes, and patients who received pharmacotherapy with RASi, BB, SGLT2i, anticoagulants, antiplatelets, statins, and antidiabetics at baseline increased significantly over time ($P<0.001$). The proportion of patients with a Charlson Comorbidity Index score >3 points increased significantly from 8.1% to 13.8% over time ($P<0.001$) (Table). Moderately and severely frail patients had lower incomes than nonfrail patients.

Table. Baseline Characteristics Stratified According to Year Group Based on Heart Failure Onset

Characteristic	1999–2002 (n=30 665)	2003–2007 (n=3 416)	2008–2012 (n=32 288)	2013–2017 (n=34 866)	Total (n=131 235)	*P* value
Age, y, median [IQR]	76 [66–82]	74 [64–82]	73 [63–81]	73 [64–81]	74 [64–81]	<0.001
Women, n (%)	13 488 (44.0)	13 449 (40.4)	11 992 (37.1)	13 065 (37.5)	52 044 (39.7)	<0.001
Low income, n (%)	8992 (29.3)	8389 (25.1)	8143 (25.2)	8797 (25.2)	34 321 (26.2)	<0.001
Charlson Comorbidity Score >3, n (%)	2488 (8.1)	3711 (11.1)	4094 (12.7)	4825 (13.8)	15 118 (11.5)	<0.001
Comorbidities at baseline, n (%)						
Atrial fibrillation/flutter	7857 (25.6)	10 008 (29.9)	10 390 (32.2)	11 988 (34.4)	40 243 (30.7)	<0.001
Cancer	2701 (8.8)	3066 (9.2)	3448 (10.7)	4456 (12.8)	13 671 (10.4)	<0.001
Cerebrovascular disease	3132 (10.2)	3623 (10.8)	3342 (10.4)	3387 (9.7)	13 484 (10.3)	<0.001
Chronic obstructive pulmonary disease	4990 (16.3)	5388 (16.1)	4730 (14.6)	5207 (14.9)	20 315 (15.5)	<0.001
Ischemic heart disease	12 242 (39.9)	14 575 (43.6)	14 119 (43.7)	13 666 (39.2)	54 602 (41.6)	<0.001
Renal disease	1669 (5.4)	2213 (6.6)	2541 (7.9)	3012 (8.6)	9435 (7.2)	<0.001
Peripheral vascular disease	2045 (6.7)	2090 (6.3)	1570 (4.9)	1486 (4.3)	7191 (5.5)	<0.001
Diabetes	4976 (16.2)	6165 (18.4)	6861 (21.2)	7719 (22.1)	25 721 (19.6)	<0.001
Pharmacotherapy at baseline, n (%)						
RASi	9965 (32.5)	13 225 (39.6)	13 909 (43.1)	14 553 (41.7)	51 652 (39.4)	<0.001
BB	7246 (23.6)	11 984 (35.9)	14 134 (43.8)	15 331 (44.0)	48 695 (37.1)	<0.001
MRA	3841 (12.5)	4325 (12.9)	3503 (10.8)	3391 (9.7)	15 060 (11.5)	<0.001
SGLT2i	0 (0.0)	0 (0.0)	0 (0.0)	129 (0.4)	129 (0.1)	<0.001
Anticoagulants	14 568 (47.5)	19 287 (57.7)	20 129 (62.3)	21 279 (61.0)	75 263 (57.3)	<0.001
Antiplatelets	11 980 (39.1)	15 935 (47.7)	16 458 (51.0)	14 399 (41.3)	58 772 (44.8)	<0.001
Loop diuretics	15 956 (52.0)	15 926 (47.7)	13 381 (41.4)	13 145 (37.7)	58 408 (44.5)	<0.001
Potassium supplements	12 953 (42.2)	12 042 (36.0)	9956 (30.8)	10 454 (30.0)	45 405 (34.6)	<0.001
Statins	3121 (10.2)	9632 (28.8)	14 018 (43.4)	15 051 (43.2)	41 822 (31.9)	<0.001
Thiazides	228 (0.7)	294 (0.9)	242 (0.7)	23 (0.1)	787 (0.6)	<0.001
Antidiabetics	3941 (12.9)	4962 (14.8)	5720 (17.7)	6656 (19.1)	21 279 (16.2)	<0.001
Digoxin	7218 (23.5)	5383 (16.1)	3751 (11.6)	2972 (8.5)	19 324 (14.7)	<0.001

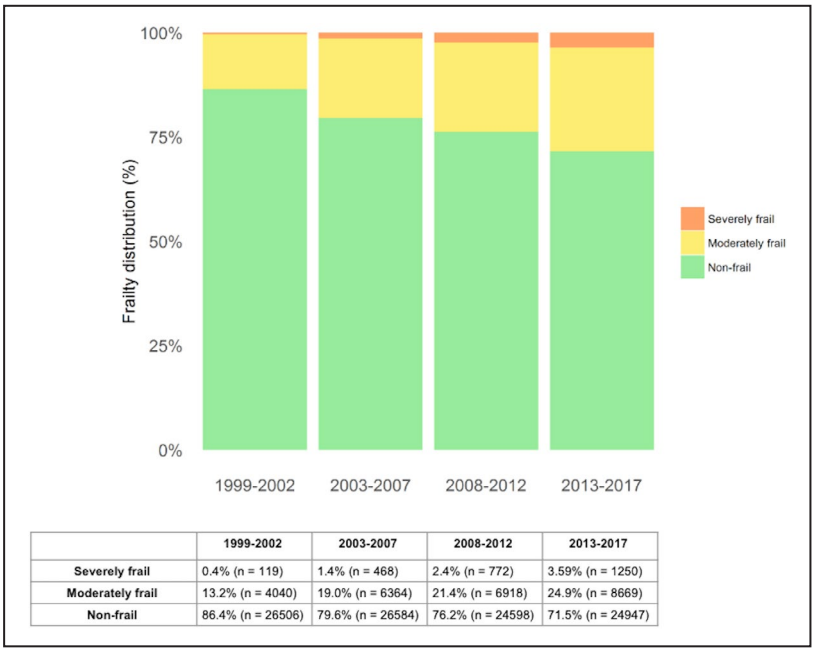
Baseline characteristics of patients with heart failure stratified according to year group based on year of receiving a new-onset heart failure diagnosis. BB indicates β-blockers; IQR, interquartile range; MRA, mineralocorticoid receptor antagonists; RASi, renin-angiotensin system inhibitors; and SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Temporal Trends According to the HFRS

There was a decline in the proportion of nonfrail patients over the study period, whereas the proportion of moderately and severely frail patients increased (Figure 2). The absolute increase in frail patients with HF increased from 13.6% to 28.4%, where the absolute increase in the proportion of moderately frail patients was the highest, going from 13% to 25%, compared with the increase in severely frail patients, going from 0.4% to 3.6%.

Risk of All-Cause Mortality, HF Hospitalization, and Non-HF Hospitalization According to the HFRS

For all-cause mortality, the absolute risk from 1999 to 2002 to 2013 to 2017 decreased from 56.4% (95% CI, 55.8%–57.0%) to 33.3% (95% CI, 32.6%–34.1%), 79.8% (95% CI, 78.5%–81.0%) to 58.6% (95% CI, 57.2%–60.1%), and 90.8% (95% CI, 85.6%–96.0%) to 79.8% (95% CI, 76.4%–83.2%) in nonfrail, moderately frail, and severely frail patients, respectively (Figure 3A). For all-cause mortality, the adjusted hazard ratios in 2013 to 2017 were 0.61 (95% CI, 0.59–0.63), 0.67 (95% CI, 0.64–0.70), and 0.72 (95% CI, 0.59–0.88) in nonfrail, moderately frail, and severely frail patients, respectively (Figure 4). For HF hospitalization, the absolute risk from 1999 to 2002 to 2013 to 2017 decreased in nonfrail patients from 27.9% (95% CI, 27.4%–28.4%) to 24.9% (95% CI, 24.3%–25.5%) (Figure 3B). Adjusted hazard ratios for HF hospitalization in 2013 to 2017 were 0.88 (95% CI, 0.85–0.91), 0.81 (95% CI, 0.75–0.87), and 0.92 (95% CI, 0.60–1.40) in nonfrail, moderately frail, and severely frail patients, respectively (Figure 4). For non-HF hospitalization, the absolute risk from 1999 to 2002 to 2013 to 2017 decreased from 74.0% (95%



	1999-2002	2003-2007	2008-2012	2013-2017
Severely frail	0.4% (n = 119)	1.4% (n = 468)	2.4% (n = 772)	3.59% (n = 1250)
Moderately frail	13.2% (n = 4040)	19.0% (n = 6364)	21.4% (n = 6918)	24.9% (n = 8669)
Non-frail	86.4% (n = 26506)	79.6% (n = 26584)	76.2% (n = 24598)	71.5% (n = 24947)

Figure 2. Temporal trend of frailty status in patients with new-onset HF.
Stacked bar chart illustrating the trend of frailty status in patients with new-onset HF stratified by year group: 1999 to 2002, 2003 to 2007, 2008 to 2012, 2013 to 2017. HF indicates heart failure.

CI, 73.5%–74.5%) to 65.8% (95% CI, 65.0%–66.5%) in nonfrail patients and remained stable overall in moderately frail and severely frail patients (Figure 3C). Adjusted hazard ratios for non-HF hospitalization in 2013 to 2017 were 0.82 (95% CI, 0.80–0.84), 0.88 (95% CI, 0.84–0.92), and 0.96 (95% CI, 0.77–1.20) in nonfrail, moderately frail, and severely frail patients, respectively (Figure 4).

Difference in Mortality Between Frail and Nonfrail Patients

The *P* value for the interaction between year group and frailty was <0.001. Adjusted hazard ratios for all-cause mortality in frail versus nonfrail patients, were: 1.59 (95% CI, 1.53–1.65), 1.73 (95% CI, 1.67–1.79), 1.80 (95% CI, 1.74–1.86), and 1.89 (95% CI, 1.82–1.96), in 1999 to 2002, 2003 to 2007, 2008 to 2012, and 2013 to 2017, respectively (Figure 5).

Prescriptions for BB, RASi, MRA, and Loop Diuretics According to the HFRS

Prescriptions for BB, RASi, and MRA 180 days before and 90 days after the index date increased from 1999 to 2017 for patients with HF in all frailty groups (Figure 6). For BB, the absolute percentage of patients prescribed medication went from 33.2% to 82.1%, 24.0% to 76.1%, and 18.2% to 69.8% in nonfrail, moderately frail, and severely frail patients, respectively. For RASi, the absolute percentage of patients prescribed medication went from 59.7% to 81.3%, 49.0% to 71.3%, and 27.3% to 63.1% in nonfrail, moderately frail, and severely frail patients, respectively. For MRA, the absolute percentage of patients prescribed medication went from: 22.9% to 35.1%, 22.6% to 30.5%, and 27.3% to 24.6% in nonfrail, moderately frail, and severely frail patients, respectively. For loop diuretics, the absolute percentage of patients prescribed medication went from 81.9% to 65.1%, 88.7% to 78.4%, and 63.6% to 84.9% in nonfrail, moderately frail, and severely frail patients, respectively. The proportion of patients prescribed MRA remained around 20 to 40% throughout the study period in all frailty groups.

Supplemental Analyses

Overall, 56 573 patients with HFrEF were identified. Baseline characteristics showed younger age and higher prevalence of ischemic heart disease than for the overall study population (Table S4). Due to the presence of microdata in analyses conducted on the severely frail patients within the HFrEF cohort, presenting results for severely frail patients was not possible. Similar to our main analyses, we found a declining trend of all-cause mortality for the HFrEF cohort. Likewise, there was a declining trend in HF hospitalization, which was more pronounced than in the overall study population. Non-HF hospitalization also displayed similar trends to those in the main analysis (Figure S2A–C).

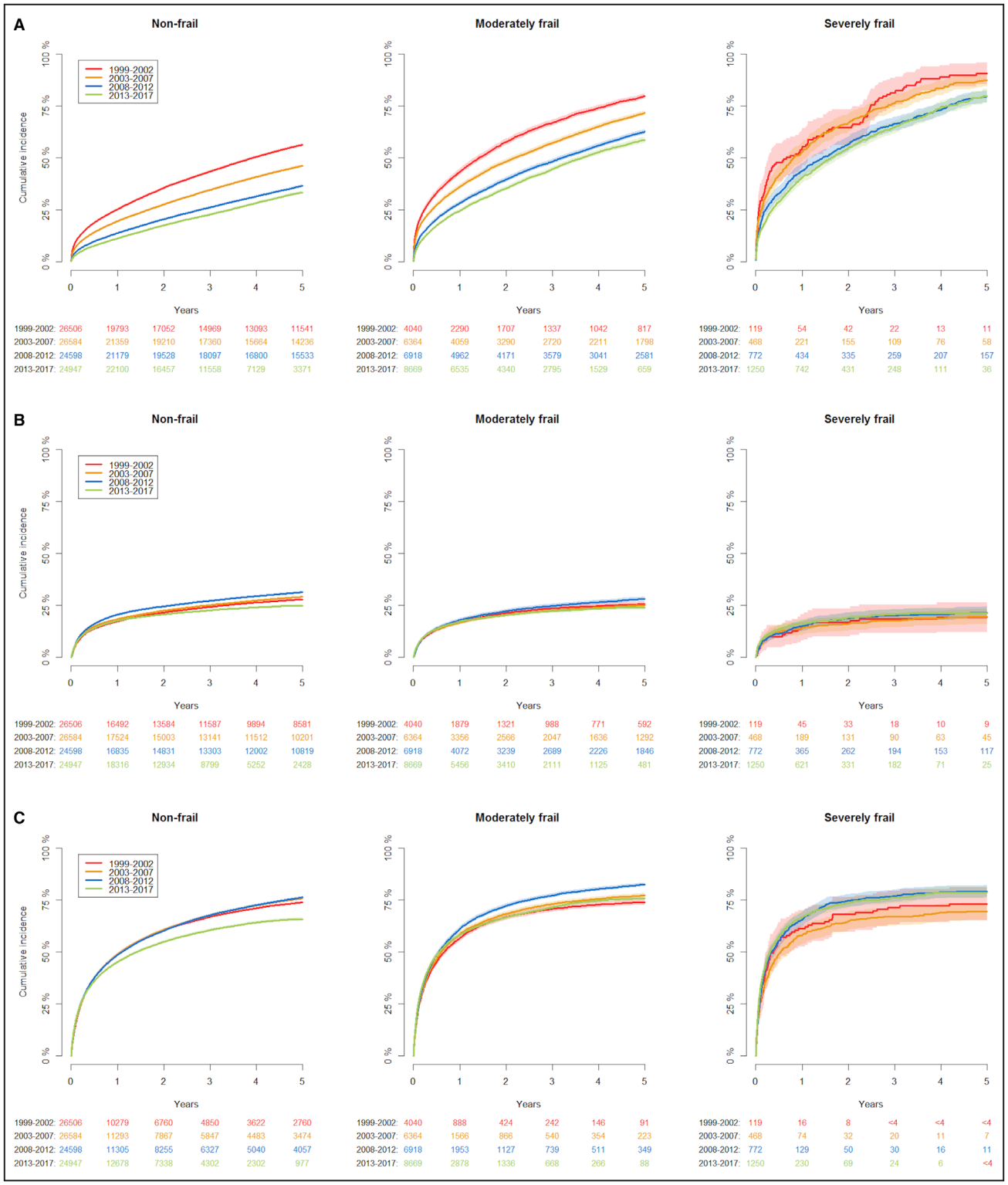


Figure 3. Temporal trends of the 5-year absolute risk of all-cause mortality, HF hospitalization, and non-HF hospitalization according to year group and frailty.

(**A**) Five-year absolute risk of all-cause mortality. (**B**) Five-year absolute risk of HF hospitalization after new-onset HF. (**C**) Five-year absolute risk of non-HF hospitalization after new-onset HF. The respective 5-year absolute risks of all-cause mortality, HF hospitalization, and non-HF hospitalization are compared by the year groups 1999 to 2002 (red), 2003 to 2007 (yellow), 2008 to 2012 (blue), 2013 to 2017 (green) in patients stratified by frailty (nonfrail, moderately frail, and severely frail) after new-onset HF. Tables show the total number of patients in each year group, stratified by frailty and year group, where bands represent 95% CIs. Competing risk has been accounted for when calculating cumulative incidence of HF hospitalization and non-HF hospitalization. HF indicates heart failure.

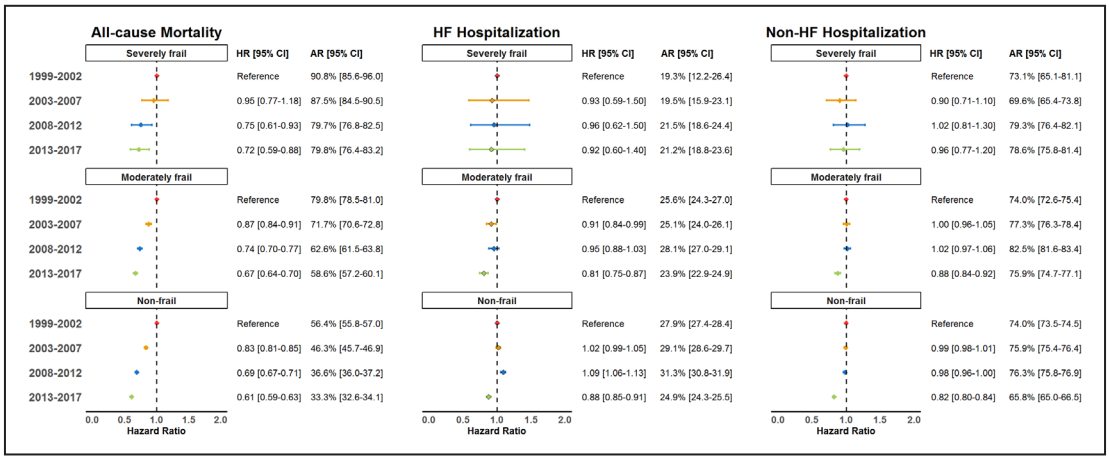


Figure 4. All-cause mortality, HF hospitalization, and non-HF hospitalization according to frailty and year group.

Forest plot depicting the 5-year absolute risk of all-cause mortality, HF hospitalization, and non-HF hospitalization after new-onset HF according to frailty and year group, with hazard ratios, absolute risks, and corresponding 95% CIs. Absolute risks represent the cumulative incidence, computed using the Kaplan-Meier estimator and the Aalen-Johansen estimator. Hazard ratios were estimated using the Cox proportional hazards model, adjusted for year group, sex, age group, and inpatient or outpatient diagnosis. AR represents the estimated cumulative incidence of 5-year mortality, 5-year risk of HF hospitalization and 5-year risk of non-HF hospitalization, calculated using the Kaplan-Meier method and the Aalen-Johansen method. AR indicates absolute risk; HF, heart failure; and HR, hazard ratio.

DISCUSSION

Main Findings

In this largescale observational study including 131 235 patients with HF, there were several notable trends from 1999 to 2017. (1) The prevalence of frail patients with HF increased from 13.6% to 28.4%. (2) The 5-year risk of all-cause mortality declined across all frailty groups, and frail patients had higher mortality rates than nonfrail patients. (3) The 5-year risk of HF hospitalization remained relatively stable across the entire frailty spectrum, as did the risk of non-HF hospitalization for moderately and severely frail patients. (4) Neurohormonal blockade was implemented in a uniform pattern in all frailty groups, yet the mortality rate improved more in nonfrail patients relative to frail patients.

Temporal Trends in Prevalence of Moderately and Severely Frail Patients With HF

The proportion of frail patients in this study was 22%. Recently published global multicenter trials investigating frailty in HF in secondary analyses have found the prevalence of frail patients to range from 55% to 63%.[11,28,29] Discrepancies between these trials and our findings could be attributed to differences in the assessment and definition of frailty, questionnaires versus administrative codes, although validated,[13] as well as the assessment of frailty status in patients at the time of HF onset in our study versus in the trials, where HF is defined not only from onset. Moreover, Danish registers predominantly include patients with HFrEF,[27] and typically the prevalence of frailty in patients with HF with preserved ejection fraction is expectedly higher.[27,30] We observed an overall increase in the prevalence of frailty, with the largest increase found in moderately frail patients. This is in accordance with a study based on real-world data, which found an increase in frailty prevalence from 2004 to 2014.[31] Overall, we observed a decrease in median age over the study period. This might be a result of a higher incidence of HF among younger patients, possibly explained by an increased prevalence of risk factors for HF in this age group, which in turn might also explain the higher incidence of younger frail patients.[32] Another potential explanation for this trend might be earlier identification of HF as a result of increased clinical awareness and attention to early indicators of HF. We also observed a 7-year age difference between the nonfrail and severely frail patients at the end of the study period, aligning with previous research, associating frailty with older age.[33,34]

Temporal Trends in All-Cause Mortality, HF Hospitalization, and Non-HF Hospitalization

The decline in mortality over time could be attributed to improvements in prescribing guideline-recommended

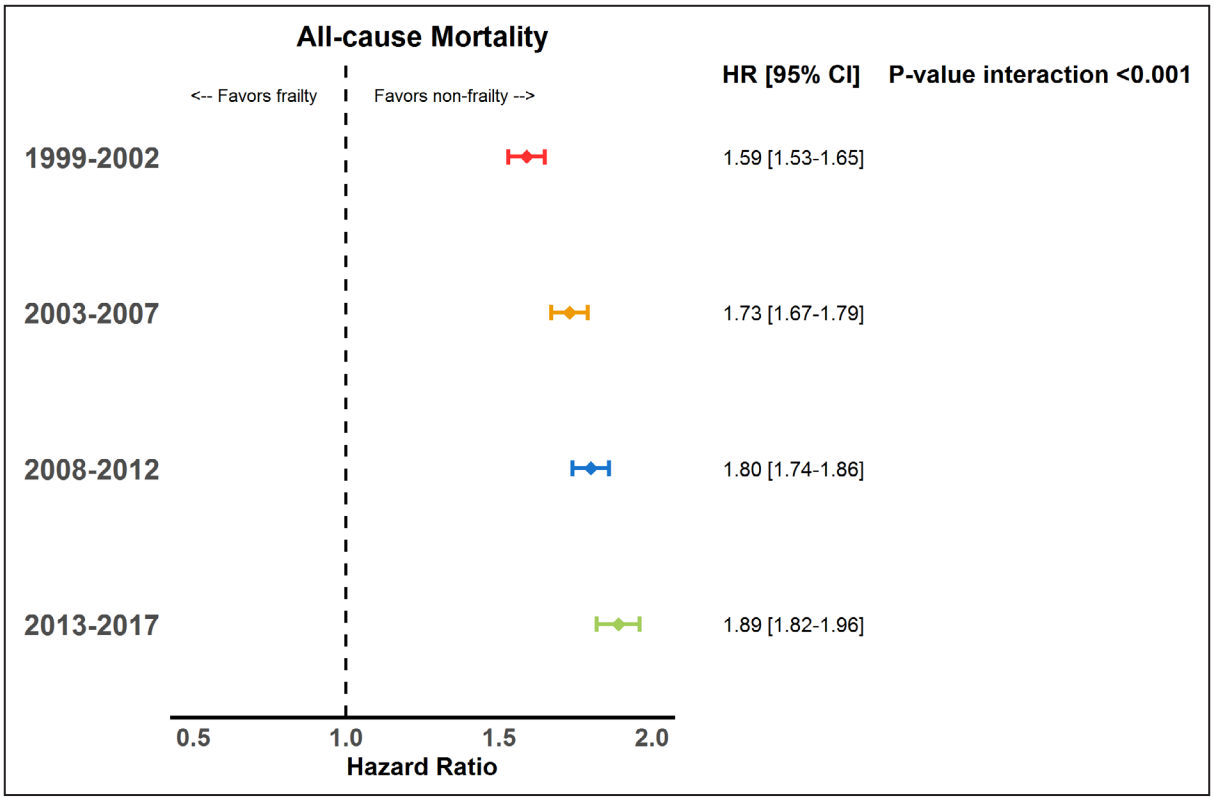


Figure 5. All-cause mortality in frail patients vs nonfrail patients.
Forest plot illustrating adjusted hazard ratios between frail patients vs nonfrail patients for all-cause mortality and corresponding 95% CIs, for the year groups 1999 to 2002, 2003 to 2007, 2008 to 2012, and 2013 to 2017, and the *P* value for the interaction between frailty and year group. Hazard ratios were estimated using the Cox proportional hazards model adjusted for year group, frailty status, the interaction between year group and frailty status, as well as sex, age group, and inpatient or outpatient diagnosis. HF indicates heart failure; and HR, hazard ratio.

therapy and earlier diagnosis of HF. Moderately frail patients displayed a decreasing all-cause mortality risk over time, mirroring the pattern observed in nonfrail patients. The absolute decrease was modest in severely frail patients, and the mortality risk was still high at the end of the study period. Hence, for all-cause mortality, moderately frail patients displayed similar trends to nonfrail patients in terms of risk reduction, but similarity to severely frail patients given the high absolute risks. This underscores the ambiguity in aligning moderately frail patients with either the severely frail or nonfrail patient group. Furthermore, our findings are consistent with other research, showing that frail patients with HF are reported to have higher mortality risks compared with nonfrail counterparts.[11,31,33,35,36] In addition, we found interaction between year group and frailty for all-cause mortality and an association between increased rate in all-cause mortality for frail patients compared with nonfrail patients for all year groups. The risk of HF hospitalization did not change significantly over time across the frailty spectrum. Some studies indicate an association between frailty and a higher risk of rehospitalization, whereas others do not.[12,33,34,37] Our results may be explained by outpatient management of HF hospitalizations,[38] which also might explain the relatively low risk of a HF hospitalization after new-onset HF over time in an international context. The risk of non-HF hospitalization did not change significantly over time for moderately frail and severely frail patients. However, the risk of non-HF hospitalization for each frailty group was markedly high. This underscores the importance of comorbidities to outcomes in patients with HF and might especially be true for patients concurrently dealing with frailty who may have a larger comorbidity burden. These findings also align with previous research, reporting high risks of non-HF hospitalizations in patients with HF after receiving a HF diagnosis.[37]

Temporal Trends in Guideline-Recommended HF Pharmacotherapy

We found a surge in the prescription of neurohormonal blockade across the frailty spectrum over the study period. Severely frail patients exhibited the lowest incidence of prescriptions of BB, MRA, and RASi. Conversely, prescriptions of loop diuretics exhibited a declining trend, with the highest proportion of loop diuretics prescribed in severely frail patients. This

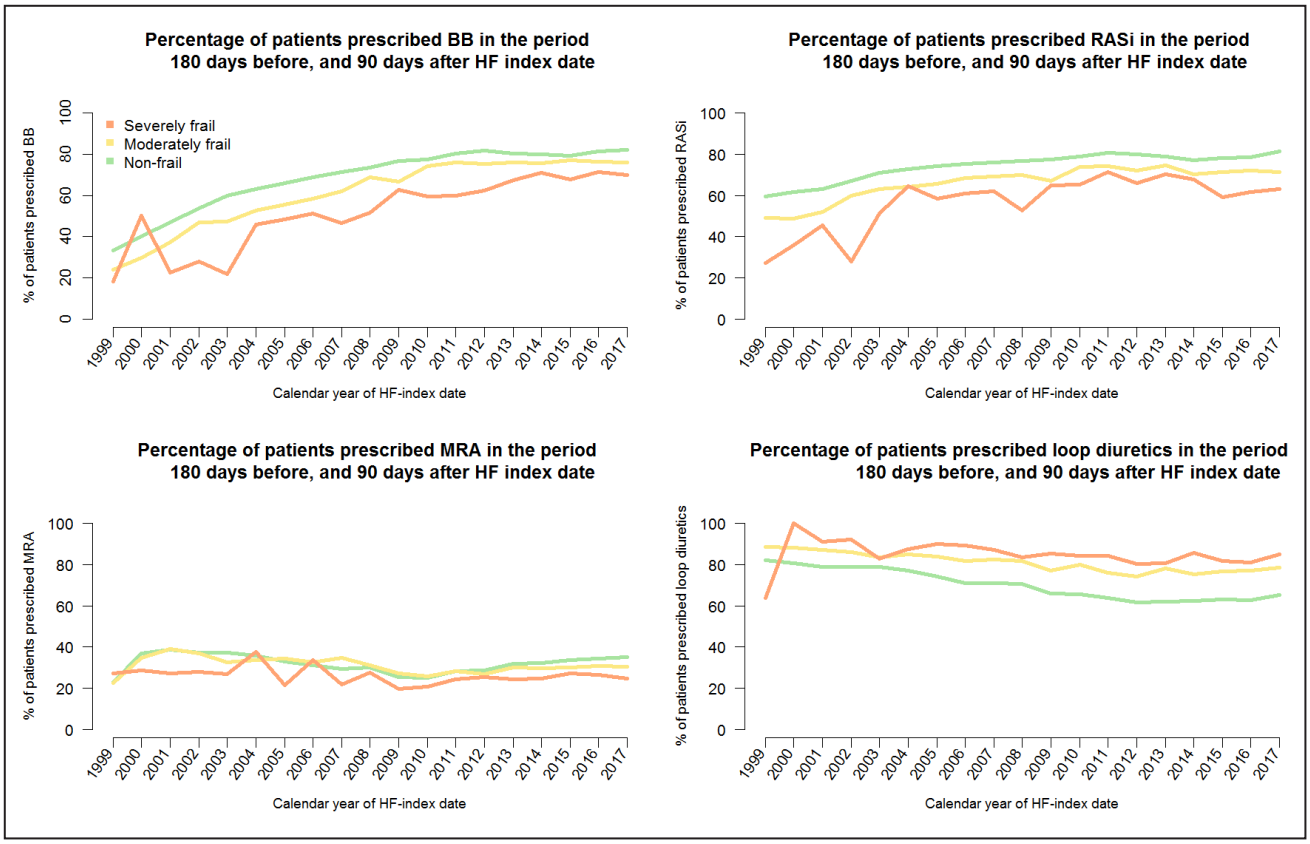


Figure 6. Temporal trend of prescription of BB, RASi, MRA, and loop diuretics.
Medicine plot illustrating the proportion of patients prescribed BB, RASi, MRA, and loop diuretics in patients with new-onset HF within 180 days before and 90 days after receiving a new-onset HF diagnosis in 1999 to 2017. BB indicates β-blockers; HF, heart failure; MRA, mineralocorticoid receptor antagonists; and RASi, renin-angiotensin system inhibitors.

phenomenon could suggest that this patient group remained the most symptomatic throughout the study period. Established research has shown that frail patients tend to exhibit a better prognosis in 30-day mortality when administered guideline-recommended HF pharmacotherapy.[9] Despite several trials showing that frail patients benefit from HF medication,[7,11,28] our real-life data suggest lower prescription rates for neurohormonal blockade in frail patients with HF compared with their nonfrail counterparts.[9,34,36] However, the lower medication prescription in severely frail patients may reflect a perceived nonfitness or ineligibility for pharmacotherapy prescriptions by the clinicians or the patients, rather than underusage.[33] Also, it is possible that severely frail patients receive less guideline-recommended pharmacotherapy, because they are more likely to have HF with preserved ejection fraction and therefore may not require guideline-recommended HF pharmacotherapy.[39]

Clinical Implications

In response to a growing population of frail patients with HF, there is an evolving need for a tailored management guideline. Notably, moderately frail patients with HF who have a high risk of all-cause mortality but are prescribed guideline-recommended HF pharmacotherapy less frequently warrant specific attention. A recent randomized clinical trial demonstrated that patients hospitalized with acute decompensated HF, who underwent tailored rehabilitation continuing for 12 weeks following hospital discharge and encompassed multiple elements for physical function, resulted in significantly greater improvement in physical function than those who received standard care. These findings suggest that individualized, transitional, and early rehabilitation is advantageous for patients with HF,[40] and might specifically benefit patients who receive less pharmacologic intervention but have high mortality rates, such as the moderately frail. Furthermore, the rise in severely frail patients presenting with even higher mortality rates underscores the importance of careful evaluation in the choice between quality of life and palliative care options versus initiation of guideline-recommended therapies. Thus, the introduction of a subspecialty, such as geriatric cardiology, offering focused care for older cardiovascular patients such as patients with HF, could be considered.[41] Although age strongly correlates

with frailty, it is important that clinicians differentiate between moderate and severe frailty and age to avoid overlooking treatment initiation in older patients. Systematic frailty assessment and a comprehensive clinical guideline are imperative for patients with HF, particularly for increasing the proportion of moderately frail patients, aiming to rectify discrepancies in care, and bettering patient outcomes.[42]

Study Strengths and Limitations

A significant strength in this study is the use of high-quality Danish data and a large sample population, reducing the risk of inclusion and selection bias. The *ICD-10* codes used for HF in this study have previously been validated with a positive predictive value of 88.0%.[24] Yet, there are some limitations to consider. The HFRS distribution of frailty is based on *ICD-10* diagnosis codes alone, and does not take clinical frailty assessments into account,[13] potentially resulting in the exclusion of older frail patients without hospitalization history. In the validation study, the HFRS used diagnoses derived from codes over a 2-year period. In contrast, our study considered comorbidities from within 5 years preceding the new-onset HF diagnosis, and although having nationwide data access, we determined that considering comorbidities up to 10 years back may not be clinically relevant. Moreover, discrepancies in documentation and coding methods might result in errors and misclassifications. The HFRS was initially designed and validated in populations aged ≥75 years; however, our study included patients as young as 18 years and up to 90 years to encompass a broader range of patients with HF. Though the median age in the current study was 74 years, there is a potential misclassification bias of younger patients. Also, grouping patients into HFRS groups solely based on accumulated *ICD-10* codes disregards disease severity as a contributing factor to frailty. Furthermore, the distinction between frailty degrees in the HFRS, differentiating nonfrail (HFRS <5) from moderately and severely frail (HFRS ≥5), raises a pivotal question about the clinical impact of a 1-point difference in score. Another limitation of the HFRS is its moderate predictive accuracy for 30-day mortality, 30-day readmissions, and long hospital stays. Despite this, we believe the HFRS remains valuable in the current study, because it facilitates risk stratification among real-world populations and highlights those who may benefit from closer monitoring and targeted interventions. Likewise, we lacked data on left ventricular ejection fraction, New York Heart Association functional class, natriuretic peptide levels, body mass index, estimated glomerular filtration rate, and blood pressure, contributing to unmeasured confounding. Last, although accounting for known confounders, complete elimination of residual confounding was not possible, for example, due to the use of diagnosis codes and medication codes rather than hemoglobin A1c for defining type 2 diabetes.

CONCLUSIONS

From 1999 to 2017, we observed an increase in the prevalence of frail patients with HF, especially moderately frail patients. The 5-year mortality risk declined across the entire frailty spectrum, and the lowest absolute decrease was found in severely frail patients, with persistently high levels of mortality. Despite prescription of neurohormonal blockade, relatively, frail patients were associated with higher mortality rates than nonfrail patients. The risk of HF hospitalization remained relatively stable across the entire frailty spectrum, and the risk of non-HF hospitalization remained relatively stable for moderately and severely frail patients. All in all, these findings underscore the importance of further research on how to better care for patients with HF and frailty to implement guidelines directed at frail patients with HF.

ARTICLE INFORMATION

Received July 28, 2024; accepted December 31, 2024.

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Acknowledgments

Author contributions: N.K.A. conducted the formal analyses and literature research, visualized and interpreted the data, and wrote the original draft of the article. N.N. contributed to visualization of the data, interpreted and verified the data, and reviewed and edited the article. M.E.M. contributed to visualization of data, interpreted the data, and reviewed and edited the article. M.A. contributed to formal analyses, data visualization, literature research, and reviewed and edited the article. D.Z. contributed to formal analyses and reviewed and edited the article. M.S. conceptualized the study as well as methodology; supervised the work; validated, interpreted, and verified the data; verified the results; and reviewed and edited the article. L.K. conceptualized the methodology, interpreted the data and results, and reviewed and edited the article. J.H.B. interpreted the data and reviewed and edited the article. C.H.G. contributed to formal analyses, interpreted the data, and reviewed and edited the article. C.F.A., C.A., J.E.S., D.M.C., E.F., and C.S.-P. interpreted the data, and reviewed a.nd edited the article. All authors reviewed and approved the final version of the article to be submitted.

Sources of Funding

This work was supported by hospital grants from Herlev-Gentofte University Hospital.

Disclosures

N.A. and M.A. report hospital grants from Herlev-Gentofte University Hospital. N.N. reports honorarium from Bayer A/S and Astra Zeneca, unrelated to the submitted work. M.E.M. reports grants from CARDIO-HGH Foundation, Herlev-Gentofte University Hospital, and Danish Cardiovascular Academy, unrelated to the submitted work. C.H.G. reports personal fees from lecture honoraria from Astra Zeneca, unrelated to the submitted work. J.H.B. reports

participation in the advisory board for Bayer, unrelated to the submitted work. C.F.A. reports grants from the Danish Heart Foundation, Toyota-Fonden, Arvid Nilsson's Foundation, Aase & Ejnar Danielsen's Foundation, Fru Asta Florida Bolding's Memorial Grant, KV Foundation, and the Research and Innovation Foundation of the Department of Cardiology (FUHAS, formerly FUKAP), Herlev and Gentofte University Hospital, Herlev, Denmark, during the conduct of her own submitted work; personal fees from Astra Zeneca; and has acted as an unpaid investigator in 2 trials from Novo Nordisk, unrelated to the submitted work. J.E.S. reports grants from Herlev-Gentofte Forskningsfond, Snedkermester Sophus Jacobz; Tobren og Alice Frimodts Fond; Dagmar Marshalls Fond; and Eva og Henry Frænkels Mindefond, unrelated to the submitted work. E.F. reports an independent research grant related to valvular heart disease and endocarditis from the Novo Nordisk Foundation and the Danish Heart Association, unrelated to the submitted work. L.K. reports speaker honoraria from Novo Nordisk, Astra Zeneca, Novartis, and Boehringer Ingelheim, unrelated to the submitted work. M.S. reports lecture fees from Novartis, Boehringer-Ingelheim, Astra Zeneca, and Novo Nordisk, unrelated to the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figures S1–S2

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