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Frailty and comorbidity predict first hospitalization after heart failure diagnosis in primary care: population-based observational study in England

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Competing interests statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: AB, DK and PA had financial support from Dr Foster® for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other

relationships or activities that could appear to have influenced the submitted work. AM and BH are general practitioners working in the NHS.

Abstract

Background: Frailty has only recently been recognised as important in patients with heart failure (HF), but little has been done to predict the first hospitalization after diagnosis in unselected primary care populations.

Objectives: To predict the first unplanned HF or all-cause admission after diagnosis, comparing the effects of comorbidity and frailty, the latter measured by the recently validated electronic frailty index (eFI).

Design: Observational study.

Setting: Primary care in England.

Subjects: All adult patients diagnosed with HF in primary care between 2010 and 2013.

Methods: We used electronic health records of patients registered with primary care practices sending records to the Clinical Practice Research Datalink (CPRD) in England with linkage to national hospital admissions and deaths data. Competing-risk time-to-event analyses identified predictors of first unplanned hospitalization for HF or for any condition after diagnosis.

Results: Of 6,360 patients, 9% had an emergency hospitalization for their HF, and 39% had one for any cause within a year of diagnosis; 578 (9.1%) died within a year without having any emergency admission. The main predictors of HF admission were older age, elevated serum creatinine and not being on a beta-blocker. The main predictors of all-cause admission were age, comorbidity, frailty, prior admission, not being on a beta-blocker, low haematocrit, and living alone. Frailty effects were largest in patients aged under 85.

Conclusions: This study suggests that the frailty has predictive power beyond its comorbidity components. HF patients in the community should be assessed for frailty, which should be reflected in future HF guidelines.

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Key words: heart failure; emergency hospitalization; frailty; CPRD

Key points:

Patients with heart failure (HF) have high readmission and mortality rates, but there has been limited work on predicting the first hospitalization after diagnosis in unselected primary care populations.

In our study of 6,360 patients diagnosed with HF in primary care in England, the main predictors of admission for HF were higher age, elevated serum creatinine level and not being on a beta-blocker.

Frailty, which can now be measured routinely in UK electronic GP databases, and comorbidity were among the predictors of all-cause hospitalizations. The effects of frailty were greater at younger ages.

Introduction

Around 40 million people had heart failure (HF) worldwide in 2015.[1] Prevalence is increasing[2] and healthcare costs are high, largely relating to hospitalizations. Studies of hospitalization often focus on readmissions in patients who have already been admitted for decompensated HF.[3] Clinical trial enrollees are younger, more frequently male and have lower ejection fraction,[4] with older people with frailty frequently excluded.[5] Both trial patients and those already hospitalized therefore differ from community-based patients in key ways.

In most healthcare systems, patients with HF are mainly managed in primary care,[6] yet little is known about initial hospitalizations after diagnosis. Many HF patients have multiple long-term conditions and so are hospitalized for a range of reasons.[7-8] It is therefore important to consider not just the first admission for HF, which represents an important milestone, with high risk of subsequent readmission and death,[9-10] but also admissions for other conditions. There has been some work on predicting admission for HF[11] but little for other conditions.

Frailty is characterized by loss of biological reserves, failure of homeostatic mechanisms and vulnerability to adverse outcomes, including hospitalization.[12] Around 10% people aged ≥65 have frailty, rising to up to a half of those aged over 85. However, as a concept, frailty has only recently gained recognition in HF prognosis.[13-15] Importantly, a new diagnosis of HF indicates additional loss of biological reserve for an older person with frailty, with associated increased vulnerability to sudden health status changes. Frailty might therefore explain some of the inconsistency of predictors of hospitalization in people with HF.[16]

The recent development and validation of an electronic frailty index (eFI) using routinely available primary care electronic medical record (EMR) data enables novel research into the relationships between HF, frailty and outcomes using population-based, representative "real world" datasets.[17] The eFI is based on the internationally established cumulative deficit model, which covers a range of "deficits" (clinical signs, symptoms, diseases, disabilities and impairments). It therefore covers more than comorbidity, and it is supported in the 2016 UK National Institute for Health and Care Excellence (NICE) multimorbidity guidelines.[18] Using EMR data for England, we investigate the predictors of a first unplanned hospital admission in a population-based cohort of patients diagnosed with HF in primary care. We pay particular attention to the effect of frailty and what it might contribute above the effects of comorbidity.

Methods

Data

Data came from the Clinical Practice Research Datalink (CPRD), one of the world's largest databases of primary care EMRs. It covers approximately 7% of UK National Health Service (NHS) general practices and is linked to England's national hospital administrative database, Hospital Episodes Statistics (HES), and the national mortality register. Patients are representative of the UK population,[19] and the CPRD is widely used for research.[20]

Patient cohort and date of HF diagnosis

We included patients aged ≥18 with a first recorded diagnosis of HF between January 1st 2010 and March 31st 2013. Cases were identified via Read codes in CPRD consultation records and ICD-10 codes in any HES diagnosis fields (Supplementary Table 1).[21] Patients

diagnosed as inpatients were excluded, except those whose primary care physician referred them to the emergency department with an HF symptom on their admission date.

We included data for the 10-year period from 2005 to 2014, to allow at least 12 months' follow-up after diagnosis and to look back at least 5 years before diagnosis to identify predictors.

The following data-related exclusion criteria were applied: CPRD records at practices not linked to HES, patients not registered in a CPRD practice for the whole ten-year study period, and standard CPRD data quality exclusions.

Outcomes and predictors

Primary outcomes were first HF emergency admission and first all-cause emergency admission after an HF diagnosis in primary care, with follow-up to April 2014.

We derived potential predictors from the HF literature that used administrative[22] or clinical data[23]: age, gender, ethnicity (white, non-white, unknown and missing), neighbourhood socio-economic deprivation (Index of Multiple Deprivation, IMD, divided into equal nationally population-weighted fifths), Body Mass Index (BMI) category, smoking, alcohol drinking, social vulnerability (codes for widowed/otherwise bereaved and living alone), comorbidities, the electronic frailty index (eFI[17]), continuity of care,[24,25] polypharmacy (5+ medications within the 12 months before diagnosis), some specific elements of the medical history before diagnosis (not on a beta-blocker, not on an ACEi/ARB, percutaneous transluminal coronary angioplasty (PTCA), coronary arterial bypass grafting (CABG), any elective admission, and any emergency admission for non-HF diagnoses), systolic blood

pressure, serum creatinine, glucose and haematocrit. We lacked reliable or commonly recorded values of the serum B-type natriuretic peptide (BNP or NT-proBNP) or echocardiogram (echo) results or for heart rate. ICD-10 and ethnicity codes for any admissions before HF diagnosis identified and augmented frequencies for ethnicity, individual comorbidities and living alone.

For certain comorbidities (hypertension, diabetes mellitus, and renal disease), we used clinical measurements in CPRD in addition to Read codes and ICD-10 codes, using established reference range cut-off values (Appendix 1). For patient physiological factors (systolic blood pressure, serum creatinine, glucose and haematocrit), we calculated the mean of all available values in the year before diagnosis.

The eFI includes 36 equally weighted deficit variables, based on Read codes. HF is one of the deficits, and all patients were therefore considered to have it. As a score, the eFI is the number of deficits present as a proportion of the total possible, categorized as: 0-0.12=fit; 0.12-0.24=mild frailty; 0.24-0.36=moderate frailty; >0.36=severe frailty. The eFI has been internally and externally validated.[19]

For each predictor other than age and gender, which were never missing, we fitted the missing-data records as an extra category.

Statistical analysis

The cumulative incidence function assessed crude associations between predictors and outcomes. Time-to-event analyses used the cause-specific hazard model to evaluate the association of the predictors with each outcome whilst handling the competing risk of

mortality.[26] Follow-up was limited to one year after diagnosis or until the practice's last submission date or the patient's date of transfer out of the practice, whichever came first.

The functional form of the continuous predictors was evaluated by plotting with local smoothers superimposed. For example, after determining that the relationship between the number of frailty deficits and our main outcomes was approximately linear, frailty was fitted as a continuous variable in the final models. Random intercepts for general practices adjusted for clustering. The only interaction we considered a priori was between age and frailty, with each fitted as categories for easier interpretation.

For each outcome we fitted two models. Model 1 included social history, polypharmacy and the comorbidity count but not the eFI; Model 2 was the same but did include eFI. Other predictors were common to both models. To simplify the large tables, we retained only those predictors with $p<0.05$, first checking that eliminating non-significant variables did not affect the coefficients of remaining ones. SAS v3.4 was used throughout.

Sensitivity analysis

Primary care physicians may have a high clinical suspicion that a patient has HF even without evidence from echo or BNP levels and will treat accordingly. We therefore expanded our cohort in several sensitivity analyses to include patients with at least two of the following pieces of evidence recorded: presenting with breathlessness, fatigue or swollen ankles, referral for echocardiography and/or BNP test, referral to a cardiologist, and prescribed treatment with diuretics or beta-blockers indicated for HF (HF-BB). This gave four sets of models: i) strict cohort as above; ii) strict cohort plus those referred, treated with diuretics/HF-BB and with at least one of HF symptoms, echo or BNP; iii) strict cohort plus

those who were not referred but who were treated with diuretics/HF-BB and had at least one of HF symptoms, echo or BNP; and iv) all combined: see Appendix.

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Results

After applying the exclusion criteria, 6,360 patients had an HF diagnosis recorded in primary care between April 2010 and March 2013. Within a year of diagnosis, 591 (9.3%) had an emergency admission with a primary diagnosis of HF, and 2,469 (38.8%) had an emergency admission for any primary diagnosis; 578 (9.1%) died within a year without having any emergency admission. 120 (1.9%) had an elective admission with a primary diagnosis of HF within a year. Most patients were aged over 65 and multimorbid, and 15% had moderate or severe frailty (Table 1).

Table 2 lists the eFI components and compares the outcome rates in the presence or absence of each component using chi-squared tests. HF admission was more common with 10 components and less common with ischaemic heart disease. All-cause admission was more common with 20 components and less common with polypharmacy.

Regression results for first emergency HF admission

Significant predictors in Model 1 were older age (HR 1.10 per five-year increase, 95%CI 1.05-1.14, p<0.001), higher average serum creatinine (HR 2.09 per 1mg/dL increase, 95%CI 1.63-2.67, p<0.001), not being on a beta-blocker (HR 1.34, 95%CI 1.14-1.58, p=0.001), and unknown ethnicity (lower hazard but unstable estimates). Neither comorbidity nor frailty was significant in either model.

Regression results for first emergency all-cause admission

Significant predictors in Model 1 were older age, white ethnicity, current smoking, living alone, number of comorbidities, not being on a beta-blocker, prior emergency hospitalization, higher average serum glucose, and lower average haematocrit (Table 3). Unlike with HF admission, average serum creatinine was not retained in any model. In Model 2, where the eFI was added, higher eFI scores were associated with a greater risk of admission but comorbidity was not significant (p=0.231). There was a significant interaction between age group and frailty: compared with the reference group aged <65 and fit, the largest hazard ratio was for those aged <65 and severely frail (HR=3.44). Being aged 65-84 and fit conferred similar hazard to being <65 and fit; in contrast, being aged 85+ appeared to confer the same hazard irrespective of frailty level.

Sensitivity analyses

Few differences existed between the various alternative cohorts in terms of their regression results. We therefore focus on the largest alternative cohort (those treated with diuretics/HF-BB and who had at least one of HF symptoms, echo or BNP: n=15,099) and how their characteristics and their regression results differ from those above.

These patients were of similar age, ethnicity and deprivation profile but were more often female, had twice the proportion of missing BMI, had fewer comorbidities, were less frail, on more medications, and had had fewer prior emergency admissions than the main cohort (see Appendix).

For regression for a first HF admission, Models 1 and 2 both retained age, ethnicity, BMI, comorbidity count, serum creatinine and glucose.

For regression for a first admission for any condition, Model 1 retained age, white ethnicity, current smoking, alcohol (lower hazard), comorbidity, polypharmacy, prior admission for non-HF conditions, serum creatinine and glucose. Model 2 retained neither comorbidity nor frailty. In view of the overlap between comorbidity and other factors and frailty, we then ran models with i) comorbidity, living alone and polypharmacy but not frailty, and ii) frailty but not comorbidity, living alone or polypharmacy, both sets with other predictors also included as before. In the latter, frailty was this time a significant predictor of all-cause admission.

Discussion

The main predictors of HF admission were age, comorbidity, serum creatinine and not being on a beta-blocker. The main predictors of all-cause admission were age, comorbidity, frailty, prior admission, not being on a beta-blocker, low haematocrit, and living alone. Frailty effects were largest in patients aged under 85.

Some previous studies also found associations between frailty and outcomes. In the longitudinal Cardiovascular Health Study of 758 community-living older people, markers of frailty predicted hospitalization after adjusting for ejection fraction and symptom

severity.[13] Similarly, in 448 community-living HF Minnesota patients, "frailty was associated with a 92% increased [adjusted] risk for ED visits and a 65% increased risk for hospitalizations".[15] FRAIL-HF, a prospective cohort study including 450 non-dependent patients aged ≥70 hospitalized for HF, looked at the impact of five frailty components on outcome after HF admission.[14] Frailty showed no association with chronic comorbidities, ejection fraction, or plasma NT-proBNP levels. After adjusting for age, gender, chronic and acute comorbidities, New York Heart Association Functional Classification of heart failure, and plasma NT-proBNP concentration, frail patients showed much higher risks of 30-day functional decline, one-year all-cause mortality and one-year readmission. Our study offers some key advantages over this prior work. Rather than selected cohorts that may not be fully representative of the community HF population, ours was much larger and unselected, with real-world data. Furthermore, instead of research-based frailty tools that are impractical for routine care, we used the eFI. This is calculated from routinely available primary care EMR data and implemented nationally, thereby facilitating translation of research findings into clinical practice; the code-set uses standard nomenclature for mapping to international systems.

Limitations

Plasma BNP concentration and left ventricular ejection fraction have been found to be important predictors of outcomes in HF but were not available for most patients in CPRD. The effect of not being able to include these variables is unclear. In Vidan's cohort[14] frail patients did not differ from non-frail ones in their ejection fraction or NT-proBNP levels, which suggests that frailty would remain a predictor of all-cause hospitalization even if we had these variables, but we cannot be certain of this.

Implications

Our results suggest that emergency hospitalization following an HF diagnosis in the community has a social functional element, with frailty identified as a notable predictor, particularly for patients <85. There is recognized overlap between frailty and comorbidity.[27] As the theoretical framework underpinning the eFI includes comorbidities but also other aspects, we included both comorbidity and frailty in Model 2. In the sensitivity analysis cohort, however, neither was significant in Model 2. The best approach for risk stratification would be to use the eFI alone, i.e. without also including comorbidity, polypharmacy or living alone.

Frailty assessment was introduced in the primary care physician contract in England in 2017. Primary care practices in England are now required systematically to identify patients ≥65 with moderate and severe frailty, record this in the EMR and carry out regular clinical reviews in severely frail people. Currently, clinical guidelines for HF (NICE, ESC, AHA) do not discuss frailty. However, the NICE guideline on comorbidity, which is not HF-specific, recommends frailty assessment and suggests its use to tailor appropriate monitoring and support to improve outcomes.[18] As the level of comorbidity has been steadily increasing in the past decade in patients with HF,[28] it would make sense to refer to frailty in HF guidelines and quality standards.

Conclusions

This study suggests that frailty identifies a subpopulation of patients with HF who are at high risk of all-cause hospital admission who could be targeted to reduce unplanned hospitalizations. Community HF patients should be assessed for frailty: this should be reflected in future guidelines.

Ethical Approval

We have approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyse them for research purposes (CAG ref 15/CAG/0005). We have approval to use them for research and measuring quality of delivery of healthcare, from the London - South East Ethics Committee (REC ref 15/LO/0824). The CPRD Group has obtained ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data. This study has been carried out as part of the work approved by their Independent Scientific Advisory Committee (ISAC) with protocol number 16_003RAR.

References

[1] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1545–1602.

[2] Association AH. (Editor). Heart Disease and Stroke Statistics 2008 Update. 2008.

[3] Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003;4(Suppl 7):S21–30.

[4] Lloyd-Williams F, Mair F, Shiels C, Hanratty B, Goldstein P, Beaton S, Capewell S, Lye M, Mcdonald R, Roberts C, Connelly D. Why are patients in clinical trials of heart failure not like those we see in everyday practice? J Clin Epidemiol 2003;56:1157–62.

[5] Clegg A, Relton C, Young J, Witham M. Improving recruitment of older people to clinical trials: use of the cohort multiple randomised controlled trial design. Age Ageing 2015;44(4):547-50.

[6] The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. Increasing the awareness and improving the management of heart failure in Europe: the IMPROVEMENT of HF initiative. Eur J Heart Failure 1999;1:139-144.

[7] Bottle A, Aylin P, Bell D. Effect of the readmission primary diagnosis and time interval in heart failure patients: analysis of English administrative data. Eur J Heart Fail 2014;16(8):846-53.

[8] Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309:355–363.

[9] Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. J Card Fail 2004;10(5):374-9.

[10] Carson PE, Anand IS, Win S, Rector T, Haass M, Lopez-Sendon J, Miller A, Teerlink JR, White M, McKelvie RS, Komajda M, Zile MR, McMurray JJ, Massie B. The Hospitalization Burden and Post-Hospitalization Mortality Risk in Heart Failure With Preserved Ejection Fraction: Results From the I-PRESERVE Trial (Irbesartan in Heart Failure and Preserved Ejection Fraction). JACC Heart Fail 2015;3(6):429-441.

[11] Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Ng LL, Metra M, Ter Maaten JM, Lang CC, Hillege HL, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD, Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. Eur J Heart Failure 2017;19:627–634.

[12] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-62.

[13] Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, Gill TM. Risk Factors for Hospitalization Among Older Persons Newly Diagnosed with Heart Failure: The Cardiovascular Health Study. J Am Coll Cardiol 2013;61(6):635–642.

[14] Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. Eur J Heart Fail 2016;18(7):869-75.

[15] McNallan SM, Singh M, Chamberlain AM, Kane RL, Dunlay SM, Redfield MM, Weston SA, Roger VL. Frailty and healthcare utilization among patients with heart failure in the community. JACC Heart Fail 2013;1(2):135-41.

[16] Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations After Heart Failure Diagnosis: A Community Perspective. J Am Coll Cardiol 2009;54(18):1695–1702.

[17] Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, Mohammed M, Parry J, Marshall T. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 2016;45(3):353-60.

[18] National Institute for Health and Care Excellence 2016. Multimorbidity: clinical assessment and management. NICE guideline NG56.

[19] Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–836.

[20] Chaudhry Z, Mannan F, Gibson-White A, Syed U, Ahmed S, Kousoulis A, Majeed A. Outputs and Growth of Primary Care Databases in the United Kingdom: Bibliometric Analysis. J Innov Health Inform 2017;24(3):942.

[21] Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: observational study using linked data in England. Heart 2017;pii:heartjnl-2017-312183.

[22] Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, Krumholz HM. Statistical models and patient predictors of readmission for heart failure: a systematic review. Arch Intern Med 2008;168(13):1371-86.

[23] Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies. Eur Heart J 2013;34(19):1404-13.

[24] Barker I, Steventon A, Deeny SR. Association between continuity of care in general practice and hospital admissions for ambulatory care sensitive conditions: cross sectional study of routinely collected, person level data. BMJ 2017;356.

[25] Romaire MA, Haber SG, Wensky SG, McCall N. Primary care and specialty providers: an assessment of continuity of care, utilization, and expenditures. Med Care 2014;52(12):1042-9.

[26] Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861-870.

[27] Yarnall AJ, Sayer AA, Clegg A, Rockwood K, Parker S, Hindle JV. New horizons in multimorbidity in older adults. Age Ageing 2017;46(6):882-888.

[28] Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2017;pii:S0140-6736(17)32520-5.

Tables

Table 1. Patient characteristics of main cohort

Predictors at diagnosis	Levels	N	%
Gender	Male	3,530	55.5
	Female	2,830	44.5
Age group	<45	114	1.8
	45-64	991	15.6
	65-74	1,480	23.3
	75-84	1,977	31.1
	85+	1,798	28.3
Ethnicity	White	5,458	85.8
	Other	344	5.4
	Unknown	376	5.9
	Missing	182	2.9
Deprivation level	5 (most)	960	15.1
	4	1,171	18.4
	3	1,393	21.9
	2	1,542	24.2
	1 (least)	1,294	20.3
BMI	Underweight	141	2.2
	Normal	1,345	21.1
	Overweight	1,738	27.3
	Obese	1,662	26.1
	Missing	1,474	23.2
Smoking status	Non-smoker	2,003	31.5
	Current smoker	879	13.8
	Former smoker	2,858	44.9
	Missing	620	9.7

Drinking status	Non-drinker	1,373	21.6
	Drinker (other amount)	2,264	35.6
	Heavy drinker	309	4.9
	Missing	2,414	38.0
Social vulnerability	Widowed or otherwise bereaved	966	15.2
	Lives alone	377	5.9
Comorbidity	Atrial fibrillation	2,197	34.5
	Other arrhythmias	973	15.3
	Myocardial infarction	714	11.2
	Coronary artery disease	1,974	31.0
	Myocarditis	123	1.9
	Hypertension	4,923	77.4
	Stroke	471	7.4
	Diabetes Mellitus	1,305	20.5
	Congenital heart disease	43	0.7
	Chronic pulmonary disease	1,270	20.0
	Peripheral vascular disease	562	8.8
	Renal disease	1,920	30.2
Number of comorbidities	0	697	11.0
	1	1,396	21.9
	2	1,550	24.4
	3	1,277	20.1
	4+	1,440	22.6
Frailty index	Fit (1 - 4 deficits)	2,068	32.5
	Mild (5- 8 deficits)	3,252	51.1
	Moderate (9 - 10 deficits)	948	14.9
	Severe (>10 deficits)	92	1.4
Continuity of care	<2 consultations	745	11.7
	Low	1,077	16.9

	Medium	2,388	37.5
	High	2,150	33.8
Number of medications	<5	1,008	15.8
	5-<10	1,613	25.4
	10-<15	1,838	28.9
	15-<20	1,111	17.5
	20+	790	12.4
Medication history	Not on a beta-blocker	3,544	55.7
	Not on an ACEI/ARB	2,652	41.7
	Previous CABG	663	10.4
	Previous PTCA	559	8.8
	Elective admission	1,666	26.2
	Emergency admission for non-HF	2,385	37.5
Average systolic blood pressure	≥140 mmHg	2,270	35.7
	<140 mmHg	3,382	53.2
	Missing	708	11.1
Average creatinine	≥1.3(F)/1.5(M) mg/dL	896	14.1
	<1.3(F)/1.5(M) mg/dL	5,338	83.9
	Missing	126	2.0
Average glucose	≥200 mg/dL	184	2.9
	<200 mg/dL	3,197	50.3
	Missing	2,979	46.8
Average haematocrit	<40%	2,735	43.0
	≥40%	2,849	44.8
	Missing	776	12.2

Table 2. Frailty components, their prevalences in the HF cohort and crude outcomes

Frailty deficit	Total		HF emergency admission with 1 year of diagnosis			All emergency admission with 1 year of diagnosis		
	Has deficit	No deficit	Has deficit	No deficit		Has deficit	No deficit	
	N (%)	N (%)	N (Rate, %)	N (Rate, %)	p-value	N (Rate, %)	N (Rate, %)	p-value
Activity limitation	52 (0.8)	6,308 (99.2)	2 (3.9)	589 (9.3)	0.174	26 (50.0)	2,443 (38.7)	0.097
Anaemia & haematinic deficiency	2,394 (37.6)	3,966 (62.4)	278 (11.6)	313 (7.9)	<0.001	1,078 (45.0)	1,391 (35.1)	<0.001
Arthritis	570 (9.0)	5,790 (91.0)	53 (9.3)	538 (9.3)	0.996	215 (37.7)	2,254 (38.9)	0.572
Atrial fibrillation	1,747 (27.5)	4,613 (72.5)	197 (11.3)	394 (8.5)	0.001	719 (41.2)	1,750 (37.9)	0.019
Cerebrovascular disease	517 (8.1)	5,843 (91.9)	54 (10.4)	537 (9.2)	0.346	225 (43.5)	2,244 (38.4)	0.022
Chronic kidney disease	1,960 (30.8)	4,400 (69.2)	217 (11.1)	374 (8.5)	0.001	836 (42.7)	1,633 (37.1)	<0.001
Diabetes Mellitus	1,235 (19.4)	5,125 (80.6)	126 (10.2)	465 (9.1)	0.220	540 (43.7)	1,929 (37.6)	<0.001
Dizziness	562 (8.8)	5,798 (91.2)	62 (11.0)	529 (9.1)	0.137	236 (42.0)	2,233 (38.5)	0.106
Dyspnoea	2,519 (39.6)	3,841 (60.4)	330 (13.1)	261 (6.8)	<0.001	1,108 (44.0)	1,361 (35.4)	<0.001
Falls	258 (4.1)	6,102 (95.9)	27 (10.5)	564 (9.2)	0.508	112 (43.4)	2,357 (38.6)	0.122
Foot problems	316 (5.0)	6,044 (95.0)	41 (13.0)	550 (9.1)	0.021	155 (49.1)	2,314 (38.3)	<0.001
Fragility fracture	264 (4.2)	6,096 (95.9)	26 (9.9)	565 (9.3)	0.751	122 (46.2)	2,347 (38.5)	0.012
Hearing impairment	672 (10.6)	5,688 (89.4)	68 (10.1)	523 (9.2)	0.435	285 (42.4)	2,184 (38.4)	0.043
Heart valve disease	133 (2.1)	6,227 (97.9)	18 (13.5)	573 (9.2)	0.089	55 (41.4)	2,414 (38.8)	0.545
Housebound	621 (9.8)	5,739 (90.2)	78 (12.6)	513 (8.9)	0.003	292 (47.0)	2,177 (37.9)	<0.001

Hypertension	1,234 (19.4)	5,126 (80.6)	114 (9.2)	477 (9.3)	0.942	438 (35.5)	2,031 (39.6)	0.008
Hypotension/syncope	459 (7.2)	5,901 (92.8)	50 (10.9)	541 (9.2)	0.220	189 (41.2)	2,280 (38.6)	0.282
Ischaemic heart disease	2,044 (32.1)	4,316 (67.9)	152 (7.4)	439 (10.2)	<0.001	794 (38.9)	1,675 (38.8)	0.978
Memory & cognitive problems	313 (4.9)	6,047 (95.1)	21 (6.7)	570 (9.4)	0.106	128 (40.9)	2,341 (38.7)	0.440
Mobility & transfer problems	304 (4.8)	6,056 (95.2)	36 (11.8)	555 (9.2)	0.117	141 (46.4)	2,328 (38.4)	0.006
Osteoporosis	376 (5.9)	5,984 (94.1)	35 (9.3)	556 (9.3)	0.991	153 (40.7)	2,316 (38.7)	0.443
Parkinsonism & tremor	77 (1.2)	6,283 (98.8)	7 (9.1)	584 (9.3)	0.951	40 (52.0)	2,429 (38.7)	0.017
Peptic ulcer	72 (1.1)	6,288 (98.9)	4 (5.6)	587 (9.3)	0.272	35 (48.6)	2,434 (38.7)	0.086
Polypharmacy	5,352 (84.2)	1,008 (15.9)	491 (9.2)	100 (9.9)	0.454	2,073 (38.7)	396 (39.3)	0.741
Peripheral vascular disease	324 (5.1)	6,036 (94.9)	36 (11.1)	555 (9.2)	0.247	157 (48.5)	2,312 (38.3)	<0.001
Requirement for care	158 (2.5)	6,202 (97.5)	11 (7.0)	580 (9.4)	0.307	59 (37.3)	2,410 (38.9)	0.699
Respiratory disease	1,628 (25.6)	4,732 (74.4)	141 (8.7)	450 (9.5)	0.309	685 (42.1)	1,784 (37.7)	0.002
Skin ulcer	290 (4.6)	6,070 (95.4)	39 (13.5)	552 (9.1)	0.013	143 (49.3)	2,326 (38.3)	<0.001
Sleep disturbance	226 (3.6)	6,134 (96.5)	24 (10.6)	567 (9.2)	0.484	97 (42.9)	2,372 (38.7)	0.198
Social vulnerability	160 (2.5)	6,200 (97.5)	17 (10.6)	574 (9.3)	0.557	69 (43.1)	2,400 (38.7)	0.258
Thyroid disease	1,122 (17.6)	5,238 (82.4)	117 (10.4)	474 (9.1)	0.149	459 (40.9)	2,010 (38.4)	0.114
Urinary incontinence	284 (4.5)	6,076 (95.5)	21 (7.4)	570 (9.4)	0.260	120 (42.3)	2,349 (38.7)	0.225
Urinary system disease	1,429 (22.5)	4,931 (77.5)	134 (9.4)	457 (9.3)	0.900	588 (41.2)	1,881 (38.2)	0.040
Visual impairment	1,148 (18.1)	5,212 (82.0)	121 (10.5)	470 (9.0)	0.108	482 (42.0)	1,987 (38.1)	0.015

Weight loss & anorexia	205 (3.2)	6,155 (96.8)	21 (10.2)	570 (9.3)	0.633	90 (43.9)	2,379 (38.7)	0.129

Table 3. Cause-specific hazards regression of time to all-cause emergency admission

	Model 1		Model 2 (Model 1 + number of frailty deficits)		Model 2 (Interaction between age group and frailty category)	
Factors and categories (baseline)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diagnosis						
per 5 years increase	1.08 (1.06-1.11)	<0.001	1.07 (1.05-1.10)	<0.001		
Ethnicity (Other)		<0.001		<0.001		<0.001
White	1.47 (1.18-1.84)	0.001	1.47 (1.18-1.84)	0.001	1.48 (1.18-1.84)	0.001
Unknown	0.86 (0.63-1.18)	0.349	0.87 (0.63-1.19)	0.387	0.87 (0.63-1.19)	0.373
Missing	0.11 (0.03-0.33)	<0.001	0.11 (0.03-0.34)	<0.001	0.11 (0.03-0.33)	<0.001
Smoking status (Non-smoker)		0.001		0.002		0.001
Current	1.24 (1.07-1.44)	0.004	1.24 (1.06-1.43)	0.005	1.25 (1.08-1.45)	0.003
Former	0.94 (0.85-1.04)	0.239	0.95 (0.86-1.04)	0.261	0.95 (0.86-1.05)	0.309
Missing	1.04 (0.85-1.28)	0.695	1.06 (0.87-1.30)	0.548	1.05 (0.86-1.29)	0.622
Social vulnerability						
Lives alone	1.35 (1.12-1.62)	0.001	1.32 (1.10-1.59)	0.003	1.35 (1.12-1.62)	0.002
Comorbidity						
per extra comorbidity (max of 12)	1.04 (1.01-1.07)	0.016	1.02 (0.99 to 1.06)	0.231	-	

Number of frailty deficits						
per unit increment (max of 36)			1.04 (1.02-1.07)	<0.001		
Interaction between age group and frailty (<65:Fit)						<0.001
<65:Mild					1.15 (0.86-1.52)	0.346
<65:Moderate					1.65 (1.08-2.54)	0.022
<65:Severe					3.44 (2.00-5.93)	<0.001
65-84:Fit					1.13 (0.88-1.46)	0.325
65-84:Mild					1.41 (1.12-1.79)	0.004
65-84:Moderate					1.60 (1.24-2.08)	<0.001
65-84:Severe					2.57 (1.69-3.90)	<0.001
85+:Fit					2.01 (1.49-2.72)	<0.001
85+:Mild					2.12 (1.65-2.73)	<0.001
85+:Moderate					1.92 (1.43-2.56)	<0.001
85+:Severe					1.70 (1.14-2.52)	<0.001
Medication history (Not polypharmacy, <5)		0.003		0.034		0.023
5-<10	0.88 (0.73-1.06)	0.188	0.83 (0.69-1.00)	0.052	0.83 (0.69-1.00)	0.051
10-<15	1.02 (0.85-1.22)	0.823	0.93 (0.78-1.12)	0.465	0.94 (0.79-1.13)	0.544

15-<20	0.98 (0.81-1.19)	0.838	0.89 (0.73-1.08)	0.244	0.91 (0.75-1.10)	0.334
20+	1.19 (0.98-1.44)	0.085	1.04 (0.84-1.28)	0.743	1.06 (0.86-1.30)	0.590
Not on a beta-blocker	1.14 (1.04-1.25)	0.004	1.12 (1.03-1.23)	0.011	1.11 (1.02-1.22)	0.019
Emergency admission for non-HF	1.48 (1.34-1.62)	<0.001	1.51 (1.38-1.66)	<0.001	1.50 (1.36-1.64)	<0.001
Average glucose						
per 10 mg/dL increase	1.01 (1.00-1.03)	0.017	1.01 (1.00-1.02)	0.035	1.01 (1.00-1.02)	0.026
Average haematocrit						
per 5% decrease	1.15 (1.09-1.22)	<0.001	1.14 (1.07-1.20)	<0.001	1.14 (1.07-1.20)	<0.001