

# BMJ Open Benefits of heart failure-specific pharmacotherapy in frail hospitalised patients: a cross-sectional study

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## ABSTRACT

**Objectives** Up to 50% of heart failure (HF) patients may be frail and have worse clinical outcomes than non-frail patients. The benefits of HF-specific pharmacotherapy (beta-blockers, ACE-inhibitors/angiotensin-receptor-blockers and mineralocorticoid-receptor-antagonist) in this population are unclear. This study explored whether HF-specific pharmacotherapy improves outcomes in frail hospitalised HF patients.

**Design** Observational, multicentre, cross-sectional study.

**Settings** Tertiary care hospitals.

**Participants** One thousand four hundred and six hospitalised frail HF patients admitted between 1 January 2013 and 31 December 2020.

**Measures** The Hospital Frailty Risk Score (HFRS) determined frailty status and patients with HFRS  $\geq 5$  were classified as frail. The primary outcomes included the days alive and out of hospital (DAOH) at 90 days following discharge, 30-day and 180-day mortality, length of hospital stay (LOS) and 30-day readmissions. Propensity score matching (PSM) compared clinical outcomes depending on the receipt of HF-specific pharmacotherapy.

**Results** Of 5734 HF patients admitted over a period of 8 years, 1406 (24.5%) were identified as frail according to the HFRS and were included in this study. Of 1406 frail HF patients, 1025 (72.9%) received HF-specific pharmacotherapy compared with 381 (27.1%) who did not receive any of these medications. Frail HF patients who did not receive HF-specific pharmacotherapy were significantly older, with higher creatinine and brain natriuretic peptide but with lower haemoglobin and albumin levels ( $p < 0.05$ ) when compared with those frail patients who received HF medications. After PSM frail patients on treatment were more likely to have an increased DAOH (coefficient 16.18, 95% CI 6.32 to 26.04,  $p = 0.001$ ) than those who were not on treatment. Both 30-day (OR 0.30, 95% CI 0.23 to 0.39,  $p < 0.001$ ) and 180-day mortality (OR 0.43, 95% CI 0.33 to 0.54,  $p < 0.001$ ) were significantly lower in frail patients on HF treatment but, there were no significant differences in LOS and 30-day readmissions ( $p > 0.05$ ).

**Conclusion** This study found an association between the use of HF-specific pharmacotherapy and improved clinical outcomes in frail HF hospitalised patients when compared to those who were not on treatment.

**Trial registration number** ANZCTR383195.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study determined benefits of heart failure-specific pharmacotherapy in frail hospitalised heart failure patients.
- ⇒ Propensity score matching was used to compare clinical outcomes according to the receipt of treatment in frail heart failure patients.
- ⇒ This study used the days alive and out of hospital as a primary outcome which considers not only mortality but also hospitalisations for heart failure.
- ⇒ Some confounders could have been missed due to the observational design of this study.
- ⇒ The severity of heart failure based on ejection fraction was not available due to lack of echocardiogram results.

## INTRODUCTION

Heart failure (HF) is commonly associated with advancing age, with a prevalence of 6% in individuals between 65 and 79 years and up to 14% in those over the age of 80 years.<sup>1</sup> The annual rates of acute decompensated HF nearly triples in individuals over the age of 75 years when compared with those between 55 and 65 years, irrespective of factors such as sex and race.<sup>1</sup> Studies<sup>2,3</sup> suggest that 15%–20% of the HF patients who are discharged alive die within 90 days of hospitalisation. HF rarely occurs in isolation in older adults and usually there is complex interplay of other factors such as non-cardiovascular comorbidities, impaired physical and cognitive function, and social and environmental factors, all of which also contribute to frailty.<sup>4</sup> Frailty, defined as a biologic syndrome with impaired physiological reserves that increases susceptibility to stressors<sup>5</sup> is common among patients with HF. A recent meta-analysis<sup>6</sup> which included 26 studies and 6896 HF patients found that the prevalence of frailty ranged from 43% with the use of physical frailty measures to 47% with multidimensional frailty measures.

Among older frail HF patients there is often an uncertainty whether to prescribe guideline directed pharmacotherapy given the



risks associated with polypharmacy along with concerns regarding adherence to treatment because studies suggest that up to 55% of patients are non-compliant with treatment.<sup>7</sup> In addition, despite a high prevalence of HF in older individuals, there is a dearth of research specifically targeting older frail patients.<sup>4,8</sup> Evidence indicates that 30% of HF clinical trials have excluded older patients, and the representation in these trials of patients who were older than 80 years of age was only 15%.<sup>9</sup> In addition, a number of HF trials have used indirect criteria such as the number of comorbidities, presence of polypharmacy and a limited life expectancy as reasons to exclude older frail patients.<sup>10</sup> Thus, the older HF patients commonly seen in clinical practice have a limited representation in clinical trials. This poses a significant challenge for the treating clinicians because of lack of information about the efficacy and tolerance of HF-specific interventions in this population.<sup>11</sup> Despite these findings, guidelines<sup>1,12</sup> still recommend targeted therapy for HF irrespective of age or comorbidities.

We conducted a retrospective study to determine the impact of HF-specific medications (beta blockers, ACE inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonist (MRA)) on clinical outcomes of frail patients who were hospitalised with HF. The primary outcomes for this study were the days alive and out of hospital (DAOH) at 90 days following hospital discharge hospital, 30-day and 180-day mortality, and 30-day readmissions and the secondary outcomes included inhospital mortality and hospital length of stay (LOS).

## MATERIALS AND METHODS

We included data of all frail patients  $\geq 18$  years of age who were hospitalised with HF over a period of 8 years at two tertiary teaching hospitals, Flinders Medical Centre and Royal Adelaide Hospital in Adelaide, Australia. We identified all adult hospital admissions, between 1 January 2013 and 31 December 2020, with a primary diagnosis of HF by using the International Classification of Diseases 10th Revision Australian Modification (ICD-10-AM) code I50, which has been previously used to define HF.<sup>13</sup> In cases where patients had multiple presentations for HF during the study period, then only the first admission was included. The study was retrospective and the data were obtained from the hospitals' electronic medical records of our central computer database. The data of all HF patients who were referred from the emergency department for a medical admission were included in this study. The data were collected independently by one of the researchers and was verified for accuracy by a second researcher. In case of any discrepancy, electronic data were verified manually by extraction of patients' case notes.

The frailty status of patients was determined by use of the Hospital Frailty Risk Score (HFRS), which was calculated according to the criteria defined by Gilbert *et al.*<sup>14</sup>

The HFRS was calculated from the data obtained from our central computer database which contains information about patients' previous presentations to hospital. We used patient's records over a 2-year period to calculate the HFRS. HFRS is based on administrative data by allocating point values for any of 109 select ICD codes as defined in the original publication. These codes include diagnoses such as falls, osteoporosis, spinal compression fractures, blindness, skin ulcers, delirium/dementia, Parkinson's disease, urinary incontinence, urinary tract infections, disorders of electrolytes, drugs/alcohol abuse and sequelae of stroke such as hemiplegia and dysphagia. None of the ICD-10 codes used for the generation of the HFRS score is for HF, atrial fibrillation, or coronary artery disease (CAD). Higher HFRS scores indicate a greater severity of frailty and, we classified patients with a HFRS score  $\geq 5$  as frail and those with HFRS scores of  $< 5$  as non-frail as has been done in previous studies.<sup>14,15</sup>

We determined medications prescribed to patients at discharge from hospital from our pharmacy database. This database contains comprehensive information about medications which patients are on prior to their hospital presentation including any new medications prescribed during the course of their hospitalisation and at the time of hospital discharge. However, we were unable to determine the doses or durations of prescribed medications. In particular, we determined whether patients received any or all of the HF-specific medications (beta blockers, ACEi/ARBs and MRA) in addition to other medications such as aspirin, warfarin, direct acting oral anticoagulants (DOACs), statins, ivabradine and digoxin. Over the course of the study, newer medications such as sodium-glucose transport protein 2 (SGLT2) inhibitors and sacubitril/valsartan were also available for management of HF. We determined the socioeconomic status of the patients by using the index of relative socioeconomic disadvantage (IRSD).<sup>16</sup> The comorbidity risk was determined by use of the Charlson comorbidity index (CCI)<sup>17</sup> and nutritional status was assessed by use of the Malnutrition Universal Screening Tool (MUST).<sup>18</sup> The severity of HF was assessed by use of the N-terminal probrain natriuretic peptide (NT-proBNP) levels.<sup>19</sup> In addition, we determined common investigations performed during hospital admission: haemoglobin, C reactive protein (CRP), albumin, creatinine and troponin levels.

The outcomes examined included: DAOH at 90 days of discharge from hospital, LOS, inhospital mortality, 30-day mortality (from day of index admission), 180-day mortality and 30-day readmissions, and placement in a nursing home. The outcome data for this study were recorded from our central computer database, which contains information about mortality including deaths outside hospital, admissions to other hospitals in the state of South Australia including patients' LOS, readmissions and placement in a nursing home.

## Patient and public involvement statement

This study was retrospective and it was not possible to involve patients in the design or conduct of this study.

## Statistics

Data were assessed for normality by visual inspection of the histograms. Continuous variables were assessed by use of the t-tests or rank sum tests, as appropriate while categorical variables were assessed by  $\chi^2$  statistics.

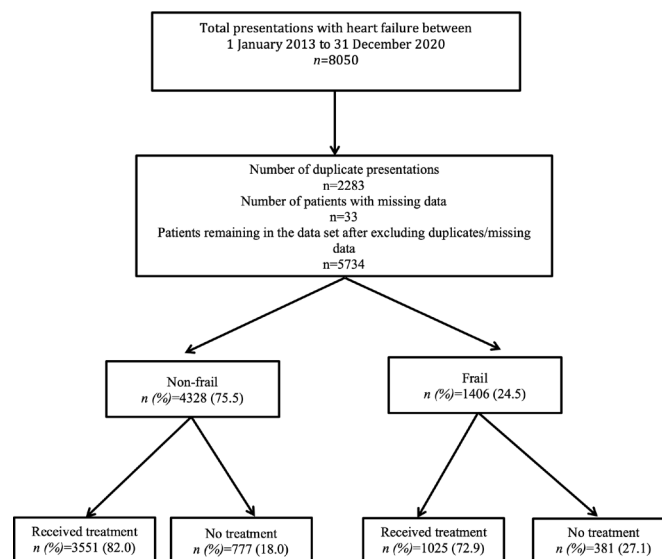
## Propensity score methods

We used propensity score matching to control for any potential confounding factors between the two cohorts of frail patients: frail patients who received HF-specific pharmacotherapy and those who did not receive treatment. We used propensity score matching to account for the fact that patients' baseline health, comorbidities and frailty status may account for their probability of receiving HF-specific pharmacotherapy. To create propensity scores, we first used multivariable logistic regression model with receipt of HF-specific pharmacotherapy as the outcome variable and the potential confounders as the explanatory variables. Seventeen confounding variables which were hypothesised to be associated both with the exposure and the outcomes included: age, age  $\geq 65$  years, sex, HFRS, MUST score, IRSD, CCI, haemoglobin, CRP, creatinine, BNP, troponins, albumin levels and the use of aspirin, warfarin, DOACs and statins. We did not analyse newer HF medications (SGLT2 inhibitors and Sacubitril-Valsartan) which were available later in course of the study because very few HF patients received this treatment. The overlap of distribution of propensity scores between the two groups was checked by visual inspection of the histogram. We used kernel matching to compare propensity scores between the two treatment groups. A kernel bandwidth of 0.06 as suggested by Heckman *et al*<sup>20</sup> was employed to optimise trade-off between variance and bias. After kernel matching, the balance of covariates was assessed using the standardised mean differences (SMR), with  $>10\%$  standard mean difference considered as significant between the two groups.<sup>21</sup> Kernel densities were plotted to examine the differences in continuous variables across matched treatment and comparison groups to determine similarity. In the matched cohort, outcomes were compared between the two groups of patients by assessment of the average treatment effect.

Sensitivity analyses were performed by use of the average treatment effect on the treated (ATET) to assess the robustness of results generated by the use of propensity score matching and coefficients with robust standard errors and 95% CIs were generated. All tests were two sided and a  $p < 0.05$  was regarded as statistically significant. All statistical analyses were performed by use of STATA software V.17.0 (StataCorp).

## RESULTS

There were 8050 admissions with HF between 1 January 2013 and 31 December 2020. After omitting multiple



**Figure 1** Study flow diagram.

admissions and missing data, 5734 patients remained in the dataset, of whom, 1406 (24.5%) patients were identified as frail according to the HFRS and were included in this study (figure 1). Frail patients were more likely to be older, with a poor nutritional status, a higher CCI and creatinine levels and were more likely to belong to a lower socioeconomic status than non-frail patients ( $p < 0.05$ ). However, there was no difference in relation to gender, severity of HF as determined by the NT-proBNP and troponin levels between the frail and non-frail group.

Overall, 4576 (79.8%) patients received one or more medications defined as HF-specific pharmacotherapy. Baseline characteristics differed among patients who received HF-specific pharmacotherapy compared with those who did not receive these medications (table 1). Patients who received HF-specific pharmacotherapy were more likely to be younger, with a lower creatinine, BNP and CRP levels and higher haemoglobin and albumin levels but there was no difference with regard to their nutritional or socioeconomic status (table 1). When compared with non-frail patients, frail patients were significantly less likely to be prescribed HF-specific pharmacotherapy (72.9% vs 82.1%,  $p < 0.001$ ). In terms of individual HF-specific medications, more non-frail patients were on beta blockers (66.9% vs 58.7%,  $p < 0.001$ ), ACEi (43.4% vs 31.6%,  $p < 0.001$ ) and MRA (37.9% vs 32.7%,  $p < 0.001$ ) but not ARBs (13.8% vs 12.4%,  $p = 0.178$ ) when compared with frail patients (figure 2).

Of 1406 frail HF patients, 1025 (72.9%) received HF-specific pharmacotherapy compared with 381 (27.1%) who did not receive any one or more these medications (figure 1). Frail HF patients who did not receive HF-specific pharmacotherapy were significantly older, with higher creatinine and BNP levels but had lower haemoglobin and albumin levels ( $p < 0.05$ ) when

**Table 1** Baseline characteristics of non-frail and frail heart failure patients according to receipt of heart failure-specific pharmacotherapy

Characteristic	Not frail and received heart failure-specific pharmacotherapy	Not frail and no heart failure-specific pharmacotherapy	P value	Frail and received heart failure-specific pharmacotherapy	Frail and no heart failure-specific pharmacotherapy	P value
Total	<b>n=3551</b>	<b>n=777</b>		<b>n=1025</b>	<b>n=381</b>	
Age years mean (SD)	74.4 (14.4)	78.6 (13.5)	<0.001	79.2 (12.5)	80.8 (12.6)	0.025
Age ≥65 years n (%)	2776 (78.2)	666 (85.7)	<0.001	902 (88)	344 (90.3)	0.230
Sex male n (%)	1895 (53.4)	371 (47.8)	0.005	513 (50.1)	195 (51.2)	0.706
Charlson index mean (SD)	2.1 (1.5)	2.2 (1.7)	0.199	3.3 (1.9)	3.3 (2.1)	0.875
IRSD mean (SD)	5.4 (2.6)	5.4 (2.7)	0.517	5.6 (2.7)	5.6 (2.8)	0.903
Haemoglobin g/L mean (SD)	124.8 (20.7)	120.3 (22.5)	<0.001	118.8 (21.4)	115.3 (23.5)	0.008
Creatinine µmol/L mean (SD)	114.1 (63.9)	119.5 (81.3)	0.047	151.4 (84.2)	166.9 (108.9)	0.005
NT-proBNP ng/L mean (SD)	1451.2 (4427.6)	1923.7 (4654.2)	0.002	2552.7 (6545.7)	4465.0 (9311.8)	<0.001
Troponin ng/L mean (SD)	0.9 (15.7)	4.7 (58.5)	0.002	0.7 (9.2)	1.2 (11.4)	0.416
CRP mg/L mean (SD)	21.8 (32.5)	24.5 (36.3)	0.092	33.9 (48.3)	43.3 (58.9)	0.006
Albumin g/L mean (SD)	34.6 (4.9)	33.8 (4.8)	0.002	32.9 (5.1)	31.5 (5.8)	<0.001
HFRS mean (SD)	1.5 (1.5)	1.7 (1.6)	0.006	8.5 (3.4)	9.1 (3.5)	0.004
MUST mean (SD)	0.5 (0.9)	0.4 (0.8)	0.437	0.7 (1.1)	0.9 (1.3)	0.145
Aspirin n (%)	1496 (42.1)	116 (14.9)	<0.001	399 (38.9)	50 (13.1)	<0.001
Warfarin n (%)	755 (21.3)	51 (6.6)	<0.001	274 (26.7)	36 (9.5)	<0.001
DOACs n (%)	770 (21.7)	45 (5.8)	<0.001	212 (20.7)	11 (2.9)	<0.001
Statins n (%)	2026 (57.1)	125 (16.1)	<0.001	517 (50.4)	60 (15.8)	<0.001
ARNI n (%)	75 (2.1)	0	<0.001	22 (2.2)	0	0.004
SGLT2 inhibitors, n (%)	70 (1.9)	2 (0.3)	0.001	19 (1.9)	1 (0.3)	0.025
Digoxin n (%)	587 (16.5)	36 (4.6)	<0.001	221 (21.6)	22 (5.8)	<0.001
Ivabradine n (%)	85 (2.4)	5 (0.6)	0.002	23 (2.2)	2 (0.5)	0.030

ARNI, angiotensin receptor-neprilysin inhibitor; CRP, C reactive protein; DOACs, direct oral anticoagulants; HFRS, hospital frailty risk score; IRSD, Index of Relative Socioeconomic Disadvantage; MUST, malnutrition universal screening tool; NT-proBNP, N-terminal probrain natriuretic peptide; SGLT2, sodium glucose co-transporter two inhibitor.

compared with those frail patients who received treatment (table 1).

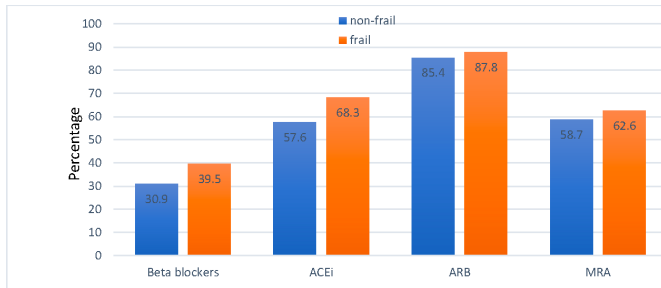
### Propensity score matching

The propensity score model which was built with the use of seventeen variables after multivariable logistic regression model in frail HF patients, included 930 observations in the treated and control group and were well matched with an SMR of <10% (figure 3, table 2).

### Clinical outcomes in frail patients depending on receipt of HF-specific pharmacotherapy

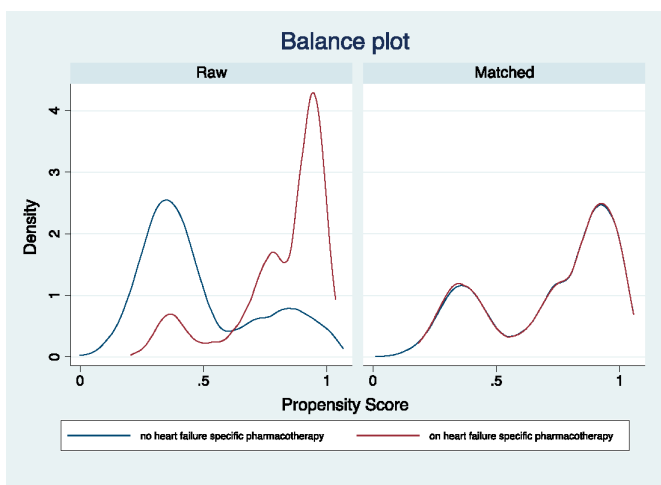
The mean (SD) DAOH was significantly increased in frail HF patients who received HF-specific pharmacotherapy compared with those who did not receive treatment (67.7 (33.1) days vs 47.1 (40.9) days,  $p<0.001$ ) and these patients had 4.9-fold higher odds of having an increased DAOH compared with those who did not receive treatment (OR 4.90, 95% CI 3.64 to 6.58,  $p<0.001$ ) (table 3).





**Figure 2** Proportion of heart failure patients not on heart failure-specific pharmacotherapy depending on frailty status. ACEi, ACE inhibitor; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist.

The differences in the DAOH90 remained statistically significant ( $p < 0.05$ ) irrespective of gender, age ( $< 65$  years or  $\geq 65$  years) or the duration of study (patients admitted before or after 31 December 2016). After PS matching, the DAOH remained significantly increased in frail HF patients who received HF-specific pharmacotherapy compared with those who did not receive treatment (coefficient 16.18, robust SE 5.03, 95% CI 6.32 to 26.04,  $p = 0.001$ ) (table 4). The in-hospital, 30-day and 180-day mortality rates were significantly lower among frail HF patients who received HF-specific pharmacotherapy when compared with those frail patients who did not receive treatment ( $p < 0.05$ ) (tables 3 and 4). At 30 days following hospital discharge, the odds of death were 70% lower among those frail patients who received HF-specific pharmacotherapy compared with those who were not on treatment (OR 0.30, 95% CI 0.23 to 0.39,  $p < 0.001$ ). The number needed to treat (NNT) to prevent one in-hospital death among frail patients was 4, and NNT needed to prevent one death at 30 days of discharge was 4.2. However, there were no significant differences in LOS or 30-day readmissions between frail patients who received or did not receive HF-specific pharmacotherapy ( $p > 0.05$ ) (tables 3 and 4).



**Figure 3** Kernel density graph showing propensity score matching.

**Table 2** Propensity score matching showing standardised mean differences and variance ratios

Variable	Standardised differences		Variance ratio	
	Raw	Matched	Raw	Matched
Age	-0.13	-0.08	1.03	1.21
Age >65	-0.11	-0.05	1.32	1.62
Sex male	-0.07	0.05	1.00	0.99
Charlson index	-0.07	0.04	1.02	1.16
IRSD	0.01	-0.03	0.89	0.86
Haemoglobin	0.13	0.09	0.87	1.08
Creatinine	-0.25	0.10	0.64	1.06
BNP	-0.23	0.08	0.50	1.13
Troponin	-0.05	0.02	0.70	1.80
CRP	-0.16	0.01	0.61	0.96
Albumin	0.20	0.05	0.76	1.07
HFRS	-0.17	0.13	0.89	1.13
MUST	0.03	0.01	0.97	1.00
Aspirin	0.63	-0.01	1.98	0.99
Warfarin	0.38	-0.12	2.11	0.74
DOACs	0.67	0.10	9.32	1.36
Statins	0.81	-0.02	1.83	0.99

BNP, brain natriuretic peptide; CRP, C reactive protein; DOACs, direct oral anticoagulants; HFRS, hospital frailty risk score; IRSD, Index of Relative Socioeconomic Disadvantage; MUST, malnutrition universal screening tool.

### Sensitivity analysis

Sensitivity analyses with determination of the ATET confirmed that DAOH at 90 days following discharge were significantly increased and in-hospital, 30-day and 180-day mortality were significantly reduced in frail patients who received HF-specific pharmacotherapy ( $p < 0.05$ ). However, there were no significant differences in 30-day readmissions and LOS ( $p > 0.05$ ) in frail patients who received or did not receive HF-specific pharmacotherapy (table 5).

## DISCUSSION

The results of this study indicate that almost a quarter of patients who were hospitalised with HF were frail. Overall, patients who received HF-specific pharmacotherapy were more likely to be younger with lower creatinine and BNP levels but with higher haemoglobin and CRP levels. Frail patients as defined by the HFRS were significantly less likely to be on HF-specific pharmacotherapy than the non-frail counterparts. After propensity score matching, an increased DAOH was more likely to be associated with prescription of HF-specific pharmacotherapy in frail HF patients. In addition, prescription of HF-specific pharmacotherapy in frail HF patients was more likely to be associated with a reduction in in-hospital, 30-day and 180-day

**Table 3** Clinical outcomes in frail depending on use of heart failure-specific pharmacotherapy

Outcome variable	No heart failure pharmacotherapy	Received heart failure pharmacotherapy	OR	95% CI	P value
	n=381	n=1025			
DAOH90 mean (SD)	47.0 (40.9)	67.7 (33.1)	4.90	3.64 to 6.59	<0.001
Inhospital deaths n (%)	131 (34.4)	96 (9.4)	0.20	0.15 to 0.27	<0.001
30-day mortality n (%) overall	161 (42.3)	185 (18.1)	0.30	0.23 to 0.39	<0.001
180-day mortality n (%) overall	202 (53.0)	335 (32.7)	0.43	0.33 to 0.54	<0.001
LOS* median (IQR) overall	4.8 (2.8, 7.8)	4.5 (2.3, 8.3)	0.99	0.95 to 1.03	0.797
30-day readmissions n (%) overall	70 (18.4)	213 (20.8)	1.16	0.86 to 1.57	0.317

\*LOS adjusted for in-hospital deaths.  
DAOH90, days alive and out of hospital at 90 days of discharge; LOS, length of hospital stay.

mortality but not with a reduction in LOS or 30-day readmissions.

The findings of our study are significant because there is a marked discrepancy between patients evaluated in most HF clinical trials and the spectrum of patients seen in clinical practice especially in terms of age and frailty status.<sup>11</sup> Patients included in the HF clinical trials are more likely to be younger males, with a significantly less comorbidity and on fewer medications than those HF patients who are seen in clinical practice.<sup>9 10 22</sup> This contrasts to a real-world scenario where HF patients are often older with a higher comorbidity burden and on polypharmacy.

Our study suggests that frail patients were less likely to receive HF-specific medications and confirm the results of a recent study,<sup>8</sup> which included 291 HF patients with reduced ejection fraction attending a community clinic, and this study also found that compared with non-frail patients, frail patients were less likely to be prescribed the three major classes of HF-specific medications (ACEi/ARA, beta blockers and MRA) and this study also found that those who did receive treatment were more likely to receive suboptimal doses. The potential reasons for less prescription of HF-specific medications in frail patients could be related to a lack of clear guidelines on management of frail HF patients, the presence of comorbidities such as renal failure or asthma, which may be a contraindication to prescription of ACEi/ARBs and beta blockers, patients' preferences and concerns about side effects of

medications (such as hypotension and fatigue) or a lack of compliance with medications in this population.<sup>4 23 24</sup>

Our study found that HF-specific pharmacotherapy was associated with improvement in clinical outcomes such as the DAOH and mortality among frail patients. However, a major limitation of our study is that we do not have echocardiogram data and thus are unable to differentiate patients based on their ejection fraction. HF with preserved ejection fraction (HFpEF) is commonly associated with comorbidities such as hypertension, atrial fibrillation, CAD, obesity, anaemia, diabetes, chronic kidney disease and sleep-disordered breathing.<sup>12 19</sup> The above-mentioned comorbidities are also associated with frailty.<sup>6</sup> Although the use of some medications such as MRA and, more recently, SGLT2 inhibitors reduce the risk of HF hospitalisation and improve quality of life, there is no clear evidence that they reduce mortality.<sup>12</sup> In addition, very few clinical trials have included frail older patients who are more likely to have comorbidities associated with HFpEF. The SENIORS trial<sup>25</sup> found that Nebivolol reduced mortality and hospital admissions in older HF patients, while another study<sup>26</sup> in older frail patients with myocardial infarction found that use of beta blockers was associated with a reduction in hospital admissions for HF. Evidence also suggests that beta blocker therapy in patients with HFpEF is associated with an improvement in echocardiogram parameters<sup>27</sup> and guidelines<sup>12</sup> suggest use of these agents as a heart rate lowering therapy, despite

**Table 4** Outcomes in frail heart failure patients after propensity score matching depending on prescription of heart failure-specific pharmacotherapy

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90	16.18	5.03	6.32 to 26.04	0.001
Inhospital mortality	-0.24	0.05	-0.34 to -0.13	<0.001
30-day mortality	-0.19	0.06	-0.30 to -0.09	<0.001
180-day mortality	-0.14	0.07	-0.28 to -0.01	0.038
30-day readmissions	0.04	0.04	-0.04 to 0.12	0.334
LOS	0.06	0.76	-1.43 to 1.55	0.938

DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay.

**Table 5** Outcomes in frail heart failure patients using the average treatment effect on the treated depending on prescription of heart failure-specific pharmacotherapy in non-frail and frail patients

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90	15.40	5.81	4.01 to 26.79	0.008
Inhospital mortality	-0.24	0.06	-0.36 to -0.11	<0.001
30-day mortality	-0.18	0.06	-0.30 to -0.06	0.004
180-day mortality	-0.15	0.08	-0.31 to -0.01	0.041
30-day readmissions	0.06	0.05	-0.03 to 0.16	0.188
LOS	0.03	0.86	-1.67 to 1.73	0.976

DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay.

a lack of proven reduction in mortality. Two recent HF clinical trials the PARADIGM HF and the DAPA HF, which investigated the role of Sacubitril/Valsartan and Dapagliflozin in HF, although, have enrolled only a minority of older patients ( $\geq 75$  years) (19% and 24%, respectively) have found that there was no evidence of lesser benefits with these agents in older patients.<sup>28 29</sup>

In an older frail population, the risk of dying from a natural cause or a non-cardiovascular condition may be a competing risk factor for potential beneficial effects of a specific treatment. It is possible that there is a threshold for biological age rather than chronological age beyond which the absolute benefits of HF-specific treatments will be difficult to prove. As the prevalence of frailty is expected to increase with an ageing population,<sup>30</sup> the management of frail HF patients will remain a significant medical challenge. The results of our study are hypothesis generating in that there may be potential benefits of prescribing HF-specific pharmacotherapy in some frail patients who are deemed suitable and such an action may potentially reduce adverse clinical outcomes. However, further studies in the frail older population are needed to verify our findings. Aggressive HF treatment may be less important in some patients who are severely frail with contraindications to treatment, who may need interventions to address frailty rather than HF. There is a need for a holistic approach when addressing issues associated with the management of frail HF patients and issues such as cognitive impairment, malnutrition and depression needs an early assessment and remedial measures.<sup>4 8</sup>

This study has several limitations. Due to its observational design, there is a possibility that a number of confounding factors, which could have influenced the clinical outcomes among frail patients have not been accounted for, so results should be interpreted with caution. It is possible that in some patients, HF-specific medications were stopped during the index admission due to reasons such as palliation which could have potentially confounded the outcomes. We were unable to secure echocardiogram data, and thus were unable to determine the ejection fraction, however, the severity of HF was judged from BNP levels.<sup>19</sup> Over the course of study, newer medications for HF were available which could have influenced clinical outcomes. Unfortunately,

we were unable to account for these medications because very few frail patients received these medications.

## CONCLUSION

Frail patients were less likely to receive HF-specific pharmacotherapy than non-frail counterparts. This study also found an association between the use of HF-specific pharmacotherapy and improved clinical outcomes measured in terms of increased number of DAOH and reduced 30-day and 180-day mortality in frail patients. There is a need for further studies to confirm our findings.

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**Patient consent for publication** Not applicable.

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**Data availability statement** Data are available on reasonable request.

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