BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059905
Article Type:	Original research
Date Submitted by the Author:	05-Dec-2021
Complete List of Authors:	Sharma, Yogesh; Flinders Medical Centre Horwood, Chris; Flinders Medical Centre, Department of Clinical Epidemiology Hakendorf, Paul; Flinders Medical Centre, Department of Clinical Epidemiology Thompson, Campbell; University of Adelaide, Discipline of Medicine
Keywords:	Heart failure < CARDIOLOGY, GERIATRIC MEDICINE, GENERAL MEDICINE (see Internal Medicine)

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Yogesh Sharma[1,2] Chris Horwood[3] Paul Hakendorf[4] Campbell Thompson[5]

1. Associate Professor Yogesh Sharma

   MBBS, MD, FRACP, PhD

   College of Medicine and Public Health

   Flinders University, Adelaide, South Australia 5042

2. Senior Consultant Physician

   Division of Medicine, Cardiac & Critical Care

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Yogesh.Sharma@sa.gov.au

3. Mr Chris Horwood

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Chris.Horwood@sa.gov.au

4. Mr Paul Hakendorf

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

Flinders Medical Centre, Adelaide, South Australia 5042

Email: Paul.Hakendorf@sa.gov.au

5. Prof Campbell Thompson

MD, DPhil, FRACP, FRCP

Professor of Medicine

Discipline of Medicine

The University of Adelaide

Adelaide, South Australia 5005

Email: Campbell.Thompson@adelaide.edu.au

Corresponding Author

Associate Professor Yogesh Sharma

College of Medicine and Public Health

Flinders University

Adelaide, South Australia 5042

Email: Yogesh.Sharma@sa.gov.au

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Abstract

Objectives Up to 50% percent of heart failure (HF) patients may be frail. Frail HF patients have worse clinical outcomes than non-frail patients. The benefits of HF specific pharmacotherapy 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 Five thousand seven hundred and thirty-four hospitalised HF patients admitted over a period of seven years

Measures Frailty status was determined by use of the Hospital-Frailty-Risk-Score (HFRS) and patients with HFRS ≥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, and 30-day readmissions. Propensity-score matching (PSM) compared clinical outcomes depending upon the receipt of HF specific pharmacotherapy.

Results Of 5734 patients, mean (SD) age 76.2 (14.0) years, 51.2% males, 1406 (24.1%) were frail. Overall, 4576 (79.8%) patients who received HF specific pharmacotherapy were younger, males with a lower creatinine and Charlson-index than those who did not receive treatment. HF specific pharmacotherapy was significantly less likely prescribed to frail than non-frail patients (72.9% vs. 82.1%, P<0.001). PSM created 228 well-matched patients in

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

each group. Frail patients on treatment had 3.6-fold higher odds of an increased DAOH (OR 3.60, 95% CI 1.36-9.79, P=0.010) than those who were not on treatment. The 30-day mortality was 15% lower, and the odds of death were 69% (OR 0.31, 95% CI 0.13-0.73, P=0.007) reduced in frail patients who were on treatment when compared to those who were not on treatment. However, there were no significant differences in 180-day mortality and 30-day readmissions between the two groups.

Conclusion

HF specific pharmacotherapy improved clinical outcomes in frail patients when compared to those who were not on treatment.

Key words: Heart failure, Pharmacotherapy, Mortality, Readmissions, Days alive and out of hospital

Trial registration no Australia and New Zealand Clinical Trial Registry ANZCTRN383195

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 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

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- The severity of heart failure based on ejection fraction was not available due to lack of echocardiogram results

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Word count 2930

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Introduction

Heart failure (HF) is commonly associated with advancing age, with a prevalence of 6% in individuals between 65-79 years and up to 14% in those over the age of 80 years.[1] The annual rates of acute decompensated heart failure nearly triples in individuals over the age of 75 years when compared to those between 55-65 years, irrespective of factors such as sex and race.[1] Studies[2, 3] suggest that 15-20% of the HF patients who are discharged alive die within 90 days of hospitalisation. Heart failure 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.[4] Frailty, defined as a biologic syndrome with impaired physiological reserves that increases susceptibility to stressors[5] is common among patients with heart failure. A recent meta-analysis[6] 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[7]. In addition, despite a high prevalence of HF in older individuals, there is a dearth of research specifically targeting older frail patients.[4, 8] 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%.[9] 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.[10] Thus,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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[11]. Despite these findings, guidelines[1, 12] still recommend targeted therapy for HF irrespective of age or co-morbidities.

We conducted a retrospective study to determine the impact of HF specific medications (beta blockers, angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and mineralocorticoid receptor blockers (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 patients ≥18 years of age who were hospitalised with HF over a period of eight years at two tertiary teaching hospitals, Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) in Adelaide, Australia. The study protocol was reviewed by the Southern Adelaide Human Research Ethics Committee and was determined to be exempt. 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 Tenth Revision Australian Modification (ICD-10-AM) code 150, which has been previously used to define HF [13]. In cases where patients had multiple presentations for heart failure during the study period, then only the first admission was included.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.[14] HFRS is based upon 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 heart failure, atrial fibrillation, or coronary artery disease (CAD). Higher HFRS scores indicate a greater severity of frailty and, we classified patients with a HFRS score ≥5 as frail and those with HFRS scores of <5 as non-frail as has been done in previous studies.[14, 15]

We determined medications prescribed to patients during their admission from our pharmacy database. In particular, we determined whether patients received any or all of the heart failure specific medications (beta blockers, ACEi/ARBs, and MRA) along with other medications such as aspirin, warfarin, Direct acting oral anticoagulants (DOACs), statins, ivabradine, digoxin, sodium-glucose transport protein 2 (SGLT2) inhibitors and sacubitril/valsartan. We determined the socio-economic status of the patients by using the index of relative socio-economic disadvantage (IRSD).[16] The comorbidity risk was determined by use of the Charlson comorbidity index (CCI)[17] and nutritional status was assessed by use of the Malnutrition Universal Screening Tool (MUST).[18] The severity of heart failure was assessed by use of the brain natriuretic peptide (BNP) levels.[19] In addition, we determined common investigations performed during hospital admission: haemoglobin, C-reactive protein (CRP), albumin, creatinine, and troponin levels.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.

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-square statistics.

Propensity score methods

We used propensity score matching to control for any potential confounding factors between the two cohorts: patients who received heart failure 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 heart failure specific pharmacotherapy. To create propensity scores, we first used multivariable logistic regression model with receipt of heart failure specific pharmacotherapy as the outcome variable and the potential confounders as the explanatory variables. The seventeen confounding variables which were hypothesised to be associated both with the exposure and the outcomes included: age, age ≥ 65 years, sex, HFRS, MUST score, IRSD, CCI, haemoglobin, C-RP, creatinine, BNP, troponins, albumin levels, and the use of aspirin, warfarin, DOACs and statins. 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[20] was employed to optimise trade-off between variance and bias. After kernel matching, the balance of covariates was assessed using the standardised mean

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

differences, with >10% standard mean difference considered as significant between the two groups.[21] 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 in the treated (ATET).

Sensitivity analyses were performed by use of inverse probability weighting (IPW) to assess the robustness of results generated by the use of propensity score matching and coefficients with robust standard errors and 95% confidence intervals were generated. All tests were two sided and a P value <0.05 was regarded as statistically significant. All statistical analyses were performed by use of STATA software version 17.0 (StataCorp, College Station, Texas, USA).

Results

There were 8050 admissions with heart failure between 1 January 2013 and 31 December 2020. After omitting multiple admissions, 5734 patients remained in the dataset **(Figure 1)**. The mean age was 76.2 (14.0) years, range 19-105 years and 51.9% were males. The mean (SD) HFRS was 3.3 (3.8) and 1406 (24.1%) patients were classified as frail. 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 heart failure as determined by the BNP and troponin levels between the frail and non-frail group.

Overall, 4576 (79.8%) patients received one or more medications defined as heart failure specific pharmacotherapy. Baseline characteristics differed among patients who received

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

heart failure specific pharmacotherapy compared to those who did not receive these medications **(Table 1)**. Patients who received heart failure specific pharmacotherapy were more likely to be younger males, with a lower CCI, creatinine, BNP, troponin, albumin, and CRP levels but there was no difference with regards to their nutritional or socio-economic status **(Table 1)**. When compared to non-frail patients, frail patients were significantly less likely to be prescribed heart failure specific pharmacotherapy (72.9% vs. 82.1%, P<0.001). In terms of individual heart failure 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 to frail patients**. (Figure 2)**

Propensity score matching

The propensity score model which was built with the use of seventeen variables after multivariable logistic regression model, included 228 patients in each group and was well matched with a standardised mean difference (SMR) of <10% **(Table 1 & Figure 3)**.

Outcomes with propensity score matching

In patients who received heart failure specific pharmacotherapy the DAOH increased by 7.6 (95% CI 2.3 to 12.9) days and the impact of treatment was even greater (14.5 (95% CI 2.5 to 26.9) days) in frail patients when compared to those patients who were not on treatment **(Table 2 & Figure 4)**. Frail patients who received heart failure specific pharmacotherapy had 3.6-fold higher odds of having an increased DAOH (OR 3.60, 95% CI 1.36 to 9.79, P=0.010) compared to those who did not receive medications. There was a trend towards reduced inhospital mortality and 30-day mortality among patient who received heart failure specific pharmacotherapy and the mortality among frail patients was respectively, 13% and 15%

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

lower compared to those who did not receive treatment **(Table 2)**. At 30 days following discharge the odds of death were 69% less among those frail patients who received heart failure specific pharmacotherapy compared to those who were not on treatment (OR 0.31, 95% CI 0.13 to 0.73, P=0.007). The number needed to treat (NNT) to prevent one inhospital death among frail patients was 4, and NNT needed to prevent one death at 30-days of discharge was 4.1. However, there were no significant differences in 180-day mortality or 30-day readmissions between patients who received or did not receive heart failure specific pharmacotherapy. When compared to patients who did not receive heart failure specific pharmacotherapy, LOS was overall reduced among patients who received heart failure specific pharmacotherapy but not among the sub-population of only those who were identified as frail (P>0.05) **(Table 2).**

Outcomes with inverse probability weighting

Analysis after inverse probability weighting confirmed that DAOH at 90 days following discharge were significantly increased and both inhospital and 30-day mortality was significantly reduced in frail patients who received heart failure specific pharmacotherapy (P<0.05). However, there were no differences in 180-day mortality, 30-day readmissions and LOS (P>0.05) in frail patients who received or did not receive HF specific treatment **(Table 3).**

Discussion

The results of this study indicate that almost a quarter of patients who were hospitalised with heart failure were frail. Patients who received heart failure specific pharmacotherapy were more likely to be younger males with a lower CCI and creatinine levels. Frail patients as defined by the HFRS were significantly less likely to be on heart failure specific

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

pharmacotherapy than the non-frail counterparts. After propensity score matching, frail patients were more likely to have an increased DAOH when compared to those who were not on these medications. In addition, both the inhospital and the 30-day mortality were significantly reduced among frail patients who had received heart failure specific pharmacotherapy but other clinical outcomes such as LOS and 30-day readmissions were not significantly different when compared to patients who were not on these treatments.

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.[11] 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.[9, 10, 22] 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 heart failure specific medications and confirm the results of a recent study[8] which included 291 HF patients with reduced ejection fraction (HFrEF) attending a community clinic, and this study also found that compared to 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 less likely to receive sub-optimal 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 heart failure patients, the presence of comorbidities such as renal failure or asthma, which may be a contraindication to

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

prescription of ACEi/ARBs and beta blockers, patients' preferences and concerns about side effects of medications or a lack of compliance with medications in this population.[4, 23, 24]

Our study found that HF specific pharmacotherapy improved some clinical outcomes among frail patients. There are only a few clinical trials which have included frail older patients. The SENIORS trial[25] included 2128 HF patients ≥70 years of age and found that Nebivolol reduced the primary outcome of all-cause mortality or cardiovascular hospital admission over a period of twelve months, when compared to placebo (HR 0.86, 95% CI 0.74-0.99, P=0.039). Another study[26] which investigated the use of beta blockers in 13,623 elderly frail patients (mean age 75.6 years) after myocardial infarction found that the use of beta blockers was associated with a 43% (HR 0.57, 95% CI 0.48-0.69) reduction in admissions for HF and 60% reduction in the risk of death (HR 0.40, 95% CI 0.34-0.47) when compared to those who were not on this treatment. Evidence also suggest that beta blocker therapy in patients with heart failure with preserved ejection fraction (HFpEF) is associated with an improvement in echocardiogram parameters[27] and guidelines[12] suggest use of these agents as a heart rate lowering therapy, despite a lack of proven reduction in mortality. In older frail patients, there is always a concern about tolerance to treatment given this population has a high prevalence of poor renal function and existing comorbidities such as COPD. Baxter et al[23] investigated the use of Bisoprolol in older HF and found that, although, the rate of withdrawal from betablocker was twice as high in older patients when compared to younger counterparts, when these drugs were tolerated, targeted doses of beta blockers were achieved without any impact on worsening heart failure symptoms. 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 (≥75 years) (19% and 24%,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

respectively) have found that there was no evidence of lesser benefits with these agents in older patients.[28, 29]

In an older frail population, the natural 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 heart failure specific treatments will be difficult to prove. As the prevalence of frailty is expected to increase with an aging population[30], the management of frail heart failure patients will remain a significant medical challenge. There may be potential benefits of prescribing heart failure specific pharmacotherapy in some patients who are deemed suitable and such an action may potentially reduce adverse clinical outcomes as suggested by the present study. On the other hand, 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 heart failure. 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.[4, 8]

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, heart failure 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

For peer review only

Enseignement Superieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

determine the ejection fraction, however, the severity of heart failure was judged from BNP levels.[19]

Conclusion

Frail patients were less likely to receive heart failure specific pharmacotherapy than non-frail counterparts. However, frail patients who received treatment had better clinical outcomes in terms of increased number of DAOH and reduced 30-day mortality than those who did not receive treatment. There is a need for further studies to confirm our findings.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available on reasonable request from the corresponding author subject to approval by the ethics committee.

Ethics statement

Patient consent for publication

Not applicable

Ethics approval

The study protocol was reviewed by the Southern Adelaide Human Clinical Research Ethics Committee and determined to be exempt.

Conflicts of interest

The authors have no conflict of interest to declare.

Funding

This study received no funding.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Author contribution

Yogesh Sharma: Conceptualization; Ethical approval; Project administration; Methodology; Statistical analyses; Resources; Writing- review and editing.

Chris Horwood: Data Curation; Methodology

Paul Hakendorf: Data Curation; Statistical analyses

Campbell Thompson: Conceptualization; Methodology; Writing-review and editing.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**:e146-e603. doi: 10.1161/cir.0000000000000485

2. Chen Y, Lawrence J, Stockbridge N. Days alive out of hospital in heart failure: Insights from the PARADIGM-HF and CHARM trials. *Am Heart J* 2021; **241**:108-19. doi: 10.1016/j.ahj.2021.03.016

3. Ariti CA, Cleland JG, Pocock SJ, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J* 2011; **162**:900-6. doi: 10.1016/j.ahj.2011.08.003

4. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. *J Am Coll Cardiol* 2018; **71**:1921-36. doi: 10.1016/j.jacc.2018.02.059

5. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008; **9**:71-2. doi: 10.1016/j.jamda.2007.11.005

6. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2017; **236**:283-9. doi: 10.1016/j.ijcard.2017.01.153

7. Leventhal MJ, Riegel B, Carlson B, et al. Negotiating compliance in heart failure: remaining issues and questions. *Eur J Cardiovasc Nurs* 2005; **4**:298-307. doi: 10.1016/j.ejcnurse.2005.04.001

8. Sze S, Pellicori P, Zhang J, et al. Effect of frailty on treatment, hospitalisation and death in patients with chronic heart failure. *Clin Res Cardiol* 2021; **110**:1249-58. doi: 10.1007/s00392-020-01792-w

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

9. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; **162**:1682-8. doi: 10.1001/archinte.162.15.1682

10. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003; **146**:250-7. doi: 10.1016/s0002-8703(03)00189-3

11. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; **171**:550-6. doi: 10.1001/archinternmed.2011.31

12. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; **23**:628-51. doi: 10.1016/j.cardfail.2017.04.014

13. Joshy G, Korda RJ, Abhayaratna WP, et al. Categorising major cardiovascular disease hospitalisations from routinely collected data. *Public Health Res Pract* 2015; **25**:e2531532. doi: 10.17061/phrp2531532

14. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; **391**:1775-82. doi: 10.1016/s0140-6736(18)30668-8

15. McAlister FA, Savu A, Ezekowitz JA, et al. The hospital frailty risk score in patients with heart failure is strongly associated with outcomes but less so with pharmacotherapy. *J Intern Med* 2020; **287**:322-32. doi: 10.1111/joim.13002

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Adams RJ, Howard N, Tucker G, et al. Effects of area deprivation on health risks and outcomes: a multilevel, cross-sectional, Australian population study. *Int J Public Health* 2009; **54**:183-92. doi: 10.1007/s00038-009-7113-x

17. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, et al. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. *J Am Geriatr Soc* 2014; **62**:342-6. doi: 10.1111/jgs.12635

18. Sharma Y, Thompson C, Kaambwa B, et al. Validity of the Malnutrition Universal Screening Tool (MUST) in Australian hospitalized acutely unwell elderly patients. *Asia Pac J Clin Nutr* 2017; **26**:994-1000. doi: 10.6133/apjcn.022017.15

19. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019; **21**:715-31. doi: 10.1002/ejhf.1494

20. Heckman JJ, Ichimura H, Todd PE. Matching As An Econometric Evaluation Estimator: Evidence from Evaluating a Job Training Programme. *The Review of Economic Studies* 1997; **64**:605-54. doi: 10.2307/2971733

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**:3083-107. doi: 10.1002/sim.3697

22. Badano LP, Di Lenarda A, Bellotti P, et al. Patients with chronic heart failure encountered in daily clinical practice are different from the "typical" patient enrolled in therapeutic trials. *Ital Heart J* 2003; **4**:84-91. doi:

23. Baxter AJ, Spensley A, Hildreth A, et al. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. *Heart* 2002; **88**:611-4. doi: 10.1136/heart.88.6.611

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24. Dulin BR, Krum H. Drug therapy of chronic heart failure in the elderly: the current state of clinical-trial evidence. *Curr Opin Cardiol* 2006; **21**:393-9. doi: 10.1097/01.hco.0000231411.15049.20

25. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**:215-25. doi: 10.1093/eurheartj/ehi115

26. Rochon PA, Tu JV, Anderson GM, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet* 2000; **356**:639-44. doi: 10.1016/s0140-6736(00)02606-4

27. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). *Eur J Heart Fail* 2004; **6**:453-61. doi: 10.1016/j.ejheart.2004.02.003

28. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**:993-1004. doi: 10.1056/NEJMoa1409077

29. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**:1995-2008. doi: 10.1056/NEJMoa1911303

30. Sze S, Zhang J, Pellicori P, et al. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017; **106**:533-41. doi: 10.1007/s00392-017-1082-5

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1 Baseline characteristics of patients before and after propensity score matching

	Cohort before propensity score matching			Cohort after propensity score matching		
Characteristic	**Received heart failure specific pharmacotherapy**	**No heart failure specific pharmacotherapy**	**P value**	**Received heart failure specific pharmacotherapy**	**No heart failure specific pharmacotherapy**	**P value**
Total	**n=4576**	**n=1158**		**n=228**	**n=228**	
Age years mean (SD)	75.4 (14.2)	79.3 (13.1)	<0.0001	77.7 (13.9)	78.6 (13.2)	0.439
Age ≥65 years n (%)	3678 (80.4)	1010 (87.2)		187 (82.0)	193 (84.7)	0.451
Sex male n (%)	2408 (52.6)	566 (48.8)	0.023	106 (46.5)	104 (45.6)	0.851
Charlson index mean (SD)	2.3 (1.7)	2.5 (1.8)	<0.001	2.5 (1.8)	2.4 (1.6)	0.722
IRSD mean (SD)	5.4 (2.7)	5.5 (2.7)	0.448	6.0 (2.6)	5.6 (2.7)	0.067
Haemoglobin g/L mean (SD)	123.4	118.6	<0.001	122.4 (20.0)	121.4 (21.4)	0.582
Creatinine µmol/L mean (SD)	122.6 (70.8)	135.4 (94.2)	<0.001	116.1 (69.0)	119.6 (67.2)	0.584
BNP ng/L mean (SD)	55.6 (1111.7)	180.0 (1691.8)	0.0337	64.8 (191.2)	36.3 (347.8)	0.382
Troponin ng/L mean (SD)	0.9 (14.5)	3.6 (48.3)	0.0035	0.2 (0.5)	0.5 (4.1)	0.089
C-RP mg/L mean (SD)	24.9 (37.7)	31.6 (47.0)	<0.001	25.6 (37.7)	22.2 (32.0)	0.291
Albumin g/L mean (SD)	34.1 (4.9)	33.1 (5.3)	<0.001	32.8 (5.4)	33.2 (4.4)	0.351
HFRS mean (SD)	3.1 (3.6)	4.1 (4.3)	<0.001	3.9 (4.1)	4.1 (4.0)	0.646
MUST mean (SD)	0.5 (0.9)	0.6 (1.1)	0.348	0.5 (0.9)	0.4 (0.8)	0.638
Aspirin n (%)	1895 (41.4)	166 (14.3)	<0.001	43 (18.8)	52 (22.8)	0.299
Warfarin n (%)	1029 (22.5)	87 (7.5)	<0.001	27 (11.8)	30 (13.2)	0.671
DOACs n (%)	982 (21.5)	56 (4.8)	<0.001	26 (11.4)	25 (10.9)	0.882
Statins n (%)	2543 (55.6)	185 (15.9)	<0.001	72 (31.6)	67 (29.4)	0.611

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; BNP, brain natriuretic peptide; C-RP, C-reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2 Clinical outcomes in frail and non-frail patients depending upon use of heart failure specific pharmacotherapy

Outcome variable	No heart failure pharmacotherapy	Received heart failure pharmacotherapy	Difference	Odds ratio	95% CI	P value
	(n=228)	(n=228)				
DAOH90 mean (SD)						
Overall	70.7 (32.6)	78.3 (24.8)	7.6	2.92	1.38-6.20	0.005
Non-frail	77.4 (25.5)	81.5 (21.2)	4.1	2.12	0.72-7.19	0.125
Frail	56.0 (40.7)	70.7 (30.7)	14.7	3.60	1.36-9.79	0.018
Inhospital deaths n (%)						
Overall	27 (11.8)	10 (4.4)	7.4	0.34	0.16-0.72	0.005
Non frail	8 (5.1)	4 (2.5)	4	0.47	0.14-1.59	0.227
Frail	19 (26.4)	6 (8.9)	13	0.27	0.10-0.74	0.010
30-day mortality n (%) overall						
Overall	39(17.1)	17 (7.5)	22	0.39	0.21-0.71	0.002
Non frail	15 (9.6)	8 (4.9)	7	0.49	0.20-1.19	0.117
Frail	24 (33.3)	9 (13.4)	15	0.31	0.13-0.73	0.007
180-day mortality n (%) overall						
Overall	54 (23.7)	44 (19.3)	10	0.77	0.49-1.20	0.255
Non frail	25 (16.0)	23 (14.3)	2	0.66	0.47-1.61	0.666
Frail	29 (40.3)	21 (31.3)	8	0.68	0.33-1.36	0.274
LOS* median (IQR) overall						
Overall	5.0 (2.9,8.6)	5.6 (3.1, 8.8)	0.8	1.08	1.0-1.17	0.028
Non frail	3.8 (2.6, 6.8)	4.4 (2.7. 7.0)	0.6	1.09	0.99-1.20	0.065
Frail	8.8 (5.3, 12.1)	8.8 (5.9, 12.8)	0	1.04	0.93-1.17	0.473
30-day readmissions n (%) overall						
Overall	46 (24.3)	42 (19.9)	4	0.77	0.48-1.20	0.286
Non frail	36 (25.5)	33 (21.6)	3	0.80	0.46-1.37	0.424
Frail	10 (20.8)	9 (15.5)	1	0.69	0.25-1.88	0.479

*LOS adjusted for inhospital deaths

CI, confidence interval; DAOH90, days alive and out of hospital at 90 days of discharge; IQR, interquartile range; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3 Outcomes using inverse probability weighting depending upon prescription of heart failure specific pharmacotherapy in non-frail and frail patients

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90				
Overall	7.37	2.44	2.58 to 12.16	0.003
Non-Frail	4.93	2.52	–0.0 to 9.88	0.050
Frail	13.60	5.53	2.78 to 24.44	0.014
Inhospital mortality				
Overall	–0.07	0.02	–0.12 to –0.03	0.002
Non-Frail	–0.03	0.02	–0.07 to 0.01	0.150
Frail	–0.17	0.06	–0.29 to –0.04	0.007
30-day mortality				
Overall	–0.09	0.03	–0.15 to –0.04	0.001
Non-frail	–0.06	0.02	–0.11 to –0.01	0.050
Frail	–0.19	0.07	–0.31 to –0.05	0.004
180-day mortality				
Overall	–0.05	0.03	–0.11 to 0.02	0.176
Non-frail	–0.03	0.04	–0.11 to 0.04	0.370
Frail	–0.07	0.07	–0.22 to 0.07	0.324
30-day readmissions				
Overall	–0.04	0.04	–0.12 to 0.04	0.316
Non-frail	–0.05	0.05	–0.14 to 0.08	0.326
Frail	–0.05	0.07	–0.18 to 0.08	0.430
LOS				
Overall	0.50	0.46	–0.39 to 1.40	0.275
Non-frail	0.66	0.45	–0.21 to 1.44	0.136
Frail	0.46	1.06	–1.62 to 2.54	0.667

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

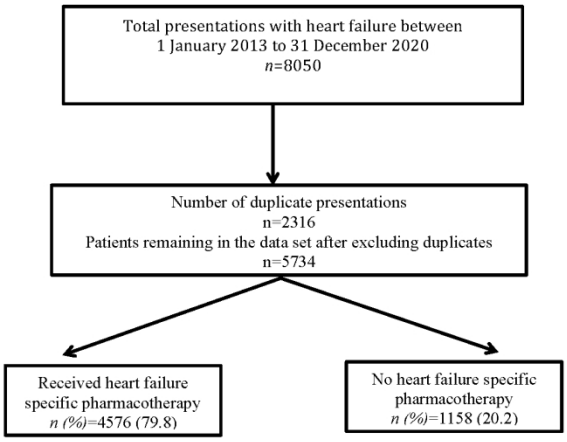

Figure 1 Study flow diagram

209x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

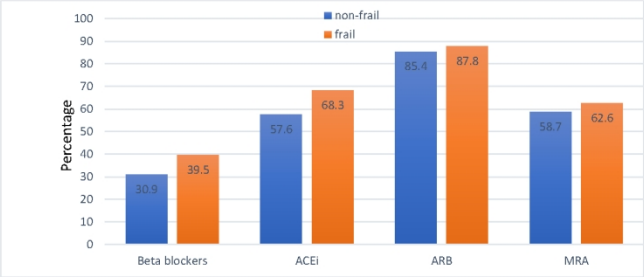

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

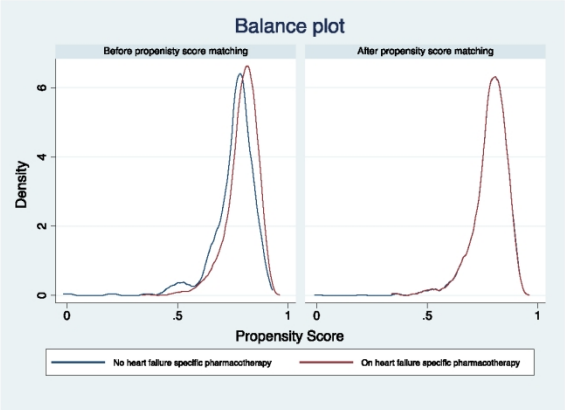

Figure 2 Kernel density graph showing propensity score matching

Figure 3 Kernel density graph showing propensity score matching

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

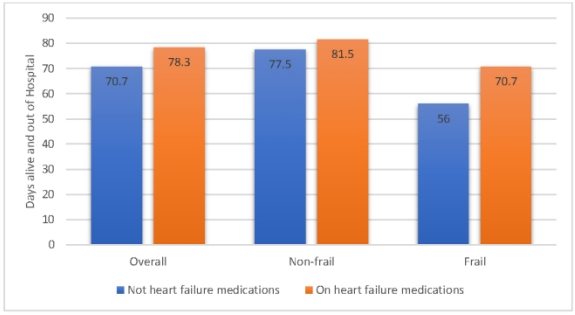

Figure 4Mean number of days alive and out of hospital (DAOH) at 90 days of discharge depending upon heart failure specific pharmacotherapy among frail and non-frail patients

210x297mm (191 x 192 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6, 7	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7	
Bias	9	Describe any efforts to address potential sources of bias	8, 9	
Study size	10	Explain how the study size was arrived at		

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

For peer review only

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Supérieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059905.R1
Article Type:	Original research
Date Submitted by the Author:	29-Apr-2022
Complete List of Authors:	Sharma, Yogesh; Flinders Medical Centre Horwood, Chris; Flinders Medical Centre, Department of Clinical Epidemiology Hakendorf, Paul; Flinders Medical Centre, Department of Clinical Epidemiology Thompson, Campbell; University of Adelaide, Discipline of Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Geriatric medicine, Medical management
Keywords:	Heart failure < CARDIOLOGY, GERIATRIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult cardiology < CARDIOLOGY, INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Yogesh Sharma[1,2] Chris Horwood[3] Paul Hakendorf[4] Campbell Thompson[5]

1. Associate Professor Yogesh Sharma

   MBBS, MD, FRACP, PhD

   College of Medicine and Public Health

   Flinders University, Adelaide, South Australia 5042

2. Senior Consultant Physician

   Division of Medicine, Cardiac & Critical Care

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Yogesh.Sharma@sa.gov.au

3. Mr Chris Horwood

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Chris.Horwood@sa.gov.au

4. Mr Paul Hakendorf

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

Flinders Medical Centre, Adelaide, South Australia 5042

Email: Paul.Hakendorf@sa.gov.au

5. Prof Campbell Thompson

MD, DPhil, FRACP, FRCP

Professor of Medicine

Discipline of Medicine

The University of Adelaide

Adelaide, South Australia 5005

Email: Campbell.Thompson@adelaide.edu.au

Corresponding Author

Associate Professor Yogesh Sharma

College of Medicine and Public Health

Flinders University

Adelaide, South Australia 5042

Email: Yogesh.Sharma@sa.gov.au

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives Up to 50% percent 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, angiotensin-converting-enzyme-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 Five thousand seven hundred and thirty-four hospitalised HF patients admitted over eight years

Measures The Hospital-Frailty-Risk-Score (HFRS) determined frailty status and patients with HFRS ≥5 were classified as frail. The primary outcomes included 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 upon the receipt of HF specific pharmacotherapy.

Results Of 5734 patients, mean (SD) age 76.2 (14.0) years, 51.2% males, 1406 (24.1%) were frail. HF specific pharmacotherapy was significantly less likely prescribed to frail than non-frail patients (72.9% vs. 82.1%, P<0.001). Of 1406 frail HF patients, 1025 (72.9%) received HF specific pharmacotherapy compared to 381 (27.1%) who did not receive any of these

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

medications. Frail HF patients who did not receive HF specific pharmacotherapy were significantly older, with higher creatinine and brain natriuretic peptide (BNP) but with lower haemoglobin and albumin levels (P<0.05) when compared to 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 6.32-26.04, P=0.001) than those who were not on treatment. Both 30-day (OR 0.30, 95% CI 0.23-0.39, P value<0.001) and 180-day mortality (OR 0.43, 95% CI 0.33-0.54, 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

HF specific pharmacotherapy improved clinical outcomes in frail patients when compared to those who were not on treatment.

Key words: Heart failure, Pharmacotherapy, Mortality, Readmissions, Days alive and out of hospital

Trial registration no Australia and New Zealand Clinical Trial Registry ANZCTRN383195

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

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- 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

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant

Word count 3188

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Introduction

Heart failure (HF) is commonly associated with advancing age, with a prevalence of 6% in individuals between 65-79 years and up to 14% in those over the age of 80 years.[1] The annual rates of acute decompensated heart failure nearly triples in individuals over the age of 75 years when compared to those between 55-65 years, irrespective of factors such as sex and race.[1] Studies[2, 3] suggest that 15-20% of the HF patients who are discharged alive die within 90 days of hospitalisation. Heart failure 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.[4] Frailty, defined as a biologic syndrome with impaired physiological reserves that increases susceptibility to stressors[5] is common among patients with heart failure. A recent meta-analysis[6] 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[7]. In addition, despite a high prevalence of HF in older individuals, there is a dearth of research specifically targeting older frail patients.[4, 8] 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%.[9] 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.[10] Thus, the older HF patients commonly seen in clinical practice have a limited representation in

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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[11]. Despite these findings, guidelines[1, 12] still recommend targeted therapy for HF irrespective of age or co-morbidities.

We conducted a retrospective study to determine the impact of HF specific medications (beta blockers, angiotensin converting enzyme 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 patients ≥18 years of age who were hospitalised with HF over a period of eight years at two tertiary teaching hospitals, Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) in Adelaide, Australia. The study protocol was reviewed by the Southern Adelaide Human Research Ethics Committee and was determined to be exempt. 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 Tenth Revision Australian Modification (ICD-10-AM) code 150, which has been previously used to define HF [13]. In cases where patients had multiple presentations for heart failure 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 (EMR) of our central computer database. The data of all HF patients who were referred from the emergency

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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.[14] The HFRS was calculated from the data obtained from our central computer database which contains information about patients' previous presentations to hospital. HFRS is based upon 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 heart failure, atrial fibrillation, or coronary artery disease (CAD). Higher HFRS scores indicate a greater severity of frailty and, we classified patients with a HFRS score ≥5 as frail and those with HFRS scores of <5 as non-frail as has been done in previous studies.[14, 15]

We determined medications prescribed to patients during their admission 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 heart failure specific medications (beta

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

blockers, ACEi/ARBs, and MRA) along with newer medications such as sodium-glucose transport protein 2 (SGLT2) inhibitors and sacubitril/valsartan in addition to other medications such as aspirin, warfarin, Direct acting oral anticoagulants (DOACs), statins, ivabradine, and digoxin. We determined the socio-economic status of the patients by using the index of relative socio-economic disadvantage (IRSD).[16] The comorbidity risk was determined by use of the Charlson comorbidity index (CCI)[17] and nutritional status was assessed by use of the Malnutrition Universal Screening Tool (MUST).[18] The severity of heart failure was assessed by use of the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[19] 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

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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-square 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 heart failure specific pharmacotherapy. To create propensity scores, we first used multivariable logistic regression model with receipt of heart failure specific pharmacotherapy as the outcome variable and the potential confounders as the explanatory variables. The seventeen confounding variables which were hypothesised to be associated both with the exposure and the outcomes included: age, age ≥ 65 years, sex, HFRS, MUST score, IRSD, CCI, haemoglobin, C-RP, creatinine, BNP, troponins, albumin levels, and the use of aspirin, warfarin, DOACs and statins. 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[20] was employed to optimise trade-off between variance and bias. After kernel matching, the balance of covariates was assessed using the standardised mean differences, with >10% standard mean difference considered as significant between the two groups.[21] 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.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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% confidence intervals were generated. All tests were two sided and a P value <0.05 was regarded as statistically significant. All statistical analyses were performed by use of STATA software version 17.0 (StataCorp, College Station, Texas, USA).

Results

There were 8050 admissions with heart failure between 1 January 2013 and 31 December 2020. After omitting multiple admissions and missing data, 5734 patients remained in the dataset **(Figure 1)**. The mean age was 76.2 (14.0) years, range 19-105 years and 51.9% were males. The mean (SD) HFRS was 3.3 (3.8) and 1406 (24.1%) patients were classified as frail. 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 heart failure 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 heart failure specific pharmacotherapy. Baseline characteristics differed among patients who received heart failure specific pharmacotherapy compared to those who did not receive these medications **(Table 1)**. Patients who received heart failure specific pharmacotherapy were more likely to be younger males, with a lower CCI, creatinine, BNP, troponin, albumin, and CRP levels but there was no difference with regards to their nutritional or socio-economic

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

status **(Table 1)**. When compared to non-frail patients, frail patients were significantly less likely to be prescribed heart failure specific pharmacotherapy (72.9% vs. 82.1%, P<0.001). In terms of individual heart failure 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 to frail patients**. (Figure 2)**

Of 1406 frail HF patients, 1025 (72.9%) received heart failure specific pharmacotherapy compared to 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 compared to those frail patients who received treatment **(Table 2).**

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 a standardised mean difference (SMR) of <10% **(Table 3 & Figure 3)**.

Clinical outcomes in frail patients depending upon receipt of heart failure specific pharmacotherapy

The mean (SD) DAOH was significantly increased in frail HF patients who received HF specific pharmacotherapy compared to those who did not receive treatment (67.7 (33.1) days vs. 47.1 (40.9) days, P value <0.001) and these patients had 4.9-fold higher odds of having an increased DAOH compared to those who did not receive treatment (OR 4.90, 95% CI 3.6-4-6.58, P value< 0.001) **(Table 4)**. After PS matching, the DAOH remained significantly

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

increased in frail HF patients who received HF specific pharmacotherapy compared to those who did not receive treatment (coefficient 16.18, robust standard error 5.03, 95% CI 6.32-26.04, P=0.001) **(Table 5).** The inhospital, 30-day and 180-day mortality rates were significantly lower among frail HF patients who received HF specific pharmacotherapy when compared to those frail patients who did not receive treatment (P<0.05) **(Table 4 and 5).** At 30 days following hospital discharge, the odds of death were 70% lower among those frail patients who received heart failure specific pharmacotherapy compared to 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 inhospital 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 heart failure specific pharmacotherapy (P>0.05) **(Tables 3 and 4).**

Sensitivity analysis

Sensitivity analyses with determination of the ATET confirmed that DAOH at 90 days following discharge were significantly increased and inhospital, 30-day and 180-day mortality were significantly reduced in frail patients who received heart failure 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 6).**

Discussion

The results of this study indicate that almost a quarter of patients who were hospitalised with heart failure were frail. Overall, patients who received heart failure specific pharmacotherapy were more likely to be younger males with a lower CCI and creatinine levels. Frail patients as

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

defined by the HFRS were significantly less likely to be on HF specific pharmacotherapy than the non-frail counterparts. After propensity score matching, frail patients were more likely to have an increased DAOH when compared to those who were not on these medications. In addition, inhospital, 30-day and 180-day mortality were significantly reduced among frail patients who had received HF specific pharmacotherapy but other clinical outcomes such as LOS and 30-day readmissions were not significantly different when compared to patients who were not on these treatments.

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.[11] 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.[9, 10, 22] 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 heart failure specific medications and confirm the results of a recent study[8] which included 291 HF patients with reduced ejection fraction (HFrEF) attending a community clinic, and this study also found that compared to 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 sub-optimal 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

prescription of ACEi/ARBs and beta blockers, patients' preferences and concerns about side effects of medications or a lack of compliance with medications in this population.[4, 23, 24]

Our study found that HF specific pharmacotherapy improved 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. Heart failure with preserved ejection fraction (HFpEF) is commonly associated with comorbidities such as hypertension, atrial fibrillation, coronary artery disease, obesity, anaemia, diabetes, chronic kidney disease and sleep-disordered breathing.[12, 19] The above-mentioned comorbidities are also associated with frailty.[6] 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.[12] In addition, very few clinical trials have included frail older patients who are more likely to have comorbidities associated with HFpEF. The SENIORS trial[25] found that Nebivolol reduced mortality and hospital admissions in older HF patients, while another study[26] 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 suggest that beta blocker therapy in patients with heart failure with preserved ejection fraction (HFpEF) is associated with an improvement in echocardiogram parameters[27] and guidelines[12] suggest use of these agents as a heart rate lowering therapy, despite 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 (≥75 years) (19% and 24%, respectively) have found that there was no evidence of lesser benefits with these agents in older patients.[28, 29]

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 heart failure specific treatments will be difficult to prove. As the prevalence of frailty is expected to increase with an aging population[30], the management of frail heart failure patients will remain a significant medical challenge. The results of our study are hypothesis generating in that there may be potential benefits of prescribing heart failure 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 heart failure. 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.[4, 8]

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, heart failure 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 heart failure was judged from BNP levels.[19]

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Conclusion

Frail patients were less likely to receive heart failure specific pharmacotherapy than non-frail counterparts. However, frail patients who received treatment had better clinical outcomes in terms of increased number of DAOH and reduced 30-day and 180-day mortality than those who did not receive treatment. There is a need for further studies to confirm our findings.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available on reasonable request from the corresponding author subject to approval by the ethics committee.

Ethics statement

Patient consent for publication

Not applicable

Ethics approval

The study protocol was reviewed by the Southern Adelaide Human Clinical Research Ethics Committee and determined to be exempt.

Conflicts of interest

The authors have no conflict of interest to declare.

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant

Author contribution

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

Yogesh Sharma: Conceptualization; Ethical approval; Project administration; Methodology; Statistical analyses; Resources; Writing- review and editing.

Chris Horwood: Data Curation; Methodology

Paul Hakendorf: Data Curation; Statistical analyses

Campbell Thompson: Conceptualization; Methodology; Writing-review and editing.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**:e146-e603. doi: 10.1161/cir.0000000000000485

2. Chen Y, Lawrence J, Stockbridge N. Days alive out of hospital in heart failure: Insights from the PARADIGM-HF and CHARM trials. *Am Heart J* 2021; **241**:108-19. doi: 10.1016/j.ahj.2021.03.016

3. Ariti CA, Cleland JG, Pocock SJ, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J* 2011; **162**:900-6. doi: 10.1016/j.ahj.2011.08.003

4. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. *J Am Coll Cardiol* 2018; **71**:1921-36. doi: 10.1016/j.jacc.2018.02.059

5. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008; **9**:71-2. doi: 10.1016/j.jamda.2007.11.005

6. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2017; **236**:283-9. doi: 10.1016/j.ijcard.2017.01.153

7. Leventhal MJ, Riegel B, Carlson B, et al. Negotiating compliance in heart failure: remaining issues and questions. *Eur J Cardiovasc Nurs* 2005; **4**:298-307. doi: 10.1016/j.ejcnurse.2005.04.001

8. Sze S, Pellicori P, Zhang J, et al. Effect of frailty on treatment, hospitalisation and death in patients with chronic heart failure. *Clin Res Cardiol* 2021; **110**:1249-58. doi: 10.1007/s00392-020-01792-w

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

9. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; **162**:1682-8. doi: 10.1001/archinte.162.15.1682

10. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003; **146**:250-7. doi: 10.1016/s0002-8703(03)00189-3

11. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; **171**:550-6. doi: 10.1001/archinternmed.2011.31

12. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; **23**:628-51. doi: 10.1016/j.cardfail.2017.04.014

13. Joshy G, Korda RJ, Abhayaratna WP, et al. Categorising major cardiovascular disease hospitalisations from routinely collected data. *Public Health Res Pract* 2015; **25**:e2531532. doi: 10.17061/phrp2531532

14. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; **391**:1775-82. doi: 10.1016/s0140-6736(18)30668-8

15. McAlister FA, Savu A, Ezekowitz JA, et al. The hospital frailty risk score in patients with heart failure is strongly associated with outcomes but less so with pharmacotherapy. *J Intern Med* 2020; **287**:322-32. doi: 10.1111/joim.13002

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Adams RJ, Howard N, Tucker G, et al. Effects of area deprivation on health risks and outcomes: a multilevel, cross-sectional, Australian population study. *Int J Public Health* 2009; **54**:183-92. doi: 10.1007/s00038-009-7113-x

17. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, et al. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. *J Am Geriatr Soc* 2014; **62**:342-6. doi: 10.1111/jgs.12635

18. Sharma Y, Thompson C, Kaambwa B, et al. Validity of the Malnutrition Universal Screening Tool (MUST) in Australian hospitalized acutely unwell elderly patients. *Asia Pac J Clin Nutr* 2017; **26**:994-1000. doi: 10.6133/apjcn.022017.15

19. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019; **21**:715-31. doi: 10.1002/ejhf.1494

20. Heckman JJ, Ichimura H, Todd PE. Matching As An Econometric Evaluation Estimator: Evidence from Evaluating a Job Training Programme. *The Review of Economic Studies* 1997; **64**:605-54. doi: 10.2307/2971733

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**:3083-107. doi: 10.1002/sim.3697

22. Badano LP, Di Lenarda A, Bellotti P, et al. Patients with chronic heart failure encountered in daily clinical practice are different from the "typical" patient enrolled in therapeutic trials. *Ital Heart J* 2003; **4**:84-91. doi:

23. Baxter AJ, Spensley A, Hildreth A, et al. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. *Heart* 2002; **88**:611-4. doi: 10.1136/heart.88.6.611

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24. Dulin BR, Krum H. Drug therapy of chronic heart failure in the elderly: the current state of clinical-trial evidence. *Curr Opin Cardiol* 2006; **21**:393-9. doi: 10.1097/01.hco.0000231411.15049.20

25. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**:215-25. doi: 10.1093/eurheartj/ehi115

26. Rochon PA, Tu JV, Anderson GM, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet* 2000; **356**:639-44. doi: 10.1016/s0140-6736(00)02606-4

27. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). *Eur J Heart Fail* 2004; **6**:453-61. doi: 10.1016/j.ejheart.2004.02.003

28. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**:993-1004. doi: 10.1056/NEJMoa1409077

29. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**:1995-2008. doi: 10.1056/NEJMoa1911303

30. Sze S, Zhang J, Pellicori P, et al. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017; **106**:533-41. doi: 10.1007/s00392-017-1082-5

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Supérieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1 Characteristics of patients who received heart failure specific pharmacotherapy compared to those who did not receive pharmacotherapy

Characteristic	Received heart failure specific pharmacotherapy	No heart failure specific pharmacotherapy	P value
Total	**n=4576**	**n=1158**	
Age years mean (SD)	75.4 (14.2)	79.3 (13.1)	<0.0001
Age ≥65 years n (%)	3678 (80.4)	1010 (87.2)	
Sex male n (%)	2408 (52.6)	566 (48.8)	0.023
Charlson index mean (SD)	2.3 (1.7)	2.5 (1.8)	<0.001
IRSD mean (SD)	5.4 (2.7)	5.5 (2.7)	0.448
Haemoglobin g/L mean (SD)	123.4	118.6	<0.001
Creatinine µmol/L mean (SD)	122.6 (70.8)	135.4 (94.2)	<0.001
NT-proBNP ng/L mean (SD)	1697.9 (5001.2)	2800.1 (6660.9)	<0.001
Troponin ng/L mean (SD)	0.9 (14.5)	3.6 (48.3)	0.0035
C-RP mg/L mean (SD)	24.9 (37.7)	31.6 (47.0)	<0.001
Albumin g/L mean (SD)	34.1 (4.9)	33.1 (5.3)	<0.001
HFRS mean (SD)	3.1 (3.6)	4.1 (4.3)	<0.001
MUST mean (SD)	0.5 (0.9)	0.6 (1.1)	0.348
Aspirin n (%)	1895 (41.4)	166 (14.3)	<0.001
Warfarin n (%)	1029 (22.5)	87 (7.5)	<0.001
DOACs n (%)	982 (21.5)	56 (4.8)	<0.001
Statins n (%)	2543 (55.6)	185 (15.9)	<0.001
ARNI n (%)	97 (2.1)	0	<0.001
SGLT2 inhibitors n (%)	89 (1.9)	3 (0.3)	<0.001
Digoxin n (%)	808 (17.7)	58 (5.0)	<0.001
Ivabradine n (%)	108 (2.4)	7 (0.6)	

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; NT-proBNP, N-terminal pro-brain natriuretic peptide; C-RP, C- reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2, sodium glucose co-transporter 2 inhibitor

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2 Baseline characteristics of frail heart failure patients according to receipt of heart failure specific pharmacotherapy

Characteristic	Received heart failure specific pharmacotherapy	No heart failure specific pharmacotherapy	P value
Total	**n=1025**	**n=381**	
Age years mean (SD)	79.2 (12.5)	80.8 (12.6)	0.025
Age ≥65 years n (%)	902 (88)	344 (92.3)	0.230
Sex male n (%)	513 (50.1)	195 (51.2)	0.706
Charlson index mean (SD)	3.3 (1.9)	3.3 (2.1)	0.875
IRSD mean (SD)	5.6 (2.7)	5.6 (2.8)	0.903
Haemoglobin g/L mean (SD)	118.8 (21.4)	115.3 (23.5)	0.008
Creatinine µmol/L mean (SD)	151.4 (84.2)	166.9 (108.9)	0.005
NT-proBNP ng/L mean (SD)	2552.7 (6545.7)	4465.0 (9311.8)	<0.001
Troponin ng/L mean (SD)	0.7 (9.2)	1.2 (11.4)	0.416
C-RP mg/L mean (SD)	33.9 (48.3)	43.3 (58.9)	0.006
Albumin g/L mean (SD)	32.9 (5.1)	31.5 (5.8)	<0.001
HFRS mean (SD)	8.5 (3.4)	9.1 (3.5)	0.004
MUST mean (SD)	0.7 (1.1)	0.9 (1.3)	0.145
Aspirin n (%)	399 (38.9)	50 (13.1)	<0.001
Warfarin n (%)	274 (26.7)	36 (9.5)	<0.001
DOACs n (%)	212 (20.7)	11 (2.9)	<0.001
Statins n (%)	517 (50.4)	60 (15.8)	<0.001
ARNI n (%)	22 (2.2)	0	0.004
SGLT2 inhibitors, n (%)	19 (1.9)	1 (0.3)	0.025
Digoxin n (%)	221 (21.6)	22 (5.8)	<0.001
Ivabradine n (%)	23 (2.2)	2 (0.5)	0.030

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; NT-proBNP, N-terminal pro-brain natriuretic peptide; C-RP, C- reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2, sodium glucose co-transporter 2 inhibitor

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Table 3 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
C-RP	-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

IRSD, index of relative socio-economic disadvantage; BNP, brain natriuretic peptide; C-RP, C-reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4 Clinical outcomes in frail depending upon use of heart failure specific pharmacotherapy

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

*LOS adjusted for inhospital deaths

CI, confidence interval; DAOH90, days alive and out of hospital at 90 days of discharge; IQR, interquartile range; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 5 Outcomes in frail heart failure patients after propensity score matching depending upon prescription of heart failure specific pharmacotherapy

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90	16.18	5.03	6.32-26.04	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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 6 Outcomes in frail heart failure patients using the average treatment effect on the treated depending upon 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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure legend/Caption

Figure 1 Study flow diagram

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

Figure 3 Kernel density graph showing propensity score matching

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

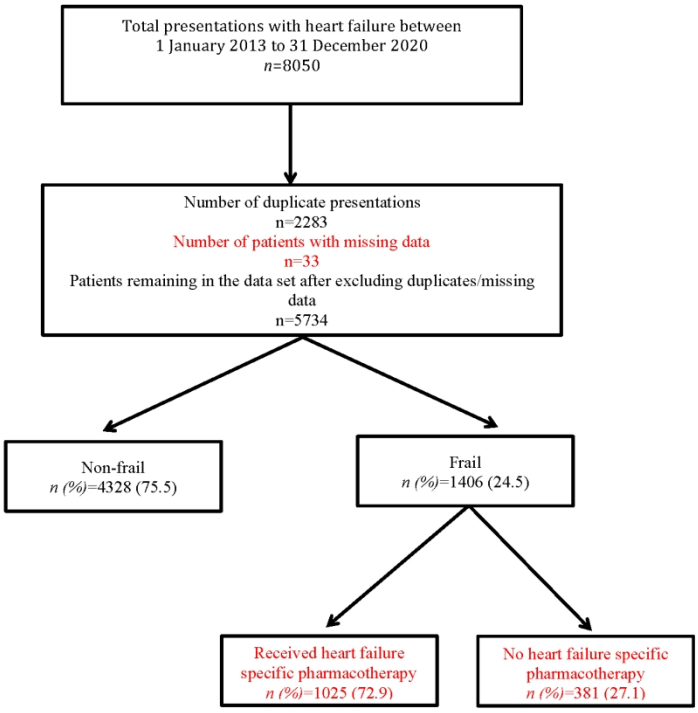

Figure 1 Study flow diagram

209x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

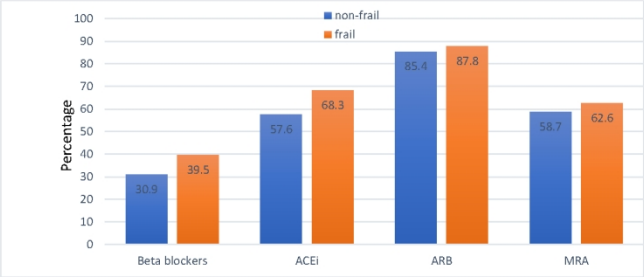

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

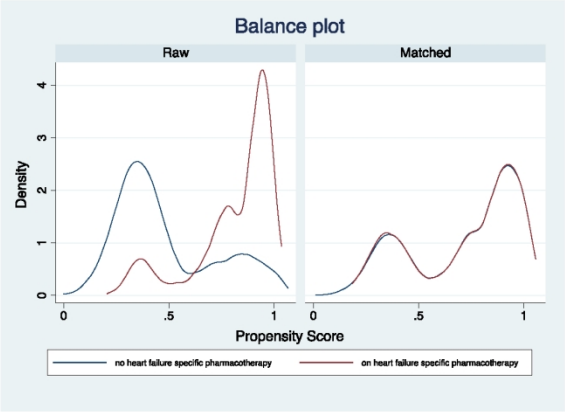

Figure 3 Kernel density graph showing propensity score matching

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6, 7	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7	
Bias	9	Describe any efforts to address potential sources of bias	8, 9	
Study size	10	Explain how the study size was arrived at		

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

For peer review only

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Supérieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059905.R2
Article Type:	Original research
Date Submitted by the Author:	04-Aug-2022
Complete List of Authors:	Sharma, Yogesh; Flinders Medical Centre Horwood, Chris; Flinders Medical Centre, Department of Clinical Epidemiology Hakendorf, Paul; Flinders Medical Centre, Department of Clinical Epidemiology Thompson, Campbell; University of Adelaide, Discipline of Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Geriatric medicine, Medical management
Keywords:	Heart failure < CARDIOLOGY, GERIATRIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult cardiology < CARDIOLOGY, INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Benefits of heart failure specific pharmacotherapy in frail hospitalised patients: an observational study

Yogesh Sharma[1,2] Chris Horwood[3] Paul Hakendorf[4] Campbell Thompson[5]

1. Associate Professor Yogesh Sharma

   MBBS, MD, FRACP, PhD

   College of Medicine and Public Health

   Flinders University, Adelaide, South Australia 5042

2. Senior Consultant Physician

   Division of Medicine, Cardiac & Critical Care

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Yogesh.Sharma@sa.gov.au

3. Mr Chris Horwood

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Chris.Horwood@sa.gov.au

4. Mr Paul Hakendorf

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

Flinders Medical Centre, Adelaide, South Australia 5042

Email: Paul.Hakendorf@sa.gov.au

5. Prof Campbell Thompson

MD, DPhil, FRACP, FRCP

Professor of Medicine

Discipline of Medicine

The University of Adelaide

Adelaide, South Australia 5005

Email: Campbell.Thompson@adelaide.edu.au

Corresponding Author

Associate Professor Yogesh Sharma

College of Medicine and Public Health

Flinders University

Adelaide, South Australia 5042

Email: Yogesh.Sharma@sa.gov.au

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives Up to 50% percent 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, angiotensin-converting-enzyme-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 ≥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 upon the receipt of HF-specific-pharmacotherapy.

Results Of 5734 HF patients admitted over a period of 8 years, 1406 (24.1%) 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 to 381 (27.1%) who did not receive any of these medications. Frail HF patients who did not receive HF-specific-

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

pharmacotherapy were significantly older, with higher creatinine and brain-natriuretic-peptide (BNP) but with lower haemoglobin and albumin levels (P<0.05) when compared to 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 6.32-26.04, P=0.001) than those who were not on treatment. Both 30-day (OR 0.30, 95% CI 0.23-0.39, P value<0.001) and 180-day mortality (OR 0.43, 95% CI 0.33-0.54, 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.

Key words: Heart failure, Pharmacotherapy, Mortality, Readmissions, Days alive and out of hospital

Trial registration no Australia and New Zealand Clinical Trial Registry ANZCTRN383195

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

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- 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

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant

Word count 3188

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Introduction

Heart failure (HF) is commonly associated with advancing age, with a prevalence of 6% in individuals between 65-79 years and up to 14% in those over the age of 80 years.[1] The annual rates of acute decompensated heart failure nearly triples in individuals over the age of 75 years when compared to those between 55-65 years, irrespective of factors such as sex and race.[1] Studies[2, 3] suggest that 15-20% of the HF patients who are discharged alive die within 90 days of hospitalisation. Heart failure 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.[4] Frailty, defined as a biologic syndrome with impaired physiological reserves that increases susceptibility to stressors[5] is common among patients with heart failure. A recent meta-analysis[6] 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[7]. In addition, despite a high prevalence of HF in older individuals, there is a dearth of research specifically targeting older frail patients.[4, 8] 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%.[9] 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.[10] Thus, the older HF patients commonly seen in clinical practice have a limited representation in

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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[11]. Despite these findings, guidelines[1, 12] still recommend targeted therapy for HF irrespective of age or co-morbidities.

We conducted a retrospective study to determine the impact of HF specific medications (beta blockers, angiotensin converting enzyme 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 ≥18 years of age who were hospitalised with HF over a period of eight years at two tertiary teaching hospitals, Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) in Adelaide, Australia. The study protocol was reviewed by the Southern Adelaide Human Research Ethics Committee and was determined to be exempt. 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 Tenth Revision Australian Modification (ICD-10-AM) code 150, which has been previously used to define HF [13]. In cases where patients had multiple presentations for heart failure 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 (EMR) of our central computer database. The data of all HF patients who were referred from the emergency

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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.[14] 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 overs a 2-year period to calculate the HFRS. HFRS is based upon 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 heart failure, atrial fibrillation, or coronary artery disease (CAD). Higher HFRS scores indicate a greater severity of frailty and, we classified patients with a HFRS score ≥5 as frail and those with HFRS scores of <5 as non-frail as has been done in previous studies.[14, 15]

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

particular, we determined whether patients received any or all of the heart failure 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 socio-economic status of the patients by using the index of relative socio-economic disadvantage (IRSD).[16] The comorbidity risk was determined by use of the Charlson comorbidity index (CCI)[17] and nutritional status was assessed by use of the Malnutrition Universal Screening Tool (MUST).[18] The severity of heart failure was assessed by use of the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[19] 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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-square 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 heart failure specific pharmacotherapy. To create propensity scores, we first used multivariable logistic regression model with receipt of heart failure specific pharmacotherapy as the outcome variable and the potential confounders as the explanatory variables. The seventeen confounding variables which were hypothesised to be associated both with the exposure and the outcomes included: age, age ≥ 65 years, sex, HFRS, MUST score, IRSD, CCI, haemoglobin, C-RP, 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[20] was employed to optimise trade-off between variance and bias. After kernel matching, the balance of covariates was assessed using the standardised mean differences, with >10% standard mean difference considered as significant between the two groups.[21] Kernel densities were plotted to examine the differences in continuous variables across matched treatment and comparison groups to

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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% confidence intervals were generated. All tests were two sided and a P value <0.05 was regarded as statistically significant. All statistical analyses were performed by use of STATA software version 17.0 (StataCorp, College Station, Texas, USA).

Results

There were 8050 admissions with heart failure between 1 January 2013 and 31 December 2020. After omitting multiple admissions and missing data, 5734 patients remained in the dataset, of whom, 1406 (24.1%) 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 heart failure 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 heart failure specific pharmacotherapy. Baseline characteristics differed among patients who received heart failure specific pharmacotherapy compared to those who did not receive these medications **(Table 1)**. Patients who received heart failure specific pharmacotherapy were more likely to be younger males, with a lower CCI, creatinine, BNP, troponin, albumin, and

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CRP levels but there was no difference with regards to their nutritional or socio-economic status **(Table 1)**. When compared to non-frail patients, frail patients were significantly less likely to be prescribed heart failure specific pharmacotherapy (72.9% vs. 82.1%, P<0.001). In terms of individual heart failure 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 to frail patients**. (Figure 2)**

Of 1406 frail HF patients, 1025 (72.9%) received heart failure specific pharmacotherapy compared to 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 compared to those frail patients who received treatment **(Table 2).**

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 a standardised mean difference (SMR) of <10% **(Table 3 & Figure 3)**.

Clinical outcomes in frail patients depending upon receipt of heart failure specific pharmacotherapy

The mean (SD) DAOH was significantly increased in frail HF patients who received HF specific pharmacotherapy compared to those who did not receive treatment (67.7 (33.1) days vs. 47.1 (40.9) days, P value <0.001) and these patients had 4.9-fold higher odds of having an increased DAOH compared to those who did not receive treatment (OR 4.90, 95% CI 3.6-4-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

6.58, P value< 0.001) **(Table 4)**. The differences in the DAOH90 remained statistically significant (P<0.05) irrespective of gender, age (<65 years or ≥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 to those who did not receive treatment (coefficient 16.18, robust standard error 5.03, 95% CI 6.32-26.04, P=0.001) **(Table 5).** The inhospital, 30-day and 180-day mortality rates were significantly lower among frail HF patients who received HF specific pharmacotherapy when compared to those frail patients who did not receive treatment (P<0.05) **(Table 4 and 5).** At 30 days following hospital discharge, the odds of death were 70% lower among those frail patients who received heart failure specific pharmacotherapy compared to 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 inhospital 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 heart failure specific pharmacotherapy (P>0.05) **(Tables 3 and 4).**

Sensitivity analysis

Sensitivity analyses with determination of the ATET confirmed that DAOH at 90 days following discharge were significantly increased and inhospital, 30-day and 180-day mortality were significantly reduced in frail patients who received heart failure 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 6).**

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Discussion

The results of this study indicate that almost a quarter of patients who were hospitalised with heart failure were frail. Overall, patients who received heart failure specific pharmacotherapy were more likely to be younger males with a lower CCI and creatinine 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 inhospital, 30-day and 180-day 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.[11] 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.[9, 10, 22] 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 heart failure specific medications and confirm the results of a recent study[8] which included 291 HF patients with reduced ejection fraction (HFrEF) attending a community clinic, and this study also found that compared to 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 sub-optimal

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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.[4, 23, 24]

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. Heart failure with preserved ejection fraction (HFpEF) is commonly associated with comorbidities such as hypertension, atrial fibrillation, coronary artery disease, obesity, anaemia, diabetes, chronic kidney disease and sleep-disordered breathing.[12, 19] The above-mentioned comorbidities are also associated with frailty.[6] 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.[12] In addition, very few clinical trials have included frail older patients who are more likely to have comorbidities associated with HFpEF. The SENIORS trial[25] found that Nebivolol reduced mortality and hospital admissions in older HF patients, while another study[26] 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 suggest that beta blocker therapy in patients with heart failure with preserved ejection fraction (HFpEF) is associated with an improvement in echocardiogram parameters[27] and guidelines[12] suggest use of these agents as a heart rate lowering therapy, despite a lack of proven reduction in mortality. Two recent HF clinical trials the PARADIGM HF and the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

DAPA HF, which investigated the role of Sacubitril/Valsartan and Dapagliflozin in HF, although, have enrolled only a minority of older patients (≥75 years) (19% and 24%, respectively) have found that there was no evidence of lesser benefits with these agents in older patients.[28, 29]

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 heart failure specific treatments will be difficult to prove. As the prevalence of frailty is expected to increase with an aging population[30], the management of frail heart failure patients will remain a significant medical challenge. The results of our study are hypothesis generating in that there may be potential benefits of prescribing heart failure 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 heart failure. 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.[4, 8]

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, heart failure specific medications were stopped during the

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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 heart failure was judged from BNP levels.[19] Over the course of study, newer medications for HF were available which could have influenced clinical outcomes. Unfortuantely, 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.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available on reasonable request from the corresponding author subject to approval by the ethics committee.

Ethics statement

Patient consent for publication

Not applicable

Ethics approval

The study protocol was reviewed by the Southern Adelaide Human Clinical Research Ethics Committee

Conflicts of interest

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The authors have no conflict of interest to declare.

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant (Grant no 2021).

Author contribution

YS and CT conceptualised and supervised the study. YS prepared the manuscript. CH and PH were involved in data curation. YS and CH performed statistical analyses. YS and CT critically revised the manuscript. All authors approved the final manuscript.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**:e146-e603. doi: 10.1161/cir.0000000000000485

2. Chen Y, Lawrence J, Stockbridge N. Days alive out of hospital in heart failure: Insights from the PARADIGM-HF and CHARM trials. *Am Heart J* 2021; **241**:108-19. doi: 10.1016/j.ahj.2021.03.016

3. Ariti CA, Cleland JG, Pocock SJ, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J* 2011; **162**:900-6. doi: 10.1016/j.ahj.2011.08.003

4. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. *J Am Coll Cardiol* 2018; **71**:1921-36. doi: 10.1016/j.jacc.2018.02.059

5. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008; **9**:71-2. doi: 10.1016/j.jamda.2007.11.005

6. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2017; **236**:283-9. doi: 10.1016/j.ijcard.2017.01.153

7. Leventhal MJ, Riegel B, Carlson B, et al. Negotiating compliance in heart failure: remaining issues and questions. *Eur J Cardiovasc Nurs* 2005; **4**:298-307. doi: 10.1016/j.ejcnurse.2005.04.001

8. Sze S, Pellicori P, Zhang J, et al. Effect of frailty on treatment, hospitalisation and death in patients with chronic heart failure. *Clin Res Cardiol* 2021; **110**:1249-58. doi: 10.1007/s00392-020-01792-w

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

9. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; **162**:1682-8. doi: 10.1001/archinte.162.15.1682

10. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003; **146**:250-7. doi: 10.1016/s0002-8703(03)00189-3

11. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; **171**:550-6. doi: 10.1001/archinternmed.2011.31

12. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; **23**:628-51. doi: 10.1016/j.cardfail.2017.04.014

13. Joshy G, Korda RJ, Abhayaratna WP, et al. Categorising major cardiovascular disease hospitalisations from routinely collected data. *Public Health Res Pract* 2015; **25**:e2531532. doi: 10.17061/phrp2531532

14. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; **391**:1775-82. doi: 10.1016/s0140-6736(18)30668-8

15. McAlister FA, Savu A, Ezekowitz JA, et al. The hospital frailty risk score in patients with heart failure is strongly associated with outcomes but less so with pharmacotherapy. *J Intern Med* 2020; **287**:322-32. doi: 10.1111/joim.13002

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

16. Adams RJ, Howard N, Tucker G, et al. Effects of area deprivation on health risks and outcomes: a multilevel, cross-sectional, Australian population study. *Int J Public Health* 2009; **54**:183-92. doi: 10.1007/s00038-009-7113-x

17. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, et al. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. *J Am Geriatr Soc* 2014; **62**:342-6. doi: 10.1111/jgs.12635

18. Sharma Y, Thompson C, Kaambwa B, et al. Validity of the Malnutrition Universal Screening Tool (MUST) in Australian hospitalized acutely unwell elderly patients. *Asia Pac J Clin Nutr* 2017; **26**:994-1000. doi: 10.6133/apjcn.022017.15

19. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019; **21**:715-31. doi: 10.1002/ejhf.1494

20. Heckman JJ, Ichimura H, Todd PE. Matching As An Econometric Evaluation Estimator: Evidence from Evaluating a Job Training Programme. *The Review of Economic Studies* 1997; **64**:605-54. doi: 10.2307/2971733

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**:3083-107. doi: 10.1002/sim.3697

22. Badano LP, Di Lenarda A, Bellotti P, et al. Patients with chronic heart failure encountered in daily clinical practice are different from the "typical" patient enrolled in therapeutic trials. *Ital Heart J* 2003; **4**:84-91. doi:

23. Baxter AJ, Spensley A, Hildreth A, et al. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. *Heart* 2002; **88**:611-4. doi: 10.1136/heart.88.6.611

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

24. Dulin BR, Krum H. Drug therapy of chronic heart failure in the elderly: the current state of clinical-trial evidence. *Curr Opin Cardiol* 2006; **21**:393-9. doi: 10.1097/01.hco.0000231411.15049.20

25. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**:215-25. doi: 10.1093/eurheartj/ehi115

26. Rochon PA, Tu JV, Anderson GM, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet* 2000; **356**:639-44. doi: 10.1016/s0140-6736(00)02606-4

27. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). *Eur J Heart Fail* 2004; **6**:453-61. doi: 10.1016/j.ejheart.2004.02.003

28. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**:993-1004. doi: 10.1056/NEJMoa1409077

29. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**:1995-2008. doi: 10.1056/NEJMoa1911303

30. Sze S, Zhang J, Pellicori P, et al. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017; **106**:533-41. doi: 10.1007/s00392-017-1082-5

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Supérieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1 Characteristics of patients who received heart failure specific pharmacotherapy compared to those who did not receive pharmacotherapy

Characteristic	Received heart failure specific pharmacotherapy	No heart failure specific pharmacotherapy	P value
Total	**n=4576**	**n=1158**	
Age years mean (SD)	75.4 (14.2)	79.3 (13.1)	<0.0001
Age ≥65 years n (%)	3678 (80.4)	1010 (87.2)	
Sex male n (%)	2408 (52.6)	566 (48.8)	0.023
Charlson index mean (SD)	2.3 (1.7)	2.5 (1.8)	<0.001
IRSD mean (SD)	5.4 (2.7)	5.5 (2.7)	0.448
Haemoglobin g/L mean (SD)	123.4	118.6	<0.001
Creatinine µmol/L mean (SD)	122.6 (70.8)	135.4 (94.2)	<0.001
NT-proBNP ng/L mean (SD)	1697.9 (5001.2)	2800.1 (6660.9)	<0.001
Troponin ng/L mean (SD)	0.9 (14.5)	3.6 (48.3)	0.0035
C-RP mg/L mean (SD)	24.9 (37.7)	31.6 (47.0)	<0.001
Albumin g/L mean (SD)	34.1 (4.9)	33.1 (5.3)	<0.001
HFRS mean (SD)	3.1 (3.6)	4.1 (4.3)	<0.001
MUST mean (SD)	0.5 (0.9)	0.6 (1.1)	0.348
Aspirin n (%)	1895 (41.4)	166 (14.3)	<0.001
Warfarin n (%)	1029 (22.5)	87 (7.5)	<0.001
DOACs n (%)	982 (21.5)	56 (4.8)	<0.001
Statins n (%)	2543 (55.6)	185 (15.9)	<0.001
ARNI n (%)	97 (2.1)	0	<0.001
SGLT2 inhibitors n (%)	89 (1.9)	3 (0.3)	<0.001
Digoxin n (%)	808 (17.7)	58 (5.0)	<0.001
Ivabradine n (%)	108 (2.4)	7 (0.6)	

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; NT-proBNP, N-terminal pro-brain natriuretic peptide; C-RP, C- reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2, sodium glucose co-transporter 2 inhibitor

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2 Baseline characteristics of frail heart failure patients according to receipt of heart failure specific pharmacotherapy

Characteristic	Received heart failure specific pharmacotherapy	No heart failure specific pharmacotherapy	P value
Total	**n=1025**	**n=381**	
Age years mean (SD)	79.2 (12.5)	80.8 (12.6)	0.025
Age ≥65 years n (%)	902 (88)	344 (92.3)	0.230
Sex male n (%)	513 (50.1)	195 (51.2)	0.706
Charlson index mean (SD)	3.3 (1.9)	3.3 (2.1)	0.875
IRSD mean (SD)	5.6 (2.7)	5.6 (2.8)	0.903
Haemoglobin g/L mean (SD)	118.8 (21.4)	115.3 (23.5)	0.008
Creatinine µmol/L mean (SD)	151.4 (84.2)	166.9 (108.9)	0.005
NT-proBNP ng/L mean (SD)	2552.7 (6545.7)	4465.0 (9311.8)	<0.001
Troponin ng/L mean (SD)	0.7 (9.2)	1.2 (11.4)	0.416
C-RP mg/L mean (SD)	33.9 (48.3)	43.3 (58.9)	0.006
Albumin g/L mean (SD)	32.9 (5.1)	31.5 (5.8)	<0.001
HFRS mean (SD)	8.5 (3.4)	9.1 (3.5)	0.004
MUST mean (SD)	0.7 (1.1)	0.9 (1.3)	0.145
Aspirin n (%)	399 (38.9)	50 (13.1)	<0.001
Warfarin n (%)	274 (26.7)	36 (9.5)	<0.001
DOACs n (%)	212 (20.7)	11 (2.9)	<0.001
Statins n (%)	517 (50.4)	60 (15.8)	<0.001
ARNI n (%)	22 (2.2)	0	0.004
SGLT2 inhibitors, n (%)	19 (1.9)	1 (0.3)	0.025
Digoxin n (%)	221 (21.6)	22 (5.8)	<0.001
Ivabradine n (%)	23 (2.2)	2 (0.5)	0.030

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; NT-proBNP, N-terminal pro-brain natriuretic peptide; C-RP, C- reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2, sodium glucose co-transporter 2 inhibitor

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Table 3 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
C-RP	-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

IRSD, index of relative socio-economic disadvantage; BNP, brain natriuretic peptide; C-RP, C-reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4 Clinical outcomes in frail depending upon use of heart failure specific pharmacotherapy

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

*LOS adjusted for inhospital deaths

CI, confidence interval; DAOH90, days alive and out of hospital at 90 days of discharge; IQR, interquartile range; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 5 Outcomes in frail heart failure patients after propensity score matching depending upon prescription of heart failure specific pharmacotherapy

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90	16.18	5.03	6.32-26.04	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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 6 Outcomes in frail heart failure patients using the average treatment effect on the treated depending upon 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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure legend/Caption

Figure 1 Study flow diagram

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

Figure 3 Kernel density graph showing propensity score matching

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

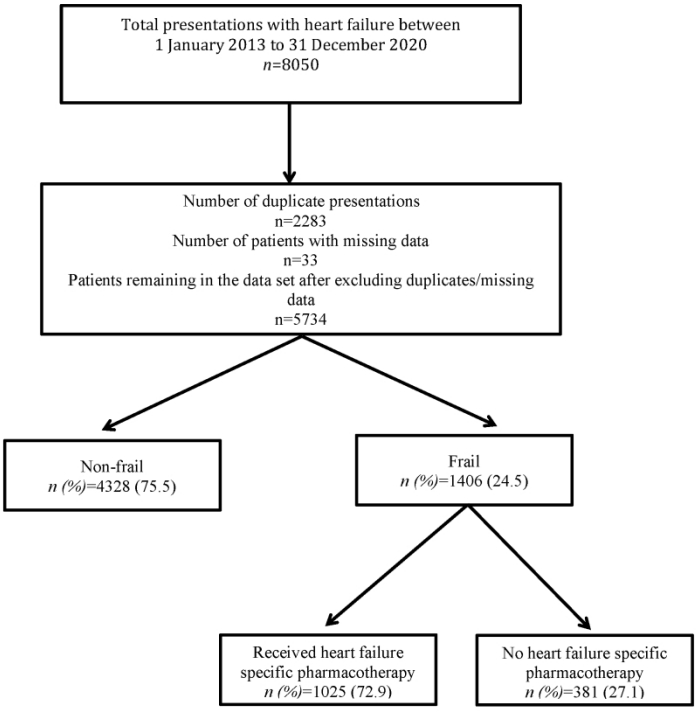

Figure 1 Study flow diagram

209x297mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

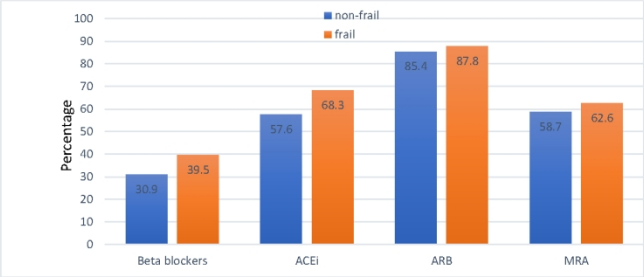

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

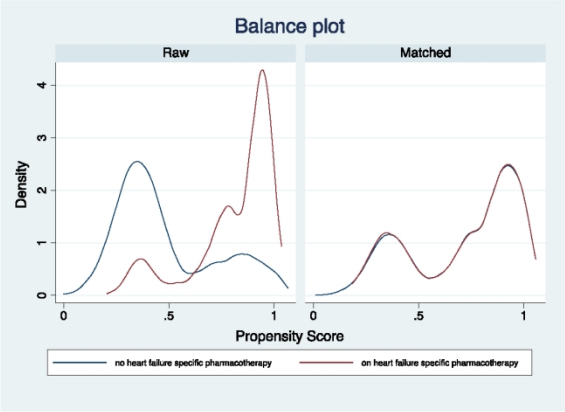

Figure 3 Kernel density graph showing propensity score matching

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6, 7	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7	
Bias	9	Describe any efforts to address potential sources of bias	8, 9	
Study size	10	Explain how the study size was arrived at		

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

For peer review only

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Supérieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059905.R3
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2022
Complete List of Authors:	Sharma, Yogesh; Flinders Medical Centre Horwood, Chris; Flinders Medical Centre, Department of Clinical Epidemiology Hakendorf, Paul; Flinders Medical Centre, Department of Clinical Epidemiology Thompson, Campbell; University of Adelaide, Discipline of Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Geriatric medicine, Medical management
Keywords:	Heart failure < CARDIOLOGY, GERIATRIC MEDICINE, GENERAL MEDICINE (see Internal Medicine), Adult cardiology < CARDIOLOGY, INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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

Yogesh Sharma[1,2] Chris Horwood[3] Paul Hakendorf[4] Campbell Thompson[5]

1. Associate Professor Yogesh Sharma

   MBBS, MD, FRACP, PhD

   College of Medicine and Public Health

   Flinders University, Adelaide, South Australia 5042

2. Senior Consultant Physician

   Division of Medicine, Cardiac & Critical Care

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Yogesh.Sharma@sa.gov.au

3. Mr Chris Horwood

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

   Flinders Medical Centre, Adelaide, South Australia 5042

   Email: Chris.Horwood@sa.gov.au

4. Mr Paul Hakendorf

   BSc, MPH

   Clinical Epidemiologist

   Department of Clinical Epidemiology

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

Flinders Medical Centre, Adelaide, South Australia 5042

Email: Paul.Hakendorf@sa.gov.au

5. Prof Campbell Thompson

MD, DPhil, FRACP, FRCP

Professor of Medicine

Discipline of Medicine

The University of Adelaide

Adelaide, South Australia 5005

Email: Campbell.Thompson@adelaide.edu.au

Corresponding Author

Associate Professor Yogesh Sharma

College of Medicine and Public Health

Flinders University

Adelaide, South Australia 5042

Email: Yogesh.Sharma@sa.gov.au

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Abstract

Objectives Up to 50% percent 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, angiotensin-converting-enzyme-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 ≥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 upon the receipt of HF-specific-pharmacotherapy.

Results Of 5734 HF patients admitted over a period of 8 years, 1406 (24.1%) 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 to 381 (27.1%) who did not receive any of these medications. Frail HF patients who did not receive HF-specific-

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

pharmacotherapy were significantly older, with higher creatinine and brain-natriuretic-peptide (BNP) but with lower haemoglobin and albumin levels (P<0.05) when compared to 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 6.32-26.04, P=0.001) than those who were not on treatment. Both 30-day (OR 0.30, 95% CI 0.23-0.39, P value<0.001) and 180-day mortality (OR 0.43, 95% CI 0.33-0.54, 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.

Key words: Heart failure, Pharmacotherapy, Mortality, Readmissions, Days alive and out of hospital

Trial registration no Australia and New Zealand Clinical Trial Registry ANZCTRN383195

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

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- 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

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant

Word count 3188

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Introduction

Heart failure (HF) is commonly associated with advancing age, with a prevalence of 6% in individuals between 65-79 years and up to 14% in those over the age of 80 years.[1] The annual rates of acute decompensated heart failure nearly triples in individuals over the age of 75 years when compared to those between 55-65 years, irrespective of factors such as sex and race.[1] Studies[2, 3] suggest that 15-20% of the HF patients who are discharged alive die within 90 days of hospitalisation. Heart failure 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.[4] Frailty, defined as a biologic syndrome with impaired physiological reserves that increases susceptibility to stressors[5] is common among patients with heart failure. A recent meta-analysis[6] 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[7]. In addition, despite a high prevalence of HF in older individuals, there is a dearth of research specifically targeting older frail patients.[4, 8] 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%.[9] 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.[10] Thus, the older HF patients commonly seen in clinical practice have a limited representation in

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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[11]. Despite these findings, guidelines[1, 12] still recommend targeted therapy for HF irrespective of age or co-morbidities.

We conducted a retrospective study to determine the impact of HF specific medications (beta blockers, angiotensin converting enzyme 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 ≥18 years of age who were hospitalised with HF over a period of eight years at two tertiary teaching hospitals, Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) in Adelaide, Australia. The study protocol was reviewed by the Southern Adelaide Human Research Ethics Committee and was determined to be exempt. 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 Tenth Revision Australian Modification (ICD-10-AM) code 150, which has been previously used to define HF [13]. In cases where patients had multiple presentations for heart failure 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 (EMR) of our central computer database. The data of all HF patients who were referred from the emergency

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

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.[14] 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 overs a 2-year period to calculate the HFRS. HFRS is based upon 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 heart failure, atrial fibrillation, or coronary artery disease (CAD). Higher HFRS scores indicate a greater severity of frailty and, we classified patients with a HFRS score ≥5 as frail and those with HFRS scores of <5 as non-frail as has been done in previous studies.[14, 15]

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

particular, we determined whether patients received any or all of the heart failure 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 socio-economic status of the patients by using the index of relative socio-economic disadvantage (IRSD).[16] The comorbidity risk was determined by use of the Charlson comorbidity index (CCI)[17] and nutritional status was assessed by use of the Malnutrition Universal Screening Tool (MUST).[18] The severity of heart failure was assessed by use of the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[19] 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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-square 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 heart failure specific pharmacotherapy. To create propensity scores, we first used multivariable logistic regression model with receipt of heart failure specific pharmacotherapy as the outcome variable and the potential confounders as the explanatory variables. The seventeen confounding variables which were hypothesised to be associated both with the exposure and the outcomes included: age, age ≥ 65 years, sex, HFRS, MUST score, IRSD, CCI, haemoglobin, C-RP, 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[20] was employed to optimise trade-off between variance and bias. After kernel matching, the balance of covariates was assessed using the standardised mean differences, with >10% standard mean difference considered as significant between the two groups.[21] Kernel densities were plotted to examine the differences in continuous variables across matched treatment and comparison groups to

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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% confidence intervals were generated. All tests were two sided and a P value <0.05 was regarded as statistically significant. All statistical analyses were performed by use of STATA software version 17.0 (StataCorp, College Station, Texas, USA).

Results

There were 8050 admissions with heart failure between 1 January 2013 and 31 December 2020. After omitting multiple admissions and missing data, 5734 patients remained in the dataset, of whom, 1406 (24.1%) 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 heart failure 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 heart failure specific pharmacotherapy. Baseline characteristics differed among patients who received heart failure specific pharmacotherapy compared to those who did not receive these medications **(Table 1)**. Patients who received heart failure specific pharmacotherapy were more likely to be younger, with a lower creatinine, BNP, and CRP levels and higher

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

haemoglobin and albumin levels but there was no difference with regards to their nutritional or socio-economic status **(Table 1)**. When compared to non-frail patients, frail patients were significantly less likely to be prescribed heart failure specific pharmacotherapy (72.9% vs. 82.1%, P<0.001). In terms of individual heart failure 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 to frail patients**. (Figure 2)**

Of 1406 frail HF patients, 1025 (72.9%) received heart failure specific pharmacotherapy compared to 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 compared to 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 a standardised mean difference (SMR) of <10% **(Table 2 & Figure 3)**.

Clinical outcomes in frail patients depending upon receipt of heart failure specific pharmacotherapy

The mean (SD) DAOH was significantly increased in frail HF patients who received HF specific pharmacotherapy compared to those who did not receive treatment (67.7 (33.1) days vs. 47.1 (40.9) days, P value <0.001) and these patients had 4.9-fold higher odds of having an increased DAOH compared to those who did not receive treatment (OR 4.90, 95% CI 3.6-4-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

6.58, P value< 0.001) **(Table 3)**. The differences in the DAOH90 remained statistically significant (P<0.05) irrespective of gender, age (<65 years or ≥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 to those who did not receive treatment (coefficient 16.18, robust standard error 5.03, 95% CI 6.32-26.04, P=0.001) **(Table 4).** The inhospital, 30-day and 180-day mortality rates were significantly lower among frail HF patients who received HF specific pharmacotherapy when compared to those frail patients who did not receive treatment (P<0.05) **(Table 3 and 4).** At 30 days following hospital discharge, the odds of death were 70% lower among those frail patients who received heart failure specific pharmacotherapy compared to 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 inhospital 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 heart failure specific pharmacotherapy (P>0.05) **(Tables 3 and 4).**

Sensitivity analysis

Sensitivity analyses with determination of the ATET confirmed that DAOH at 90 days following discharge were significantly increased and inhospital, 30-day and 180-day mortality were significantly reduced in frail patients who received heart failure 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).**

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Discussion

The results of this study indicate that almost a quarter of patients who were hospitalised with heart failure were frail. Overall, patients who received heart failure 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 inhospital, 30-day and 180-day 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.[11] 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.[9, 10, 22] 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 heart failure specific medications and confirm the results of a recent study[8] which included 291 HF patients with reduced ejection fraction (HFrEF) attending a community clinic, and this study also found that compared to 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

study also found that those who did receive treatment were more likely to receive sub-optimal 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.[4, 23, 24]

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. Heart failure with preserved ejection fraction (HFpEF) is commonly associated with comorbidities such as hypertension, atrial fibrillation, coronary artery disease, obesity, anaemia, diabetes, chronic kidney disease and sleep-disordered breathing.[12, 19] The above-mentioned comorbidities are also associated with frailty.[6] 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.[12] In addition, very few clinical trials have included frail older patients who are more likely to have comorbidities associated with HFpEF. The SENIORS trial[25] found that Nebivolol reduced mortality and hospital admissions in older HF patients, while another study[26] 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 suggest that beta blocker therapy in patients with heart failure with preserved ejection fraction (HFpEF) is associated with an improvement in echocardiogram parameters[27] and guidelines[12] suggest use of these agents as a heart rate lowering therapy, despite a lack of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

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 (≥75 years) (19% and 24%, respectively) have found that there was no evidence of lesser benefits with these agents in older patients.[28, 29]

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 heart failure specific treatments will be difficult to prove. As the prevalence of frailty is expected to increase with an aging population[30], the management of frail heart failure patients will remain a significant medical challenge. The results of our study are hypothesis generating in that there may be potential benefits of prescribing heart failure 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 heart failure. 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.[4, 8]

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

possible that in some patients, heart failure 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 heart failure was judged from BNP levels.[19] Over the course of study, newer medications for HF were available which could have influenced clinical outcomes. Unfortuantely, 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.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available on reasonable request from the corresponding author subject to approval by the ethics committee.

Ethics statement

Patient consent for publication

Not applicable

Ethics approval

The study protocol was reviewed by the Southern Adelaide Human Clinical Research Ethics Committee

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Conflicts of interest

The authors have no conflict of interest to declare.

Funding

This research was funded by the Southern Adelaide Local Health Network (SALHN) Research Enquiry Grant (Grant no 2021).

Author contribution

YS and CT conceptualised and supervised the study. YS prepared the manuscript. CH and PH were involved in data curation. YS and CH performed statistical analyses. YS and CT critically revised the manuscript. All authors approved the final manuscript.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017; **135**:e146-e603. doi: 10.1161/cir.0000000000000485

2. Chen Y, Lawrence J, Stockbridge N. Days alive out of hospital in heart failure: Insights from the PARADIGM-HF and CHARM trials. *Am Heart J* 2021; **241**:108-19. doi: 10.1016/j.ahj.2021.03.016

3. Ariti CA, Cleland JG, Pocock SJ, et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. *Am Heart J* 2011; **162**:900-6. doi: 10.1016/j.ahj.2011.08.003

4. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. *J Am Coll Cardiol* 2018; **71**:1921-36. doi: 10.1016/j.jacc.2018.02.059

5. Abellan van Kan G, Rolland YM, Morley JE, et al. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008; **9**:71-2. doi: 10.1016/j.jamda.2007.11.005

6. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: A systematic review and meta-analysis. *Int J Cardiol* 2017; **236**:283-9. doi: 10.1016/j.ijcard.2017.01.153

7. Leventhal MJ, Riegel B, Carlson B, et al. Negotiating compliance in heart failure: remaining issues and questions. *Eur J Cardiovasc Nurs* 2005; **4**:298-307. doi: 10.1016/j.ejcnurse.2005.04.001

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

8. Sze S, Pellicori P, Zhang J, et al. Effect of frailty on treatment, hospitalisation and death in patients with chronic heart failure. *Clin Res Cardiol* 2021; **110**:1249-58. doi: 10.1007/s00392-020-01792-w

9. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; **162**:1682-8. doi: 10.1001/archinte.162.15.1682

10. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003; **146**:250-7. doi: 10.1016/s0002-8703(03)00189-3

11. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med* 2011; **171**:550-6. doi: 10.1001/archinternmed.2011.31

12. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail* 2017; **23**:628-51. doi: 10.1016/j.cardfail.2017.04.014

13. Joshy G, Korda RJ, Abhayaratna WP, et al. Categorising major cardiovascular disease hospitalisations from routinely collected data. *Public Health Res Pract* 2015; **25**:e2531532. doi: 10.17061/phrp2531532

14. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018; **391**:1775-82. doi: 10.1016/s0140-6736(18)30668-8

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

15. McAlister FA, Savu A, Ezekowitz JA, et al. The hospital frailty risk score in patients with heart failure is strongly associated with outcomes but less so with pharmacotherapy. *J Intern Med* 2020; **287**:322-32. doi: 10.1111/joim.13002

16. Adams RJ, Howard N, Tucker G, et al. Effects of area deprivation on health risks and outcomes: a multilevel, cross-sectional, Australian population study. *Int J Public Health* 2009; **54**:183-92. doi: 10.1007/s00038-009-7113-x

17. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, et al. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: a prospective cohort study. *J Am Geriatr Soc* 2014; **62**:342-6. doi: 10.1111/jgs.12635

18. Sharma Y, Thompson C, Kaambwa B, et al. Validity of the Malnutrition Universal Screening Tool (MUST) in Australian hospitalized acutely unwell elderly patients. *Asia Pac J Clin Nutr* 2017; **26**:994-1000. doi: 10.6133/apjcn.022017.15

19. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019; **21**:715-31. doi: 10.1002/ejhf.1494

20. Heckman JJ, Ichimura H, Todd PE. Matching As An Econometric Evaluation Estimator: Evidence from Evaluating a Job Training Programme. *The Review of Economic Studies* 1997; **64**:605-54. doi: 10.2307/2971733

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**:3083-107. doi: 10.1002/sim.3697

22. Badano LP, Di Lenarda A, Bellotti P, et al. Patients with chronic heart failure encountered in daily clinical practice are different from the "typical" patient enrolled in therapeutic trials. *Ital Heart J* 2003; **4**:84-91. doi:

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

23. Baxter AJ, Spensley A, Hildreth A, et al. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. *Heart* 2002; **88**:611-4. doi: 10.1136/heart.88.6.611

24. Dulin BR, Krum H. Drug therapy of chronic heart failure in the elderly: the current state of clinical-trial evidence. *Curr Opin Cardiol* 2006; **21**:393-9. doi: 10.1097/01.hco.0000231411.15049.20

25. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**:215-25. doi: 10.1093/eurheartj/ehi115

26. Rochon PA, Tu JV, Anderson GM, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet* 2000; **356**:639-44. doi: 10.1016/s0140-6736(00)02606-4

27. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). *Eur J Heart Fail* 2004; **6**:453-61. doi: 10.1016/j.ejheart.2004.02.003

28. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**:993-1004. doi: 10.1056/NEJMoa1409077

29. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; **381**:1995-2008. doi: 10.1056/NEJMoa1911303

30. Sze S, Zhang J, Pellicori P, et al. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017; **106**:533-41. doi: 10.1007/s00392-017-1082-5

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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	**n=3551**	**n=777**		**n=1025**	**n=381**	
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
C-RP 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

SD, standard deviation; IRSD, index of relative socio-economic disadvantage; NT-proBNP, N-terminal pro-brain natriuretic peptide; C-RP, C- reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT2, sodium glucose co-transporter 2 inhibitor

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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
C-RP	-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

IRSD, index of relative socio-economic disadvantage; BNP, brain natriuretic peptide; C-RP, C-reactive protein; HFRS, hospital frailty risk score; MUST, malnutrition universal screening tool; DOACs, direct oral anticoagulants

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3 Clinical outcomes in frail depending upon use of heart failure specific pharmacotherapy

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

*LOS adjusted for inhospital deaths

CI, confidence interval; DAOH90, days alive and out of hospital at 90 days of discharge; IQR, interquartile range; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

Outcome	Coefficient	Robust SE	95% CI	P value
DAOH90	16.18	5.03	6.32-26.04	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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 5 Outcomes in frail heart failure patients using the average treatment effect on the treated depending upon 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

SE, standard error; CI, confidence interval; DAOH90, days alive and out of hospital at 90 days following discharge; LOS, length of hospital stay

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Figure legend/Caption

Figure 1 Study flow diagram

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

Figure 3 Kernel density graph showing propensity score matching

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

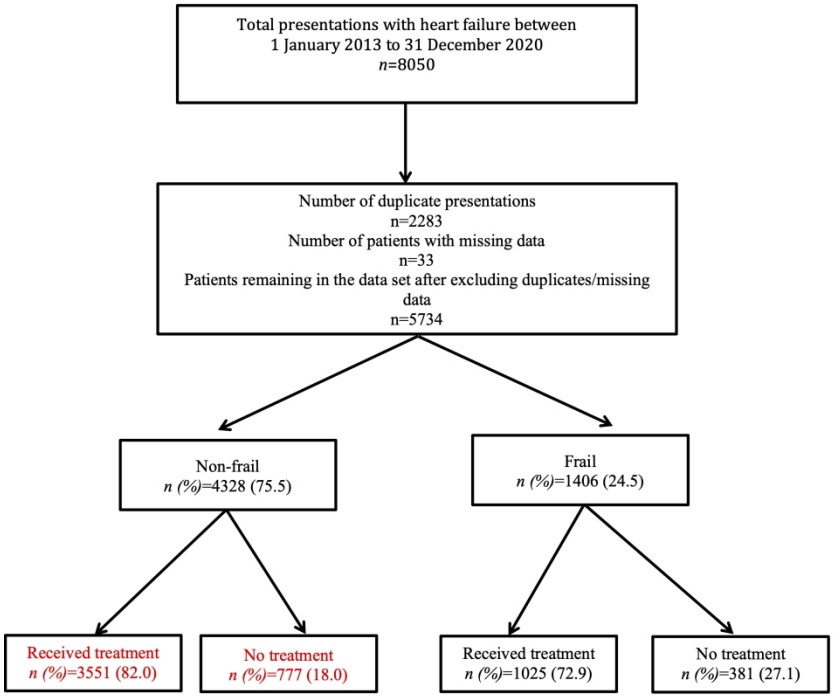

Figure 1 Study flow diagram

874x1237mm (72 x 72 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

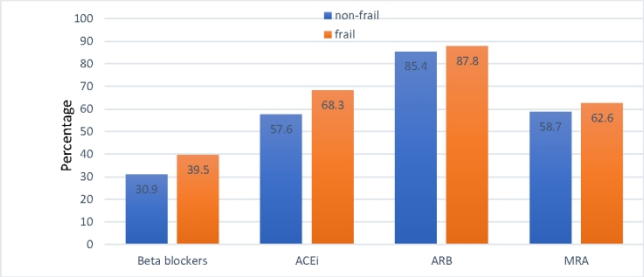

Figure 2 Proportion of heart failure patients not on heart failure specific pharmacotherapy depending upon frailty status

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

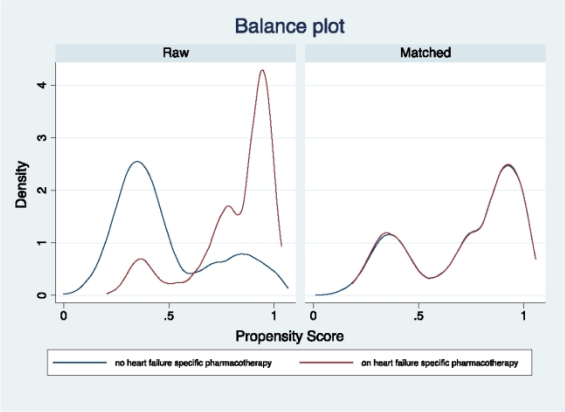

Figure 3 Kernel density graph showing propensity score matching

210x297mm (200 x 200 DPI)

BMJ Open: first published as 10.1136/bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6, 7	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7	
Bias	9	Describe any efforts to address potential sources of bias	8, 9	
Study size	10	Explain how the study size was arrived at		

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8, 9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9,10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	10, 11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11

Continued on next page

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

For peer review only

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2021-059905 on 19 September 2022. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.