Title

Characteristics and Clinical Outcomes in Patients with Heart Failure with Preserved Ejection Fraction Compared to Heart Failure with Reduced Ejection Fraction: Insights from the VCOR Heart Failure Snapshot

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Competing interest

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Abstract

Background: Heart failure is increasing in prevalence, creating a greater public health and economic burden on our healthcare system. With a rising proportion of hospitalisations for heart failure with preserved ejection fraction (HFpEF) compared to heart failure with reduced ejection fraction (HFrEF) and lack of proven therapies for HFpEF, patient characterisation and defining clinical outcomes are important in determining optimal management of heart failure patients. There is scarce Australian-specific data with regards to the burden of disease of patients with HFpEF which further limits our ability to appropriately manage this syndrome.

Aim: To determine the characteristics, management practices and outcomes of patients with HFpEF compared to patients diagnosed with HFrEF.

Method: Data was sourced from the Victorian Cardiac Outcomes Registry- Heart Failure (VCOR-HF) snapshot of patients admitted with acute heart failure to one of 16 Victorian health services between 2014-2017 over one consecutive month annually. Outcomes measured were in-hospital mortality, and 30-day readmission and mortality.

Results: Of the 1132 HF patients, 436 patients were diagnosed with HFpEF and were more likely to be female (59%) and older (81.5 ± 9.8 vs. 73.2 ± 14.5 years). They were also more likely to have hypertension (80%), atrial fibrillation (59.9%), chronic obstructive airways disease (36.2%) and chronic kidney disease (68.8%). Patients with HFrEF were more likely to have ischaemic heart disease with a history of previous myocardial infarction (36.6%), percutaneous coronary intervention and cardiac bypass surgery (35.2%). There were no significant differences in 30-day mortality between HFpEF and HFrEF (10.2% vs. 7.8%; p= 0.19, respectively) and 30-day readmission rates (22.1% vs. 25.9%; p= 0.15, respectively).

Conclusion: VCOR-HF Snapshot data provides important insight into the burden of acute heart failure. Whilst patients with HFpEF and HFrEF have differing clinical profiles, morbidity, mortality and re-admission rates are similar.

Key Words

Heart failure; acute heart failure; mortality; readmission

Introduction

Heart failure is one of the most prevalent cardiovascular diseases worldwide, and is attributed to be a leading cause of hospitalisation in patients aged ≥ 65 years [1]. In Australia's ageing population, heart failure is projected to increase significantly in prevalence and create an even higher public health and economic burden on the Australian healthcare system [2, 3]. Heart failure (HF) is a clinical syndrome that has been described to encompass two distinct entities – heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). HFrEF is defined as clinical symptoms of heart failure and a measured left ventricular ejection fraction (LVEF) of less than 50%, where HFpEF is defined as clinical symptoms of heart failure with and LVEF of at least 50%.[4] The proportion of hospitalisations for HFpEF is increasing relative to HFrEF [5], making the diagnosis and characterisation of HFpEF imperative for optimal and efficient management of patients. Despite this, there is insufficient Australian-specific data with regards to the burden of disease of patients with HFpEF, thus limiting our ability to appropriately manage this syndrome.

Previous studies in other countries have demonstrated variable differences in patient characteristics and co-morbidities between these groups of patients. [6-9] Data surrounding clinical outcomes of these two patient groups has thus far been inconsistent. Some studies have suggested that patients with HFpEF have lower mortality compared with patients with HFrEF [10, 11], and others suggesting that there are no significant differences between these groups [8, 12]. In addition, medical therapies with documented benefit in HFrEF, such as such as Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptor Blockers (ARB), Angiotensin Neprilsyn Inhibitors (ARNIs), Beta Blockers, and Mineralocorticoid antagonists have shown mixed efficacy in HFpEF [13]. Differentiation between these patients is therefore imperative, as recognition of differing underlying aetiologies and demographics can have significant impacts on determining patients' response to therapies [14].

The aim of our study is to determine patient characteristics and clinical outcomes of patients admitted with acute heart failure, and compare the subgroups of patients with HFpEF and HFrEF.

Methods

The Victorian Cardiac Outcomes Registry (VCOR) is a state-wide, population-based registry aimed at improving the quality of care provided to patients with cardiovascular disease. The registry is designed to collect a minimum standard set of data from patients undergoing specific cardiac management at participating hospitals and have previously been described in detail.[15] Medical outcomes and complications from cardiac interventions or admissions are followed up to 30 days from discharge from hospital. In the VCOR-HF Snapshot module, data is prospectively collected from patients admitted with a diagnosis of acute decompensated heart failure between 2014-2017 over one consecutive month each year, across 16 Victorian hospitals. VCOR-HF methods have been described previously. [16]

For the purposes of this study, patients hospitalised with an admission diagnosis of acute heart failure, which was also confirmed at discharge, and aged ≥18 years were included. The diagnosis of heart failure was confirmed on the Boston criteria [17] and echocardiography.

Heart failure groups were stratified into 2 categories, according to assessment of left ventricular function by echocardiography. 'Heart failure with reduced ejection fraction' (HFrEF) where predominantly contractile dysfunction was identified ejection fraction was <50%, and 'Heart failure with preserved ejection fraction' (HFpEF) where predominantly relaxant dysfunction was identified or if no LV dysfunction ejection fraction ≥ 50% was identified. Patients with mixed systolic and diastolic dysfunction were classified as HFrEF. Patients whose LV function was not assessed (16%) were excluded from the analysis. Patient demographics, medical history, admission data, and discharge data including 30-day outcomes and mortality were all compared amongst these patient groups.

Continuous variables are presented as means ± standard deviations (SD). Categorical variables are expressed as the number of patients using a percentage. Chi-square and independent t-tests were used to compare categorical and continuous variables between the heart failure groups respectively. A p-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed on IBM SPSS Statistics Software version 22.

Results

Between 2014- 2017, data from 1132 patients were collected from the VCOR-HR registry. Of the 1132 patients, 696 patients were classified as having HFrEF and 436 were classified as having HFpEF.

Patients with HFpEF were more likely to be female (58.7%, $p < 0.01$), and older (80.5 ± 9.8 vs. 73.2 ± 14.5; $p<0.01$), compared with patients with HFrEF (Table 2). They were also more likely to have a past medical history of hypertension (80.3% vs. 71.5%; $p<0.01$), atrial fibrillation (59.9% vs. 50.9%; $p<0.01$), and chronic obstructive airways disease (36.2% vs. 26.4%; $p<0.01$). Chronic kidney disease was also more common in the HFpEF group compared to patients with HFrEF (68.8% vs. 63.2%; $p=0.04$). There was no significant difference between HFpEF and HFrEF groups having a history of heart failure or previous heart failure hospitalisations.

Ischaemic heart disease, including previous myocardial infarction (36.6% vs. 24.8%; $p<0.01$), percutaneous coronary intervention or cardiac bypass surgery (35.2% vs. 28.0%; $p<0.01$), was more common in patients with HFrEF. Unsurprisingly therefore, in patients with HFrEF, ischaemic aetiology was almost twice as common compared with patients with HFpEF (46.6% vs. 24.5%; $p<0.01$). Hypertensive (21.1% vs. 13.8%; $p<0.01$) and valvular heart failure (22.2% vs. 11.4%; $p<0.01$) was a more common aetiology for heart failure in HFpEF patients.

Patients with HFpEF were more commonly admitted to a General Medicine Unit (58.3% vs. 38.4%; $p<0.01$) as opposed to a Cardiology Unit (25.7% vs. 45.3%; $p<0.01$), compared with patients with HFrEF.

Patients with HFrEF were more likely to receive intravenous (IV) inotropes (8.9% vs. 2.5%; p <0.01) and invasive ventilation (3.9% vs. 1.4%; p=0.02), compared to HFpEF patients (Table 2). Despite the differences in co-morbidities and recommended pharmacotherapy for HFrEF, there was no significant difference in the number of medications at discharge (Table 2).

In-hospital mortality was similar between HFrEF and HFpEF patients (4.8% vs. 4.2% respectively) (Table 4). The 30-day mortality rates were high for both patient groups (8.0% vs. 8.3%; p= 0.19). Similarly, readmissions within 30 days were very frequent (22.6% vs. 26.5%; p=0.15) although differences in both 30-day outcomes were not significant.

Discussion

In this population-based cohort study on acute heart failure admissions in Victoria, we found that patients admitted with HFpEF were more likely to be older, female, and have a history of hypertension, atrial fibrillation and chronic kidney disease. These differences in patient characteristics have also been documented by similar studies performed in other centres [6, 8, 9, 18]. Previous epidemiological data have suggested that patients with HFpEF have higher rates of non-cardiovascular related death, which is unsurprising given that this group of patients have a higher prevalence of comorbid conditions [19, 20]. Given the lack of effectiveness of heart failure therapies in patients with HFpEF, a focus on addressing these non-cardiac comorbidities may have an impact on outcomes in this group of patients.

Non-ischaemic aetiology of heart failure was more prevalent in our HFpEF cohort, particularly relating to a significantly higher rate of hypertensive and valvular heart disease. This is consistent with findings of other studies [21]. Further research into early, more aggressive treatment of these conditions in preventing HFpEF may be warranted.

Our study found that patients with HFrEF were more frequently admitted to a Cardiology or heart failure unit, compared with patients with HFpEF, who were more frequently admitted to General Medicine units. Evidence has shown that patients admitted to Cardiology units with heart failure have improved mortality and outcomes compared to patients admitted to General Medicine units [22, 23]. Given that patients with

HFpEF are frequently underdiagnosed, early recognition of HFpEF patients is paramount in initiating prompt specialist involvement, which in turn may impact in-hospital and long-term outcomes [24].

We did not demonstrate that there were significant differences between most medical treatments received by HFrEF or HFpEF patients. Patients with HFrEF were only more likely to have received IV inotrope therapy and invasive ventilation, which is in keeping with our understanding of the pathophysiology of acute decompensated heart failure and the subsequent utility of inotropic agents to increase cardiac output in these patients. This has also been found in the OPTIMIZE-HF Registry, which examined more than 48,000 patients in 259 hospitalised hospitalised for heart failure[6]. However, we did find that there was no significant difference in the number of medications prescribed at discharge between HFrEF and HFpEF. Clinical guidelines recommend pharmacotherapy in HFrEF patients but not in HFpEF. However, the average number of discharge medications was similar indicating that HFpEF patients are prescribed additional medications to treat their co-morbidities.

Data regarding clinical outcomes has been shown to be inconsistent [12]. Similar to previous studies, our study demonstrated that mortality rate for patients with heart failure was high [25]. We found that patients with HFpEF and HFrEF had similar observed rates of 30-day mortality. Similar to our data, Bhatia et al. and Bursi et al. both showed no significant difference in the rates of 30-day mortality between patients with HFpEF and patients with HFrEF [8, 26]. In-hospital mortality was high in both groups, and the observed higher rate in patients with HFrEF was not significant, despite this group receiving more intensive therapies.

Our data did not find any significant differences in 30-day readmission rates. However, our 30-day readmission rates were all-cause and did not include specific heart failure readmissions. This may account for the difference in findings to Cheng et al, who found that 30-day cardiovascular and heart failure readmission was higher in patients with HFrEF [9]. Further research regarding long-term outcomes in our patient population is needed to compare our Australian data with other studies.

There were several limitations within our study. A number of patients (225, 16.6%) did not have their left ventricular function assessed during their admission, and therefore their data was not included in our study.

We also excluded a category of patients with 'mixed' heart failure, whose characteristics were not aligned with either one of the HFpEF or HFrEF groups as the EF and/or grade of EF was missing. We expect however, that this would only strengthen our findings by excluding any potential for including a misdiagnosis in heart failure categories.

Our study was performed using data from the VCOR-HF Snapshot. We acknowledge that although registry data allows the observation of outcomes in a real-world setting and the application of these findings to the broader population, inherent limitations exist. Although VCOR undergoes a rigorous auditing process, we cannot exclude that ascertainment bias may be present, with under-reporting of adverse events and outcomes. Using a 'snapshot' sample of patients may also introduce selection bias to the data collected from this particular VCOR module. Data from this module was also dependent on voluntary participation from Victorian hospitals, which can similarly introduce bias with site enrolment.

Patients were followed up to 30-days with respect to mortality and re-admission. Longer follow up may have provided further insights into the long-term outcomes of patients with HFpEF and HFrEF in this population.

Conclusion

The VCOR-HF Snapshot data highlights real world outcomes of heart failure patients in Victoria. HFrEF and HFpEF have differing clinical characteristics but similarly high burden of morbidity and mortality. Our study provides unique insights into the characteristics and outcomes of patients with different types of heart failure within Victoria, and has the potential to help guide our practice and improve clinical outcomes in these groups.

Tables and Figures

Table 1: Baseline characteristics of the patients

Patient Characteristics	**HFrEF** (696)	**HFpEF** (436)	**p-value**
Demographic			
Age, mean±SD	73.2±14.5	80.5±9.8	< 0.01
Gender (Male)	481 (69.1%)	180 (41.3%)	< 0.01
Medical history			
Diabetes Mellitus	397 (57.0%)	233 (53.4%)	0.24
Hypertension	497 (71.5%)	350 (80.3%)	< 0.01
History of heart failure	537 (77.2%)	337 (77.3%)	0.96
Previous heart failure hospitalisation	452 (84.3%)	267 (79.2%)	0.05
Cerebrovascular disease	107 (15.4%)	89 (20.4%)	0.03
History of angina	271 (38.9%)	159 (36.6%)	0.42
History of PCI or CABG	245 (35.2%)	122 (28.0%)	0.01
History of MI	255 (36.6%)	108 (24.8%)	< 0.01
Atrial fibrillation	354 (50.9%)	261 (59.9%)	< 0.01
Dementia	38 (5.5%)	31 (7.1%)	0.26
Depression	116 (16.7%)	94 (21.6%)	0.04
Current malignancy	54 (7.8%)	26 (6.0%)	0.25
COPD	184 (26.4%)	158 (36.2%)	< 0.01
OSA	92 (13.2%)	71 (16.3%)	0.16
Chronic kidney disease: None Mild Moderate	 256 (22.6%) 128 (18.4%) 206 (29.6%)	 136 (12.0%) 83 (19.0%) 162 (37.2%)	0.04

Severe	106 (15.2%)	55 (12.6%)	
Liver disease	43 (6.2%)	36 (8.2%)	0.40
Anaemia	189 (27.2%)	169 (38.8%)	< 0.01
Iron deficiency	124 (18.0%)	106 (24.8%)	< 0.01
Heart failure aetiology :			
Ischaemic	324 (46.6%)	107 (24.5%)	< 0.01
Hypertensive	96 (13.8%)	92 (21.1%)	< 0.01
Hypertrophic	18 (2.6%)	16 (3.7%)	0.30
Valvular	79 (11.4%)	97 (22.2%)	< 0.01
Arrhythmia	89 (12.8%)	70 (16.1%)	0.12
Idiopathic	89 (12.8%)	30 (6.9%)	< 0.01

COPD: Chronic obstructive pulmonary disease; OSA : Obstructive sleep apnoea

Table 2: Inpatient management

Variables	**HFrEF** (696)	**HFpEF** (436)	**p-value**
Admission Location			
Emergency Department	585 (84.1%)	402 (92.2%)	< 0.01
Direct to ward (including CCU/ICU)	111 (15.9%)	34 (7.8%)	
Admission Specialty			
Heart Failure Unit	68 (9.8%)	40 (9.2%)	< 0.01
Cardiology Unit	315 (45.3%)	112 (25.7%)	
Geriatrics Unit	18 (2.6%)	13 (3.0%)	
General Medicine Unit	267 (38.4%)	254 (58.3%)	
Other	28 (4.0%)	17 (3.9%)	
Medical treatment during admission			
Intravenous diuretics	600 (86.6%)	381 (87.4%)	0.70
Intravenous GTN infusion	31 (4.5%)	17 (3.9%)	0.65
Intravenous inotrope infusion	62 (8.9%)	11 (2.5%)	< 0.01
Oral diuretics	617 (88.9%)	383 (88.0%)	0.66
Oxygen therapy	454 (65.6%)	303 (69.7%)	0.16
Non-invasive ventilation	100 (14.4%)	69 (15.9%)	0.50
IABP/ECMO	8 (1.2%)	1 (0.2%)	0.09
Invasive ventilation	27 (3.9%)	6 (1.4%)	0.02
Medical treatment on discharge			
Total number of medications	10.7 ± 4.3	10.2 ± 4.0	0.08

CCU : Coronary care unit ; ICU : Intensive care unit; GTN : Glyceryl trinitrate ; IABP : Intra-aortic balloon pump ; ECMO : Extra-corporeal membrane oxygenation

Table 3: In-hospital mortality and 30-day readmissions and mortality

Variables	**HFrEF** (696)	**HFpEF** (436)	**p-value**
In-hospital outcomes			
Mortality	29 (4.2%)	21 (4.8%)	0.61
30-day outcomes			
Mortality	56 (8.0%)	36 (8.3%)	0.90
Readmission	151 (22.6%)	110 (26.5%)	0.15

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