Original Article

Prevalence, Presentation, and Outcome of Heart Failure with Preserved Ejection Fraction among Patients Presenting with Undifferentiated Dyspnoea to the Emergency Room: A 10-year Analysis from a Tertiary Centre

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Abstract

Introduction: We assessed the local prevalence, characteristics and 10-year outcomes in a heart failure (HF) cohort from the emergency room (ER). Materials and Methods: Patients presenting with acute dyspnoea to ER were prospectively enrolled from December 2003 to December 2004. HF was diagnosed by physicians' adjudication based on clinical assessment and echocardiogram within 12 hours, blinded to N-terminal-pro brain natriuretic peptide (NT-proBNP) results. They were stratified into heart failure with preserved (HFPEF) and reduced ejection fraction (HFREF) by left ventricular ejection fraction (LVEF). Results: At different cutoffs of LVEF of ≥50%, ≥45%, ≥40%, and >50% plus excluding LVEF 40% to 50%, HFPEF prevalence ranged from 38% to 51%. Using LVEF ≥50% as the final cutoff point, at baseline, HFPEF (n = 35), compared to HFREF (n = 55), had lower admission NT-proBNP (1502 vs 5953 pg/mL, *P* <0.001), heart rate (86 ± 22 vs 98 ± 22 bpm, *P* = 0.014), and diastolic blood pressure (DBP) (75 ± 14 vs 84 ± 20 mmHg, *P* = 0.024). On echocardiogram, compared to HFREF, HFPEF had more LV concentric remodelling (20% vs 2%, *P* = 0.003), less eccentric hypertrophy (11% vs 53%, *P* <0.001) and less mitral regurgitation from functional mitral regurgitation (60% vs 95%, *P* = 0.027). At 10 years, compared to HFREF, HFPEF had similar primary endpoints of a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and rehospitalisation for congestive heart failure (CHF) (HR 0.886; 95% CI, 0.561 to 1.399; *P* = 0.605), all-cause mortality (HR 0.663; 95% CI, 0.400 to 1.100; *P* = 0.112), but lower cardiovascular mortality (HR 0.307; 95% CI, 0.111 to 0.850; *P* = 0.023). Conclusion: In the long term, HFPEF had higher non-cardiovascular mortality, but lower cardiovascular mortality compared to HFREF.

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Key words: Acute heart failure, Asian, Prognosis

Introduction

Heart failure (HF) with preserved ejection fraction (HFPEF) occurs in almost half of HF population and the prevalence is rising.[1-4] Detecting the abnormalities associated with diastolic dysfunction in HFPEF using echo- and tissue-Doppler techniques requires expert acquisition and interpretation.[5] No echo parameter has emerged that is pathognomonic of diastolic HF, and definition of HFPEF largely depends on an agreed, albeit arbitrary, left ventricular ejection fraction (LVEF) cutoff value. The threshold for normal LVEF is set at 50% in the 2012 European Society of Cardiology guidelines,[5] although cutoff values of LVEF ranging from 40% to 50% have been used in various clinical studies.[3,4,6,7]

Given the above issues regarding the choice of LVEF threshold, it is not unexpected that the proportion of HFPEF compared with HF with reduced ejection fraction (HFREF) has been variably observed in HF registries.[3,4,6,7] Diverse practice settings;[3,4,8] burden of comorbidities; regional characteristics including social, economic and genetic (ethnic) difference all may impact on HFPEF prevalence in registry data. Unlike HFREF whose outcome has gradually improved with evidence-based medical therapy, optimal treatment of HFPEF is still unresolved[9,10] and data for long-term outcomes are limited, especially in Asian populations.[11]

The objectives of this analysis were to assess the prevalence, presenting features and outcomes of HFPEF

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among patients presenting to the emergency room (ER) with undifferentiated dyspnoea, and to compare these with HFREF patients, in the local population.

Materials and Methods

Patients and Study Design

Between December 2003 and December 2004, a single centre prospective study was performed in which consecutive patients presenting with undifferentiated dyspnoea to the ER had N-terminal-pro brain natriuretic peptide (NT-proBNP) (which was not standard of care in local hospitals at that time) performed to validate its diagnostic accuracy for HF in local population. HF diagnosis was based on consideration of Framingham's criteria for congestive HF, response to diuretic treatment and echocardiographic findings. Exclusion criteria were patients less than 40 years old; whose dyspnoea was clearly not a result of HF (eg. pneumothorax, asthma, malignant pleural effusion); and patients with definite acute coronary syndrome, as determined by electrocardiogram changes and cardiac enzymes.[12] Patients with known systolic HF, evidenced by documented LVEF <50% demonstrated by echocardiogram within 12 months were deliberately excluded in order to ensure recruitment of more subjects whose diagnosis of HF was less immediately apparent, and which could potentially have been aided by the then novel NT-proBNP biomarker.

Diagnosis of HF were adjudicated by pairs of doctors comprising one each of cardiologists, internists or emergency physicians, based on all medical records pertaining to the patient, including: (a) Framingham's criteria for congestive heart failure (CHF) (2 major or one major and 2 minor criteria);[13] (b) response to treatment directed towards HF[14] and (c) echocardiographic findings (eg. reduced LVEF or diastolic dysfunction). All adjudicators were blinded to the NT-proBNP levels.

For the patients who were diagnosed to have dyspnoea not due to CHF, confirmation on the basis of the following observation will be attempted: (a) presence of fever and cough with yellowish sputum, (b) absence of heart enlargement and pulmonary venous congestion on chest radiography, (c) abnormal lung function test, response to treatment with nebulizers corticosteroids or antibiotics and (d) absence of admission to the hospital for CHF in the following 6 months. Patients assessed to have both HF and other contributing non-HF presentations, were categorised into the HF group.

Routine electrocardiogram, chest radiograph, laboratory results (full blood count, cardiac enzymes, renal panel) were recorded on admission. Blood sampling for NT-proBNP were taken after 10 minutes of supine rest. Echocardiograms were performed within 12 hours of blood sampling of NT-proBNP. The following measurements were recorded: left ventricular end diastolic dimension, left ventricular end systolic dimension, fractional shortening, ejection fraction (by biplane Simpson's method), wall thickness, transmitral flow profiles E (early wave), A (atrial contraction), deceleration time (DT), E/A ratio and valvular abnormalities.

Patients were admitted or discharged and managed at the discretion of the treating physicians. The treating physicians were blinded to the results of NT-proBNP. At that time, NT-proBNP was not standard of care.

N-terminal-pro Brain Natriuretic Peptide

Immunoassay for the quantitative determination of NT-proBNP was performed using Elecsys proBNP II STAT assay (Roche Diagnostics). The measurement range of this assay is 5 to 35,000 pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values above the measuring range were reported up to 70,000 pg/mL for 2-fold diluted samples.

Ethics

The study protocol was approved by the local hospital ethics committee in our hospital. All subjects gave written informed consent to participate in the study.

Echocardiogram

At baseline, study participants underwent standard echocardiography with Doppler measurements. Left ventricular (LV) chamber dimensions were measured by M-mode according to the American Society of Echocardiography (ASE) recommendations.[15] LV mass (LVM) and relative wall thickness (RWT) were calculated using ASE recommended formulas.[15] Based on LV mass and geometry, participants were classified into normal, concentric remodelling, concentric hypertrophy and eccentric hypertrophy patterns.[15]

Outcomes

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and rehospitalisation for CHF events. Secondary endpoints were individual components of the primary endpoint as well as all-cause death.

Events were ascertained from review of case records linked to the Hospital Care Inpatient Discharge Care and Electronic Medical Record Exchange system of hospitals in Singapore. In addition, information on deaths was obtained

from death certificates issued by the National Registry of Births and Deaths.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) for parametric, and median (quartile range) for non-parametric data. Dichotomous variables are presented as number and percentage. Baseline features of patients with HFPEF and HFREF were compared. Dichotomous variables were compared by Pearson Chi-square test. Continuous variables were compared by Student's t-test for parametric and Mann Whitney U test for non-parametric data. Survival time was measured from date of study registration to the date of outcome or date of last contact. The Kaplan-Meier survival curves were constructed, the significance of which was tested by the log-rank Cox regression test. Sensitivity tests were performed using different thresholds of LVEF for HFPEF (≥45%, ≥40%), as well as comparing only extreme phenotypes by omitting those LVEF between 40% and 50%. Notably, patients in the latter group possess distinctly different physiological and prognostic behaviours.[11] Sensitivity analysis using a different gold standard to diagnose HF (Framingham's criteria plus elevated NT-proBNP >900 pg/mL) was performed to determine the robustness of the survival relationship pertaining to LVEF. Statistical analysis was performed using SPSS statistical software package (version 21; SPSS Inc., Chicago, IL) for all analyses. A P value of <0.05 was considered to indicate statistical significance.

Results

Clinical Characteristics

A total of 152 consecutive patients with undifferentiated dyspnoea presenting to the ER agreed to participate in the study; 90 (59%) patients were diagnosed to have HF by physician adjudication; 3 patients who were initially adjudicated not to have HF had subsequent HF hospitalisation within 6 months. Two of these had fluid overload states which were initially thought to be attributable to proteinuria and endstage renal failure, respectively, and were subsequently adjudicated into HF group upon review at 6-month postinitial presentation. The third subject, whose breathlessness was due to thyrotoxicosis, remained classified in the non-HF group.

Using LVEF ≥50% as the cutoff, 35 (39%) and 55 (61%) were classified into HFPEF and HFREF groups, respectively. Sensitivity test was performed using different diagnostic criteria for HF. Among 86 (57%) patients who were diagnosed HF by a combination of Framingham's criteria plus elevated NT-proBNP >900 pg/mL for HF, HFPEF and HFREF prevalence was 35 (41%) and 51(59%), respectively.

Subjects were followed up to 10 years. Follow-up was 96% complete. Among 90 HF patients, 2 were lost to follow-up at 2 weeks (non-residents); and another 2 were lost to follow-up at 18 months and 23 months, respectively.

Baseline characteristics of patients with HFPEF versus HFREF are shown in Table 1. There was a trend towards prevalence of female gender in HFPEF (52%) compared to HFREF (36%), but no statistically significant difference was found. HFPEF patients had lower baseline NT-proBNP compared to HFREF. Numerically, but not statistically significantly, HFPEF had higher numbers of prior obstructive lung disease, and lower numbers of prior myocardial infarction with less previous use of angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers, nitrates, diuretics, digoxin and antiplatelets compared to HFREF. Notably, the prevalence of diabetes was high in both groups. Clinical presentations (lung rales, cardiomegaly, elevated jugular venous pressure, presence of pleural effusion or pulmonary oedema on chest radiograph, ankle oedema and paroxysmal nocturnal dyspnoea) were similar in general, except HFPEF patients were less tachycardic, had lower diastolic blood pressures (DBPs) at baseline, and less LV hypertrophy by voltage criteria on electrocardiogram compared to HFREF. There was no statistically significant difference between HFPEF and HFREF in number of patients requiring intravenous diuretics as well as dosage of the diuretics given in ER. Other than 1 in HFPEF and 3 in HFREF patients who require intravenous nitrates, none of the patients in this study require intravenous inotropic support in ER.

Echocardiographic Features

Echocardiographic measurements are shown in Table 2. HFPEF had smaller LV end diastolic dimensions than HFREF. Mean LV mass was raised in both groups. HFPEF patients tended to present with concentric LV remodelling compared to HFREF (20% vs 2%, $P = 0.003$). In contrast, eccentric LV hypertrophy was more common in HFREF compared to HFPEF (53% vs 17%, $P <0.001$). On Doppler measurements, deceleration time was longer in HFPEF compared to HFREF.

In patients with more than moderate degree of valvular heart disease, mitral valve regurgitation (MR) was the most common condition in both HFPEF (17%) and HFREF (41%) patients. In terms of aetiology, MR subjects with HFPEF had lower proportion diagnosed with functional MR (60% vs 95%, $P = 0.027$) compared to HFREF group.

Outcomes

The primary composite outcome occurred in 31 and 48

Table 1. Baseline Clinical Characteristics

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
Age, years	72 ± 9	72 ± 11	0.806
Female sex, n (%)	18 (52)	20 (36)	0.158
Comorbidities			
Prior diabetes, n (%)	20 (57)	33 (60)	0.788
Prior hypertension, n (%)	43 (78)	27 (77)	0.908
Prior atrial fibrillation, n (%)	11 (31)	17 (31)	0.959
Prior heart failure, n (%)	10 (29)	17 (31)	0.813
Prior myocardial infarct	2 (6)	9 (16)	0.133
Prior stroke, n (%)	3 (9)	8 (15)	0.399
Prior chronic obstructive lung disease, n (%)	5 (14)	2 (4)	0.066
Prior chronic kidney disease, n (%)	4 (11)	4 (7)	0.499
Medications at presentation			
Dihydropyridine, n (%)	5 (15)	7 (13)	0.817
Betablockers, n (%)	5 (14)	9 (16)	0.791
ACEI/ARB, n (%)	6 (17)	17 (31)	0.144
Diuretics, n (%)	8 (23)	18 (33)	0.238
Nitrates, n (%)	8 (23)	19 (33)	0.640
Digoxin, n (%)	1 (3)	6 (11)	0.164
Antiplatelet, n (%)	4 (11)	15 (27)	0.073
Medications in ER			
Intravenous furosemide in ER, n (%)	27 (77)	43 (78)	0.908
Mean IV furosemide dosage, mg	45 ± 37	46 ± 32	0.866
IV GTN, n (%)	1 (3)	3 (6)	0.560
Biochemistry			
NT-proBNP at ER (pg/mL)	1502 (164 – 4885)	5953 (3390 – 14393)	<0.001
NT-proBNP on discharge (pg/mL)	868 (127 – 3504)	2541 (1439 – 6891)	0.002
Change in NT-proBNP (pg/mL)	353 (26 – 2011)	3298 (875 – 6540)	0.004
Haemoglobin (g/L)	12 ± 2	13 ± 2	0.053
Anaemia, n (%)	21 (60)	26 (47)	0.239
Glucose (mmol/L)	8 ± 4	10 ± 4	0.051
Sodium (mmol/L)	136 ± 4	137 ± 4	0.444
Hyponatraemia (<135 mmol/L), n (%)	8 (23)	12 (22)	1.000
Urea (mmol/L)	10 ± 7	9 ± 5	0.456
Creatinine (μmol/L)	142 ± 92	126 ± 67	0.341
Urea/creatinine ratio* (SI unit)	19 ± 7	19 ± 6	0.602
NYHA functional classification			
Class I and II, n (%)	20 (51)	27 (49)	0.456
Class III, n (%)	11 (31)	21 (38)	0.514
Class IV, n (%)	4 (11)	7 (13)	0.855
Systolic blood pressure (mmHg)	142 ± 29	150 ± 33	0.260
Diastolic blood pressure(mmHg)	75 ± 14	84 ± 20	0.024
Heart rate (bpm)	86 ± 22	98 ± 22	0.014

ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blockers; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; JVP: Jugular venous pressure; NT-proBNP: N-terminal-pro brain natriuretic peptide; S3: Third heart sound; NYHA: New York Heart Association; ECG: Electrocardiogram; ER: Emergency room; LVH: Left ventricular hypertrophy; QRS: Time from the start of Q wave to the end of S wave on electrocardiogram; QTc: Corrected QT interval; IV: Intravenous; GTN: Glyceryl trinitrate

*Normal range for urea-to-creatinine ratio is 40-100:1, >100:1 indicates prerenal cause and <40:1 is suggestive of intrarenal cause.

Table 1. Baseline Clinical Characteristics (Con't)

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
Initial ECG characteristics			
Presence of LVH, n (%)	2 (6)	13 (24)	0.026
QRS width (ms)	95 ± 22	97 ± 19	0.714
QTc duration (ms)	433 ± 34	445 ± 34	0.160

ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blockers; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; JVP: Jugular venous pressure; NT-proBNP: N-terminal-pro brain natriuretic peptide; S3: Third heart sound; NYHA: New York Heart Association; ECG: electrocardiogram; ER: Emergency room; LVH: Left ventricular hypertrophy; QRS: Time from the start of Q wave to the end of S wave on electrocardiogram; QTc: Corrected QT interval; IV: Intravenous; GTN: Glyceryl trinitrate
*Normal range for urea-to-creatinine ratio is 40-100:1, >100:1 indicates prerenal cause and <40:1 is suggestive of intrarenal cause.

patients in the HFPEF and HFREF groups, respectively. Over 10 years' follow-up, 64 deaths occurred (71%). The median survival was 3.2 and 2.2 years in the HFPEF and HFREF cohort, respectively. At 10 years, all-cause death occurred in 27 and 37; and cardiovascular death in 5 and 15 patients in HFPEF and HFREF groups, respectively (Table 3). Kaplan-Meier survival curves showed no difference in rates of primary endpoints and all-cause mortality between the 2 groups (Figs. 1 and 2). Cardiovascular mortality was higher in HFREF versus HFPEF group (27% vs 14%, *P* = 0.023) (Fig. 3).

Using different thresholds of LVEF for HFPEF (≥45%, and ≥40%, >50% plus excluding LVEF between 40% and 50% inclusive), yielded different proportions of HFPEF versus HFREF (Fig. 4). Sensitivity testing of outcomes using different thresholds of LVEF for HFPEF showed no

Table 2. Echocardiographic Parameters

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
LVIDd (cm)	4.7 ± 0.9	5.8 ± 0.9	<0.001
IVSd (cm)	1.1 ± 0.3	1.1 ± 0.2	0.081
PW thickness (cm)	1.1 ± 0.2	1.1 ± 0.2	0.442
RWT (cm)	0.5 ± 0.1	0.4 ± 0.1	<0.001
LVM (g)	199 ± 69	256 ± 77	0.004
LV geometry*			
Normal geometry, n (%)	13 (37)	13 (24)	0.168
Concentric remodelling, n (%)	7 (20)	1 (2)	0.003
Concentric hypertrophy, n (%)	11 (31)	12 (22)	0.308
Eccentric hypertrophy, n (%)	4 (11)	29 (53)	<0.001
Mitral inflow			
E (mm/s)	95 ± 45	99 ± 33	0.615
A (mm/s)	83 ± 28	74 ± 36	0.350
E/A	1.1 ± 0.8	1.6 ± 1.0	0.066
DT (ms)	210 ± 92	151 ± 44	0.001
M-mode LA diameter (cm)	4.4 ± 0.9	4.4 ± 0.9	0.786
TR velocity (mm/s)	290 ± 41	316 ± 67	0.200
Mitral regurgitation (MR)† n (%)	5 (17)	21 (41)	0.028
Ischaemic MR, n (%)	3 (60)	20 (95)	0.027

HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; LVIDd: Left ventricular end diastolic dimension; RWT: Relative wall thickness (measured by 2 x posterior wall thickness divided by LV diastolic diameter); LVM: Left ventricular mass; E: Early diastolic mitral inflow velocity; A: Late diastolic mitral inflow velocity; DT: E wave deceleration time; LA: Left atrium; TR: Tricuspid regurgitation
*Definition of elevated LVM (female ≥162 g and male ≥224g). Normal geometry (LVM normal and RWT <0.42), concentric remodelling (LVM normal but RWT ≥0.42), eccentric hypertrophy (LVM elevated but RWT <0.42), and concentric hypertrophy (LVM elevated and RWT ≥0.42).
†Mitral regurgitation only accounts for regurgitation of more than moderate degree.

Table 3. Comparison of Outcomes between HFPEF and HFREF

	HFPEF (n = 35)	HFREF (n = 55)	HR (95%CI)	*P* Value
Composite endpoint, n (%)	31 (89)	48 (87)	0.886 (0.561 – 1.399)	0.605
Non-fatal myocardial infarction, n (%)	1 (3)	8 (15)	0.168 (0.021 – 1.344)	0.093
Non-fatal stroke, n (%)	1 (3)	2 (4)	0.672 (0.061 – 7.439)	0.746
HF hospitalisation, n (%)	20 (57)	32 (58)	0.843 (0.480 – 1.481)	0.553
Cardiovascular mortality, n (%)	5 (14)	15 (27)	0.307 (0.111 – 0.850)	0.023
All-cause mortality, n (%)	27 (77)	37 (67)	0.663 (0.400 – 1.100)	0.112
Non-cardiovascular death, n (%)	22 (63)	22 (40)	1.048 (0.515 – 2.135)	0.896
Sepsis, n (%)	9 (26)	11 (20)	0.699 (0.266 – 1.679)	0.392
Cancer, n (%)	3 (9)	3 (5)	1.160 (0.233 – 5.772)	0.856
Lung disease, n (%)	3 (9)	0 (0)	NA	NA
Kidney disease, n (%)	0 (0)	0 (0)	NA	NA
Others*, n (%)	7 (20)	8 (15)	NA	NA

HF: Heart failure; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio

*Other causes of death: 1 case died from subarachnoid hemorrhage in HFPEF group, 1 case died from hypoxic ischaemic brain injury in HFREF group, and the rest were unknown causes of death.

difference in outcomes. Sensitivity testing using different method for HF diagnosis as mentioned above did not alter the conclusions.

Discussion

The prevalence of HFPEF was reported to be 36% to 61% based on various LVEF cutoffs ranging from 40% to 50% in western populations.[3,4,16-20] We observed a prevalence of HFPEF at 39% at LVEF cutoff of 50%, which is similar to another Asian HF registry ATTEND (43%).[2] However, differing LVEF cutoffs of ≥50% and ≥40% were used in our and ATTEND studies, respectively. The choice of LVEF threshold can alter HFPEF prevalence significantly, and may limit direct comparison between studies. In our study, by shifting the LVEF threshold from 50% to 40%, HFPEF prevalence increased from 39% to 51%, which was very similar to western cohorts (using LVEF thresholds ranging from 40% to 50%).[3,16,20]

In large clinical trials, compared to HFREF, HFPEF patients were usually older, more frequently female, and more likely to have history of atrial fibrillation, diabetes, hypertension, renal insufficiency, and pulmonary disease.[1,6,7,9] We found a similar trend towards female gender, more chronic pulmonary disease, and less prior myocardial

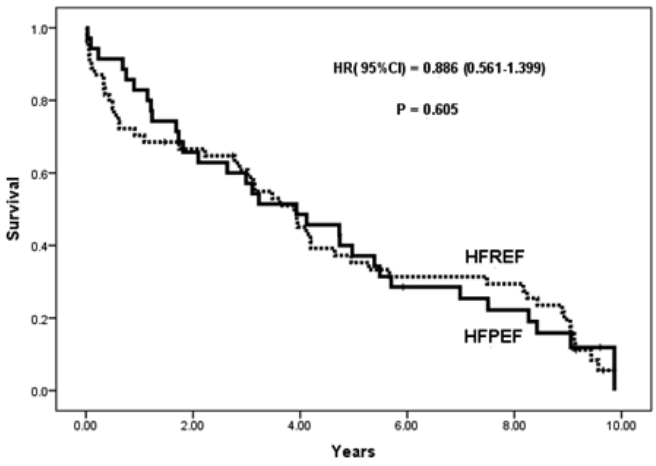

Fig.1. Kaplan-Meier analysis of composite primary endpoints among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

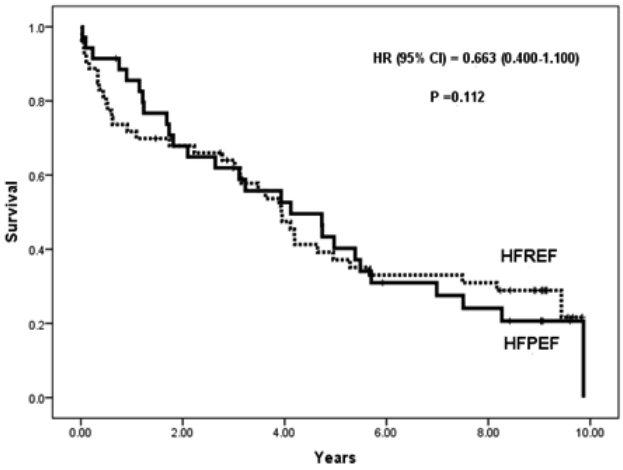

Fig.2. Kaplan-Meier analysis of overall survival among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

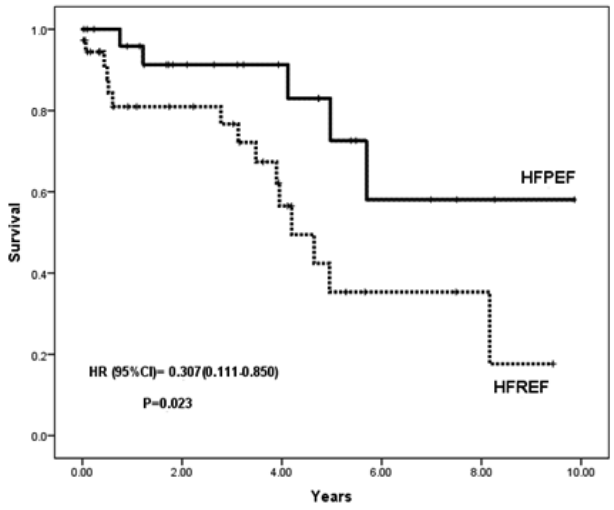

Fig.3. Kaplan-Meier analysis of cardiovascular mortality among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

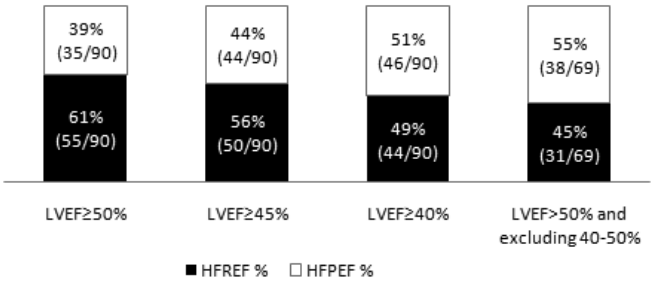

Fig.4. Chart showing the prevalence of HFPEF at different cutoff points of LVEF. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction.

infarction in HFPEF, although there was insufficient power to demonstrate statistical significance.

Diabetes is a global health concern and important cause of systolic and diastolic HF. In Singapore, 1 out of 9 people aged 18 to 69 has diabetes. That's about 11.3% of our population or more than 400,000 people.[21] Notably, the prevalence of diabetes in our cohort was extremely high in both HFPEF (57%) and HFREF (60%) compared with contemporaneous global data in acute (32% to 47%)[2,3,22] and chronic (20% to 32%) HF cohorts.[1,5,18,23] Microvascular disease, in particular, associated with diabetes, has been invoked as a putative pathophysiological and aetiological explanation for HFPEF.[24] With rising diabetes prevalence,[25] HF can be expected to rise commensurately.

In contrast to some other studies,[17,26] significantly lower heart rates and diastolic arterial pressure were observed in HFPEF compared to HFREF in our study; proportion of hyponatremia was similar in HFPEF and HFREF (Table 1). Of note, our study recruited acute HF subjects, whereas most other trials enrolled chronic ambulatory HF patients. HFPEF subjects may have impaired chronotropicity[27] and may exhibit lower heart rates and arterial DBPs,[28] especially in stress situations (like in our acute HF cohort). In the acute HF study RELAX-AHF, a similar trend was observed in which DBP was significantly lower in HFPEF compared to HFREF patients (79.6 ± 13.9 vs 82.6 ± 13.6 mmHg, $P = 0.0015$).[29]

In our HFPEF subjects, we observed higher prevalence of concentric LV remodelling on echocardiography compared with HFREF. In contrast, in HFREF, the eccentric hypertrophy pattern is more prevalent. Such LV remodelling differentiation is similar to other HF studies.[30,31] This higher prevalence of concentric LV remodelling, and potential attenuation of coronary perfusion due to lower DBP, may result in increased myocardial oxygen consumption and subendocardial ischaemia.[32]

We observe lower baseline NT-proBNP level in HFPEF than HFREF. Despite lower NT-proBNP levels, HFPEF patients have been reported to exhibit similar levels of renin-angiotensin-aldosterone system (RAAS) activation and clinical severity of HF compared to HFREF. It was postulated that HFPEF is associated with relative NT-proBNP deficiency which was induced by renal impairment, RAAS activation, sodium retention and vasoconstriction.[28]

Anaemia, particularly iron-deficient anaemia, is common in chronic HF patients, and is associated with worse symptoms and outcomes in both HFPEF and HFREF.[33] In this study, a trend towards higher prevalence of anaemia was present in HFPEF (60%) compared with HFREF (47%) ($P = 0.239$), which is consistent with other studies of chronic HF[17,18,28] as well as acute HF.[3,28] The reason for this is unclear. Most likely, the high prevalence of anaemia in HFPEF is a surrogate marker of the higher burden of comorbidities (in our cohort, prevalence of prior chronic obstructive lung disease and chronic kidney disease, but not diabetes, were numerically higher in HFPEF).

Substantial mortality in HFPEF, similar to HFREF, has been reported in both epidemiological and clinical trials. In population-based studies, unadjusted 5-year all-cause mortality rates of 52% to 76% versus 54% to 73% for HFPEF and HFREF, respectively, have been reported.[4,8,17,19] On the other hand, randomised clinical trials reported lower all-cause mortality rates. For instance, in the placebo-control arms in I-PRESERVE[34] and CHARM-Preserved,[7] cumulative all-cause mortality were 21% and 25% at 4 years and 3 years, respectively. However, the subjects in the above trials were largely ambulatory and were not required to have

been hospitalised at the time of recruitment, which may explain the difference in mortality results from our cohort.

Our study is based on patients recruited from the ER, all of whom were subsequently hospitalised. Median survival was 3.2 years and 2.2 years in HFPEF and HFREF cohorts, respectively. As mentioned, discrepancies of mortality rates between different studies may be due to differences in baseline patient characteristics and the burden of comorbidities. Indeed, our patient group comprised older subjects, many with comorbidities.

High proportions of non-cardiac deaths ranging from 24% to 61% have been observed in other HFPEF studies.[19,35,36] In our study, patients with HFPEF were similarly more likely to die from non-cardiovascular causes including sepsis (26%), cancer (9%), chronic obstructive lung disease (9%) (Table 3). This is in keeping with the principal non-cardiac causes of death in Singapore general population which includes cancer (30.5%), sepsis such as pneumonia (18.5%) and urinary tract infection (2.6%), nephritis, nephrotic syndrome and nephrosis (2.4%), and chronic obstructive lung disease (1.6%) reported by the Ministry of Health in 2013.[37]

On the other hand, in Singapore, ischaemic heart disease (15.5%) is still the leading cause of cardiovascular death, followed by cerebral vascular disease (8.9%) and hypertensive heart disease (3.1%).[37] In our study, HFPEF subjects had less cardiovascular death events and a trend towards less HF rehospitalisation rate. This is perhaps in keeping with the lower biomarker (NT-proBNP) burden in HFPEF compared with HFREF. The burden of non-cardiovascular death appears to be inversely related to the extent of coronary artery disease (CAD) in HFPEF population.[38] Patients with HFPEF, who are more likely to be free from epicardial CAD, are conceivably more likely to be spared from cardiac deaths, and only to die from non-cardiovascular causes.[36]

Studies have shown that older age, higher NT-proBNP, and burden of comorbidities such as cancer, pulmonary disease, and diabetes were independent predictors of mortality.[17,36] Unfortunately, our cohort is too small to permit multivariable analysis of these relevant risk predictors.[22]

Limitations

This is a relatively small study conducted in a single centre and results of this study may not be generalisable. Nevertheless, it comprises a hitherto relatively unstudied group of Asian patients presenting with undifferentiated dyspnoea to the ER. The very long follow-up allows meaningful analyses of outcomes despite the small numbers. While we primarily used LVEF ≥50% as the threshold for HFPEF, this is not universally applied across all studies, which limited comparison. However, sensitivity analyses performed for different cutoff ranging from 40% to 50% did not alter the conclusions regarding primary outcome events and mortality rates. Neither does sensitivity analysis using a combination of Framingham's criteria plus elevated NT-proBNP for HF diagnosis alter the analysis.

One of our study objectives then was to evaluate the diagnostic accuracy of NT-proBNP assay for HF diagnosis in a local population. This necessitated the exclusion of patients with known recent systolic dysfunction. There is thus a possibility overt HFREF might have been under-represented in our study. However, we believe the effect is minor. We obtained similar balance of HFPEF versus HFREF subjects as other contemporaneous registries. Importantly, we believe that comparisons of clinical characteristics and outcomes between HFPEF and HFREF remain valid.

Conclusion

This prospective single centre Singapore cohort study demonstrated that all-cause mortality in HFPEF and HFREF did not differ significantly. HFPEF had significantly higher non-cardiac mortality but lower cardiovascular mortality at 10 years. Diabetes is extremely prevalent in both HFPEF and HFREF, and may be an important driver of burgeoning HF incidence.

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REFERENCES

1. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004;25:1214-20.
2. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, et al. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. Am Heart J 2010;159:949-55.e1.
3. West R, Liang L, Fonarow GC, Kociol R, Mills RM, O'Connor CM, et al. Characterization of heart failure patients with preserved ejection fraction: a comparison between ADHERE-US registry and ADHERE-International registry. Eur J Heart Fail 2011;13:945-52.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.

5. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
6. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail 2008;10:149-56.
7. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
8. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008;29:339-47.
9. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.
10. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! J Am Coll Cardiol 2010;55:526-37.
11. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 2014;16:1049-55.
12. Vengoechea F. Management of acute coronary syndrome in the hospital: a focus on ACCF/AHA guideline updates to oral antiplatelet therapy. Hosp Pract (1995) 2014;42:33-47.
13. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-6.
14. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005 ;18:1440-63.
16. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-63.
17. Carlsen CM, Bay M, Kirk V, Gotze JP, Kober L, Nielsen OW. Prevalence and prognosis of heart failure with preserved ejection fraction and elevated N-terminal pro brain natriuretic peptide: a 10-year analysis from the Copenhagen Hospital Heart Failure Study. Eur J Heart Fail 2012;14:240-7.
18. Maeder MT, Rickenbacher P, Rickli H, Abbuhl H, Gutmann M, Erne P, et al. N-terminal pro brain natriuretic peptide-guided management in patients with heart failure and preserved ejection fraction: findings from the Trial of Intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF). Eur J Heart Fail 2013;15:1148-56.
19. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. J Card Fail 2012;18:749-54.
20. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109:494-9.
21. Lim RB, Ma S, Fong CW, Chua L, Chia KS, Heng D, et al. How healthy is the singaporean worker? Results from the Singapore national health survey 2010. J Occup Environ Med 2014;56:498-509.
22. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.
23. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.
24. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-71.
25. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
26. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009;119:3070-7.
27. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138-47.
28. Bishu K, Deswal A, Chen HH, LeWinter MM, Lewis GD, Semigran MJ, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J 2012;164:763-70.e3.
29. Filippatos G, Teerlink JR, Farmakis D, Cotter G, Davison BA, Felker GM, et al. Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial. Eur Heart J 2014;35:1041-50.
30. Velagaleti RS, Gona P, Pencina MJ, Aragam J, Wang TJ, Levy D, et al. Left ventricular hypertrophy patterns and incidence of heart failure with preserved versus reduced ejection fraction. Am J Cardiol 2014;113:117-22.
31. Klabunde RE. Cardiovascular Physiology Concepts. 2nd ed. Lippincott Williams & Wilkins; 2011. 77 p.
32. Aumont MC, Morisson-Castagnet JF. ["Diastolic" heart failure and pulsed pressure]. Arch Mal Coeur Vaiss 2003;96:125-30.
33. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. Eur J Heart Fail 2012;14:423-9.
34. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.
35. Wang AY, Wang M, Lam CW, Chan IH, Lui SF, Sanderson JE. Heart failure with preserved or reduced ejection fraction in patients treated with peritoneal dialysis. Am J Kidney Dis 2012;61:975-83.
36. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail 2013;15:604-13.
37. Ministry of Health [Internet]. Singapore: Principal Causes of Death [updated 1 Oct 2014]. Available at: https://www.moh.gov.sg. Accessed on 7 April 2015.
38. Rickenbacher P, Pfisterer M, Burkard T, Kiowski W, Follath F, Burckhardt D, et al. Why and how do elderly patients with heart failure die? Insights from the TIME-CHF study. Eur J Heart Fail 2012;14:1218-29.