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Predictors of two-year mortality in Asian patients with heart failure and preserved ejection fraction

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ABSTRACT

Introduction: Mortality in patients with heart failure and preserved ejection fraction (HFpEF) remains high. Data from Asia is lacking. We aim to study the impact of ethnicity and other predictors of mortality in patients admitted for HFpEF in a multi-ethnic Asian country.
Material and methods: Consecutive patients admitted to two local institutions with heart failure and ejection fraction ≥50% on transthoracic echocardiogram from Jan 2008 to Dec 2009 were included. All patients were followed-up for 2 years. Overall mortality was obtained from the national registry of deaths in our country.
Results: A total of 1960 patients with heart failure were included. 751 (38.3%) patients had HFpEF. Overall mortality at two years was 26.6% (n = 200) compared to 37.1% (n = 449) in patients with reduced ejection fraction (HR 0.618 (95% CI 0.508–0.753), p < 0.001). Ethnicity did not predict mortality. On multivariable Cox regression analysis, significant predictors of two-year mortality in HFpEF patients were older age (HR 1.027 (1.011–1.044)), prior myocardial infarction (HR 1.577 (1.104–2.253)), prior stroke (HR 1.475 (1.055–2.061)), smoking (HR 1.467 (1.085–1.985)), higher creatinine levels (HR 1.002 (1.001–1.003)) and use of mineralocorticoid receptor antagonists (HR 1.884 (1.226–2.896)). Use of warfarin (HR 0.506 (0.304–0.842)) and statins (HR 0.585 (0.435–0.785)) were associated with significantly lower mortality.
Conclusions: In our Asian population presenting with HFpEF, two-year mortality was 26.6%. Ethnicity did not predict mortality. Older age, prior myocardial infarction, prior stroke, smoking, and higher creatinine levels were found to be significant predictors of mortality.

1. Introduction

Heart failure (HF) occurs in patients with preserved ejection fraction (EF) [1]. This entity, commonly known as heart failure with preserved ejection fraction (HFpEF), has been increasing in prevalence and accounts for about half of all heart failure presentations [2]. HFpEF is associated with mortality rates higher than the general population [3]. Registries such as the Acute Decompensated Heart Failure National Registry (ADHERE) [4] and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [5] showed similar 60–90 day mortality among HFpEF patients compared to those with heart failure and reduced EF (HFrEF) [5]. Previous studies looking at longer-term mortality also yielded mixed results. Several registry/population-based studies showed similar longer-term mortality rates between both groups [6–8], while others [2,9], including a recent meta-analysis [9], showed better outcomes among those with HFpEF [2,9].

Ethnicity has been shown to play an important role in mortality outcomes in heart failure [10–12]. Previous studies in Asian patients with heart failure showed increased adverse outcomes in Malays and Indians compared to Chinese, but these did not focus on patients with HFpEF [11,12]. Furthermore, the ADHERE registry showed that patients from Asia were younger and had more severe clinical symptoms when compared to western cohorts [13,14]. The impact of ethnicity as well as other predictors of mortality has hitherto not been well studied in Asian patients with HFpEF. We report the clinical demographics and

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SCDB, Singapore Cardiac DataBank; DRG, diagnosis-related group; NRDO, National Registry of Diseases Office; MI, myocardial infarction; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

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2-year mortality of patients admitted with HFpEF compared to those with HFrEF in a multi-ethnic Asian country, and investigate the impact of ethnicity and other predictors on mortality.

2. Material and methods

Singapore is a multi-ethnic city-state in Asia comprising 5.31 million people (74% Chinese, 13% Malay, 9% Indian) [15]. Tertiary care in Singapore is served by an efficient healthcare network of public hospitals accounting for 77% of all hospital admissions [16]. The Singapore Cardiac Databank (SCDB) collects a national registry of various cardiovascular diseases as described previously [17,18]. The SCDB Heart Failure (SCDB-HF) registry prospectively collects data on all heart failure admissions to all public hospitals in Singapore starting from 1 January 2008. The registry collects information on demographics, comorbidities, medical history, clinical characteristics, initial evaluations, laboratory and imaging results, treatment and discharge outcomes. All consecutive patients ≥21 years and admitted with the diagnosis-related group (DRG) code 252 (Heart Failure) will be included in the registry. Data were collected by trained coordinators using a standardized case report form, entered into an electronic database and subsequently internally and externally validated. Ejection fraction was obtained from transthoracic echocardiogram within 1 month of the admission. In this registry, the optimal echocardiographic method of assessing EF for each case was determined by the cardiologist reporting the echocardiogram and not limited to one particular method. Registry participation did not alter any treatment or medical care and was not linked to specific therapy/medication. The study was approved by the institutional review board of the respective institutions. The study complies with the Declaration of Helsinki.

2.1. Study population

We identified 2176 consecutive patients who were admitted with DRG code 252 (Heart Failure) from two institutions in the SCDB-HF registry from 1 Jan 2008 to 31 Dec 2009. HFpEF was defined as heart failure patients with EF ≥ 50% and ≥grade 1 diastolic dysfunction on the echocardiogram or NT-proBNP level > 220 pg/mL. 55 patients were excluded due to incomplete follow-up; 93 patients with no recent documented EF and 68 patients with EF ≥ 50% that did not fulfill the criteria were excluded.

2.2. Outcomes

All mortality data in Singapore are kept by the National Registry of Diseases Office (NRDO). All patients were followed-up for 2 years. Mortality data and cause of death was obtained from NRDO. Primary outcome measure was 2-year all-cause mortality and secondary outcome measures were 2-year cardiovascular mortality, in-hospital mortality and length of stay.

2.3. Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS®, version 16.0). The demographic and risk factor profile of the study population was characterized using descriptive statistics. All parameters analyzed were taken at admission with the exception of medications which were taken on discharge. The χ^2 test was used to compare categorical variables and the t-test used to investigate the relationship between continuous variables between the 2 groups. Cox proportional hazard modeling was applied to all-cause and cardiovascular mortality. Variables significant on univariate analysis ($p < 0.05$) were selected for the multivariate models. Multivariate Cox proportional hazard models were run separately for each group to calculate the hazard ratios and associated confidence intervals for mortality for the respective variable. A separate multivariate analysis using variables with $p < 0.1$ was performed as well. A p value of <0.05 was taken to be statistically significant.

3. Results

3.1. Study population

A total of 1960 patients were analyzed in the study (Table 1). 38.3% (n = 751) of these patients had HFpEF. The HFpEF group had a significantly higher proportion of patients of Chinese ethnicity and a lower proportion of Malay ethnicity compared to patients with HFrEF. HFpEF patients were also significantly older and had a significantly higher proportion of females. HFpEF patients had a lower proportion of coronary artery disease, previous myocardial infarction, diabetes, hyperlipidemia and peripheral vascular disease, and a higher proportion of atrial fibrillation, hypertension and stroke.

Patients with HFpEF presented with a higher systolic blood pressure, lower diastolic blood pressure, lower heart rate and narrower QRS duration on ECG. They also had a lower creatinine, hemoglobin and NT-proBNP level.

3.2. Outcomes

The all-cause mortality rate of patients with HFpEF at 2 years was 26.6% (n = 200) compared to 37.1% (n = 449) of patients with HFrEF (HR 0.668 (95% CI 0.566–0.790), p < 0.001). This was significant even on multivariate analysis (HR 0.618 (95% CI 0.508–0.753), p < 0.001). See Fig. 1.

The cardiovascular mortality at 2 years in patients with HFpEF was 13.3% (n = 100) compared to 24.7% (n = 299) in patients with HFrEF (HR 0.503 (95% CI 0.401–0.631), p < 0.001). This was significant even on multivariate analysis (HR 0.535 (95% CI 0.411–0.696), p < 0.001). Noncardiovascular mortality accounted for 50.0% (100/200) of overall mortality in HFpEF patients compared to 33.4% (150/449) in HFrEF patients (p = 0.012).

There was no significant difference in in-hospital mortality rate of patients with HFpEF compared to those with HFrEF (1.2% (n = 9) vs 1.1% (n = 13), p = 0.801). The average length of stay of patients with

Table 1
Demographics and clinical characteristics of study population.

	Overall (n = 1960)	HFpEF (n = 751)	HFrEF (n = 1209)	P value[a]
Demographics				
Mean age (SD)	69.1 (12.2)	73.1 (10.6)	66.6 (12.5)	<0.001
Male	53.1	35.3	64.1	<0.001
Race				0.011
Chinese	70.7	74.2	68.6	
Malay	15.5	12.1	17.6	
Indian	11.9	12.0	11.9	
Others	1.8	1.7	1.9	
Clinical characteristics				
Prior coronary artery disease	45.7	41.0	48.6	0.001
Prior myocardial infarction	28.9	16.2	36.7	<0.001
Atrial fibrillation	25.8	34.0	20.7	<0.001
Diabetes mellitus	52.0	47.1	55.1	0.001
Hypertension	73.5	80.3	69.3	<0.001
Hyperlipidemia	62.0	57.9	64.6	0.003
Stroke	16.2	18.4	14.8	0.037
Peripheral vascular disease	6.8	5.3	7.7	0.043
Chronic obstructive pulmonary disease	12.6	14.2	11.5	0.074
Ever smoker	38.1	26.5	45.2	<0.001
Systolic blood pressure 5(SD) (mm Hg)	139 (30)	143 (30)	136 (30)	<0.001
Diastolic blood pressure (SD (mm Hg))	76 (18)	73 (17)	78 (19)	<0.001
Heart rate (SD)	88 (23)	84 (24)	90 (22)	<0.001
QRS (SD) (ms)	101 (25)	94 (20)	106 (27)	<0.001
NT-proBNP (SD) (pg/mL)[b]	9720 (14,030)	5814 (10,147)	12,323 (15,619)	<0.001
Creatinine (SD) (μmol/L)	137 (104)	129 (100)	142 (106)	0.005
Sodium (SD) (mmol/L)	136 (7)	136 (5)	136 (8)	0.246
Potassium (SD) (mmol/L)	4.2 (1.2)	4.2 (0.8)	4.3 (1.3)	0.252
Hemoglobin (SD) (g/dL)	12.2 (3.6)	11.7 (2.0)	12.6 (4.2)	<0.001
Discharge medications				
ACE inhibitor	50.4	41.9	55.7	<0.001
ARB	20.1	20.2	20.0	0.905
ACE inhibitor/ARB	68.9	59.9	74.4	<0.001
Betablocker	59.2	50.1	64.9	<0.001
Mineralocorticoid-receptor antagonist	16.7	8.3	21.9	<0.001
Nitrate	47.5	39.9	52.2	<0.001
Diuretic	83.3	77.9	86.7	<0.001
Digoxin	23.1	17.2	26.7	<0.001
Aspirin	51.3	40.3	58.1	<0.001
Plavix	14.1	10.9	16.1	0.001
Warfarin	13.7	16.8	11.7	0.002
Statin	67.6	60.9	71.8	<0.001

Mean and SD are reported for continuous data and frequency and percentages for categorical data.
[a] Comparing HFpEF vs HFrEF.
[b] 375 patients with missing data (159 with HFpEF).