

Interaction of sex and diabetes in Asian patients with heart failure with mildly reduced left ventricular ejection fraction

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ABSTRACT

Introduction: The impact of sex and diabetes mellitus (DM) on patients with heart failure with mildly reduced ejection fraction (HFmrEF) is not well elucidated. This study aims to evaluate sex differences in the clinical profile and outcomes in Asian HFmrEF patients with and without DM.

Methods: Patients admitted nationally for HFmrEF (ejection fraction 40–49%) between 2008 and 2014 were included and followed up until December 2016. The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular (CV) death and/or heart failure (HF) rehospitalisations.

Results: A total of 2,272 HFmrEF patients (56% male) were included. More women had DM than men (60% versus 55%, $P=0.013$). Regardless of DM status, HFmrEF females were older, less likely to smoke, had less coronary artery disease, narrower QRS and lower haemoglobin compared to men. The odds of having DM decreases in smokers who are women as opposed to men ($P_{\text{interaction}}=0.017$).

In multivariate analysis, DM reached statistical analysis for all-cause mortality and combined CV mortality or HF rehospitalisation in both men and women. However, the results suggest that there may be sex differences in terms of outcomes. DM (vs non-DM) was less strongly associated with increased all-cause mortality (adjusted hazards ratio [adj HR] 1.234 vs adj HR 1.290, $P_{\text{interaction}} < 0.001$) but more strongly associated with the combined CV death/HF rehospitalisation (adj HR 1.429 vs adj HR 1.317, $P_{\text{interaction}} = 0.027$) in women (vs men).

Conclusion: Asian women with HFmrEF had a higher prevalence of DM, with differences in clinical characteristics, compared to men. While diabetes conferred poor outcomes regardless of sex, there were distinct sex differences. These highlight the need for sex-specific management strategies.

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INTRODUCTION

Diabetes mellitus (DM) is a common comorbidity worldwide with global prevalence among adults above 18 years of age increasing from 4.7% in 1980 to 8.5% in 2014.¹ DM has been shown to be a common comorbidity in heart failure (HF) patients ranging from 4.3–28%² and when present, portends a poorer prognosis in these patients.^{3,4}

There have been increasing epidemiologic data showing Asian patients with HF to be significantly

younger, leaner and with a higher predisposition for DM compared to their Western counterparts.^{5,6} Prior studies have also shown that Asian patients with HF with mildly reduced ejection fraction (HFmrEF) represent a distinct HF phenotype riddled with a high burden of cardiovascular diseases such as DM, peripheral vascular disease, and coronary artery disease with distinct major adverse cardiac events outcomes.⁷⁻⁹ While research on sex differences among patients with both DM and other subtypes of HF has been gaining traction¹⁰ with distinct

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CLINICAL IMPACT

What is New

- In our Asian cohort with heart failure with mildly reduced ejection fraction (HFmrEF), women with HFmrEF were found to have a higher prevalence of diabetes mellitus (DM), with differences in clinical characteristics, compared to men.
- While diabetes conferred poor outcomes regardless of sex, there were distinct sex differences with women experiencing a higher composite rate of cardiovascular mortality and heart failure readmission than men.
- We also found that women with HFmrEF, particularly those without DM, were less likely to be prescribed with guideline-directed medical therapy (GDMT) of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or beta-blockers despite having comparable baseline haemodynamics, mean left ventricular ejection fraction and mean serum creatinine levels.

Clinical Implications

- Our findings highlight the need for sex-specific management strategies for HFmrEF patients with DM to improve outcomes.
- Concerted effort should be made to review the discrepant GDMT prescribing practices by clinicians for women with HFmrEF to further reduce morbidity and mortality.

sex-specific differences noted, data in HFmrEF have been scarce. This study aimed to evaluate sex differences in the clinical profile and outcomes in Asian HFmrEF patients with/without DM.

METHODS

Study population and setting

The Singapore Cardiac Databank Heart Failure (SCDB-HF) registry is a nationwide prospective, observational data collection registry for all consecutive patients ≥ 21 years of age admitted for heart failure to all Singapore public hospitals. Comprehensive data collection at baseline such as demographics, clinical signs and symptoms, characteristics, biochemistry, treatments and discharge outcomes were captured in this registry. Details of the registry have been previously described with numerous publications ensuing from this registry.^{11–15} Trained coordinators collected data with the use of a standardised case report form and entered

these findings into an electronic database, which underwent internal and external validation. Registry participation was independent of medical care received. The study was approved by the Institutional Ethics Review Board. Consecutive unique patients who were admitted to the SCDB-HF registry from 1 January 2008 to 31 December 2014 were included. Only patients with a mildly reduced ejection fraction of 40–49% at index presentation were included in this study.

Outcomes

All patients were followed-up until 31 December 2016. DM was defined as having a prior history of diabetes and/or currently receiving antidiabetic therapies. The primary outcome measured was all-cause mortality. The secondary outcome was a composite of cardiovascular death and/or heart failure rehospitalisation. These outcomes were obtained from national registries.

Statistical analyses

Baseline characteristics of individual subgroups were described using frequencies and percentages for categorical variables, and as mean $\pm$ standard deviation (SD) or medians with interquartile range (IQR) for continuous variables. Differences between groups were tested using chi-square tests for categorical variables and independent samples t-tests or one-way analysis of variance for continuous variables. Differences in baseline demographics, clinical profile, comorbidities and pharmacotherapy were tested between DM and non-DM in men and women separately; and men and women in DM and non-DM groups separately. The significance of correlations among the factors was applied using the Benjamini-Hochberg procedure with a false discovery rate of 0.05. Variables with significant *P* values after correction were indicated with an asterisk.

To examine clinical correlates of DM, a multivariable logistic regression model using DM as a dependent variable was built with a stepwise approach, by considering variables with significant univariable *P* values ($P < 0.05$) and a priori choice of clinically important factors to obtain the most parsimonious model. Male and female groups in the clinical correlates of DM were tested with an interaction term and main effect terms, and adjusted for other significant factors. Time-to-event analyses were examined using a multivariable Cox proportional hazards model in the absence of violation of the proportion hazard assumption. The endpoints of overall all-cause mortality, cardiovascular mortality and first HF rehospitalisation were censored at time of event; for those without event, the last date of follow-up was used. To determine if DM modifies the

relationship between sex and outcomes in HFmrEF, the interaction between DM and sex, adjusted for age, was examined in the Cox model. Patients with incomplete data on adjusted clinical and demographic factors were excluded from multivariable logistic and Cox regression analyses. SAS version 9.4 (SAS Institute Inc, Cary, US) was used to conduct the analyses.

RESULTS

Baseline demographics and clinical characteristics

A total of 2,272 Asian patients with HFmrEF were included in this study. The mean age was 70.6 ± 12.7 years, and 56.1% were men. Among these patients, the prevalence of DM was higher in women than in men (60.4% versus 55.0%, respectively, $P=0.013$). For both DM and non-DM patients, women with HFmrEF were more likely to be older, less likely to smoke, had narrower QRS duration, lower mean haemoglobin on presentation, and less likely to have coronary artery disease compared to men (all $P<0.05$). Within the DM group, women had lower mean creatinine (147.2 vs 177.1 mmol/L), and were less likely to have hyperlipidaemia (75.9 vs 82.0%) and prior myocardial infarction (20.6 vs 26.8%) than men. In the non-DM group, women had lower mean diastolic blood pressure than men (78.7 vs 82.3 mmHg).

With regards to guideline-directed medical therapy, we also noted significant sex differences in the medication uptake particularly in patients without DM. Female patients without DM were less likely to be prescribed with angiotensin-converting enzyme inhibitors (ACEi) or angiotension receptor blockers (ARBs) and beta-blockers. Comparing DM and non-DM patients, DM patients were more likely to be prescribed with BBs, antiplatelets and statins but less likely to be prescribed with digoxin and warfarin (Table 1).

Clinical correlates of DM

In both men and women, multivariate correlates of DM included younger age, Indian ethnicity, lower haemoglobin levels, hypertension, hyperlipidaemia, absence of AF and peripheral vascular disease. Among the independent correlates for DM, those that differed between men and women were serum potassium levels and smoking history. DM was more strongly correlated with higher potassium levels in men vs women ($P_{\text{interaction}}=0.034$), and was more strongly inversely correlated with smoking history in women vs men ($P_{\text{interaction}}=0.017$) (Fig. 1).

Clinical outcomes

Follow-up data were available in all 2,272 patients with no loss to follow-up in any groups. On multivariable analysis, diabetes was a significant predictor of overall mortality, CV mortality, HF rehospitalisations, and the composite of CV mortality/HF rehospitalisations in both men and women. However, there were distinct sex-specific differences for the outcomes of mortality and composite of CV mortality/HF rehospitalisations. DM was more significantly associated with overall mortality in men compared to women (adjusted hazards ratio [adj HR] 1.290, 95% confidence interval [CI] 1.094–1.522 vs adj HR 1.234, 95% CI 1.032–1.476; $P_{\text{interaction}}<0.001$) and with combined CV mortality/HF rehospitalisations in women compared to men (adj HR 1.429; 95% CI 1.195–1.710 vs adj HR 1.317; 95% CI 1.137–1.526; $P_{\text{interaction}}=0.027$). There were no sex-specific differences for the individual outcomes of CV mortality and HF rehospitalisations. In the absence of DM as a comorbidity, women and men have similar outcomes for overall mortality ($P=0.511$), cardiovascular mortality ($P=0.825$), HF hospitalisation ($P=0.074$), and composite of cardiovascular mortality and HF hospitalisation ($P=0.922$) (Table 2 and Supplementary Table S1 in online Supplementary Material, and Fig. 2).

DISCUSSION

In this prospective observational cohort of 2,272 Asian patients with HFmrEF, we demonstrated several pertinent findings: (1) there is a higher prevalence of DM in women with HFmrEF than in men; (2) distinct sex differences exist in clinical characteristics in this cohort; and (3) DM is a potent disease modifier that worsens all outcomes of HFmrEF patients, with a differential effect of higher overall mortality in men, and a higher composite outcome of cardiovascular mortality and HF readmissions in women. No sex differences in outcomes were noted in our HFmrEF cohort in the absence of DM.

In our study, we observed an increased prevalence of DM in women than men despite a greater representation of men. The International Diabetes Federation reported that the current global prevalence of DM in women and men was 9.0% and 9.6%, respectively, with greater affliction for men up until the age of 69 years, followed by a reversal in trend with greater female preponderance in adults aged 70 years and above.¹⁶ This could explain our findings given that the mean age of our cohort was 70.6 years. Furthermore, a recent study suggests that Asian females with HFmrEF were more likely to have DM than males, despite having a lean body mass index.¹⁰

Table 1. Clinical characteristics of study population

	% missing		Men		Women		P value	DM	Men vs Women	No DM
	DM	No DM	DM	No DM	DM	No DM				
No. (%)	704 (55)	571 (45)	602 (60)	395 (40)	0.013					
Demographics										
Mean age (SD), years	0	68.1 (11.3)	69.3 (13.3)	0.069	71.6 (11.9)	75.2 (14.1)	<0.001*	<0.001*		<0.001*
Ethnicity, no. (%)	0									
Chinese	425 (60.4)	417 (73.0)	351 (58.3)		302 (76.5)					
Malay	142 (20.2)	96 (16.8)	135 (22.4)		57 (14.4)					
Indian	112 (15.9)	34 (6.0)	95 (15.8)		27 (6.8)					
Others	25 (3.6)	24 (4.2)	21 (3.5)		9 (2.3)					
Clinical parameters										
Mean LVEF (SD), %	0	42.9 (2.7)	42.9 (2.7)	0.966	43.1 (2.7)	42.9 (2.7)	0.448	0.449		0.947
Mean systolic blood pressure (SD), mmHg	0	150.8 (31.4)	145.2 (31.0)	0.001*	153.6 (29.0)	147.3 (29.9)	0.001*	0.099		0.295
Mean diastolic blood pressure (SD), mmHg	0	80.8 (19.7)	82.3 (20.6)	0.176	78.7 (17.5)	78.7 (19.2)	0.957	0.045		0.007*
Mean heart rate (SD), beats/min	0	88.0 (21.6)	90.3 (24.3)	0.079	90.1 (20.9)	91.4 (24.5)	0.399	0.073		0.498
Mean BMI (SD), kg/m ²	58.1	26.3 (6.5)	24.6 (5.7)	0.001*	26.6 (5.7)	24.6 (6.8)	0.002*	0.582		0.943
BMI categories, kg/m ²	58.1									
Underweight (<18.5)	10 (3.1)	31 (11.1)	7 (3.2)	<0.001*	20 (14.5)		<0.001*	0.776		0.180
Normal (18.5–23)	96 (30.1)	88 (31.4)	56 (25.9)		45 (32.6)					
Overweight (23–27.5)	101 (31.7)	101 (36.1)	73 (33.8)		36 (26.1)					
Obese (≥27.5)	112 (35.1)	60 (21.4)	80 (37.0)		37 (26.8)					
Mean QRS duration (SD), ms	0.8	101.4 (22.1)	103.2 (23.0)	0.171	95.7 (21.0)	97.4 (22.6)	0.235	<0.001*		<0.001*
Mean creatinine (SD), mmol/L	0.4	177.1 (146.3)	132.4 (97.3)	<0.001*	147.2 (111.3)	126.5 (127.5)	0.007*	<0.001*		0.421
Mean sodium (SD), mmol/L	0.5	136.7 (4.7)	137.2 (4.3)	0.053	136.6 (5.1)	137.5 (4.7)	0.004*	0.628		0.307
Mean potassium (SD), mmol/L	0.5	4.3 (0.7)	4.1 (0.8)	<0.001*	4.2 (0.7)	4.2 (0.7)	0.051	0.379		0.302
Mean haemoglobin (SD), g/dL	1.7	11.9 (2.2)	12.6 (2.3)	<0.001*	10.9 (1.8)	11.8 (1.9)	<0.001*	<0.001*		<0.001*
Comorbidities, no. (%)										
Prior coronary artery disease	0	386 (54.8)	249 (43.6)	<0.001*	279 (46.3)	131 (33.2)	<0.001*	0.002*		0.001*
Prior myocardial infarction	0	189 (26.8)	108 (18.9)	0.001*	124 (20.6)	62 (15.7)	0.052	0.008*		0.197

Table 1. Clinical characteristics of study population (Cont'd)

	% missing		Men		Women		P value	DM Men vs Women	No DM Men vs Women
	DM	No DM	DM	No DM					
Atrial fibrillation	0	111 (15.8)	163 (28.5)	107 (17.8)	123 (31.1)	<0.001*	0.332	0.385	
Hypertension	0	616 (87.5)	396 (69.4)	539 (89.5)	285 (72.2)	<0.001*	0.252	0.348	
Hyperlipidaemia	0	577 (82.0)	326 (57.1)	457 (75.9)	215 (54.4)	<0.001*	0.007*	0.412	
Stroke	0	120 (17.0)	63 (11.0)	97 (16.1)	59 (14.9)	0.002*	0.617	0.073	
Peripheral vascular disease	0	78 (11.1)	11 (1.9)	58 (9.6)	9 (2.3)	<0.001*	0.394	0.706	
Chronic obstructive pulmonary disease	0	63 (8.9)	78 (13.7)	56 (9.3)	41 (10.4)	0.008*	0.825	0.127	
Ever smoker	0	409 (58.1)	326 (57.1)	36 (6.0)	49 (12.4)	<0.001*	<0.001*	<0.001*	
Discharge medications									
ACEi	0	337 (47.9)	323 (56.6)	280 (46.5)	176 (44.6)	0.002*	0.545	<0.001*	
ARB	0	159 (22.6)	82 (14.4)	142 (23.6)	65 (16.5)	<0.001*	0.007*	0.373	
ACEi or ARB	0	488 (69.3)	402 (70.4)	409 (67.9)	241 (61.0)	0.675	0.025*	0.002*	
Beta-blocker	0	551 (78.3)	413 (72.3)	467 (77.6)	256 (64.8)	0.014*	<0.001*	0.013*	
Spirinolactone/aldosterone antagonist	0	72 (10.2)	59 (10.3)	40 (6.6)	41 (10.4)	0.951	0.021	0.981	
Nitrate	0	267 (37.9)	182 (31.9)	222 (36.9)	97 (24.6)	0.024*	<0.001*	0.014*	
Diuretic	0	578 (82.1)	446 (78.1)	491 (81.6)	301 (76.2)	0.075	0.041	0.487	
Digoxin	0	75 (10.7)	107 (18.7)	86 (14.3)	89 (22.5)	<0.001*	0.001*	0.150	
Antiplatelets (aspirin, clopidogrel)	0	525 (74.6)	364 (63.7)	416 (69.1)	226 (57.2)	<0.001*	0.028	0.041	
Anticoagulants (warfarin)	0	56 (8.0)	100 (17.5)	49 (8.1)	63 (15.9)	<0.001*	0.902	0.523	
Statins (lipid-lowering)	0	582 (82.7)	403 (70.6)	495 (82.2)	255 (64.6)	<0.001*	0.833	0.048	

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; SD: standard deviation. Values are n (%). The *P* values are based on Pearson's chi-square test (for categorical variables) and t-tests or one-way analysis of variance (for continuous variables).

* Significant *P* values after Benjamini-Hochberg procedure with false discovery rate 0.05.

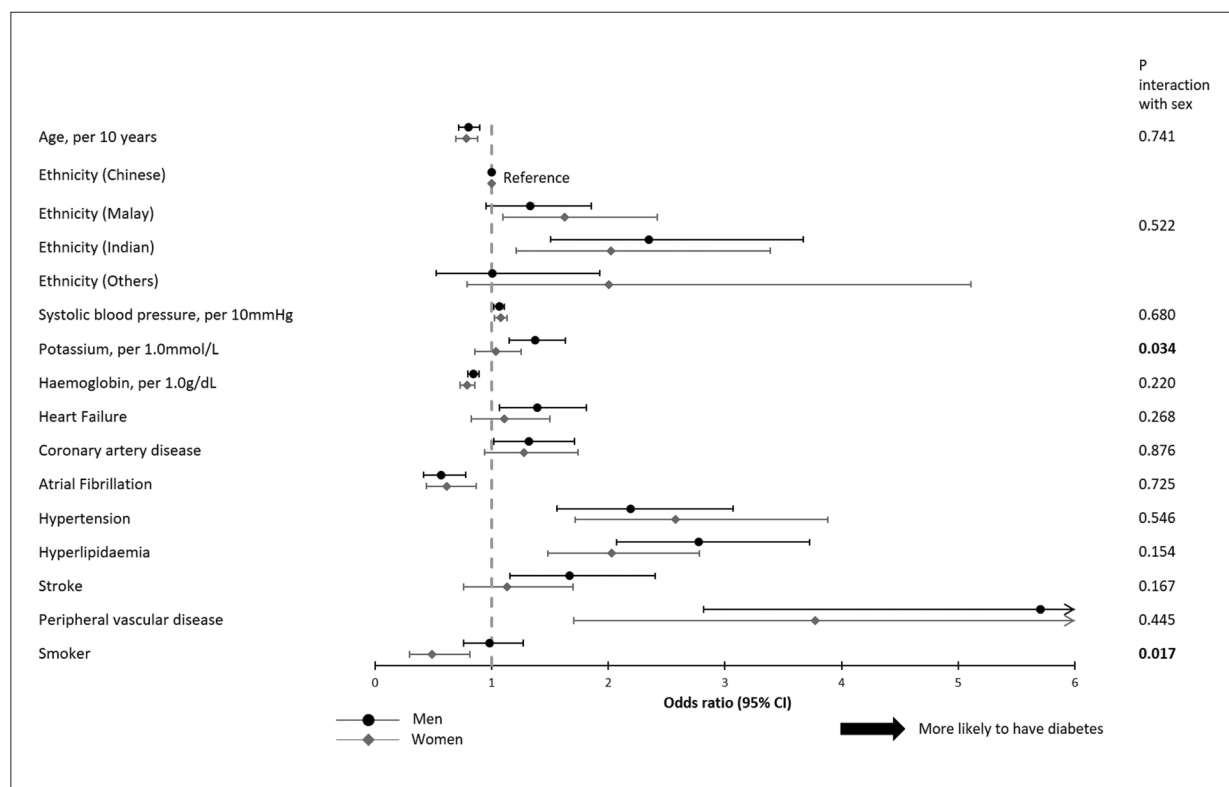


Fig. 1. Association of clinical correlates and diabetes mellitus. Odds ratio adjusted for age, ethnicity, systolic blood pressure, potassium, haemoglobin, heart failure, coronary artery disease, atrial fibrillation, hypertension, hyperlipidaemia, stroke, peripheral vascular disease and smoker.
CI: confidence interval

In our cohort, we found that sex differences did not alter outcomes in the absence of DM as a comorbidity. Previous studies assessing sex-based differences in HF prognosis have yielded conflicting results.^{17–19} In the Swedish HF registry of 42,987 patients, Stolfo et al. demonstrated a higher crude risk of mortality/morbidity in female HFmrEF patients compared to their male cohorts, although this effect was lost upon adjustment for other variables with mortality outcomes favouring females instead. HF admission outcomes were similar for both males and females in this study.¹⁷ In contrast, Martines-Selles et al. and O'Meara et al. demonstrated better survival in women than in men, irrespective of left ventricular ejection fraction (LVEF)^{18,19} These differences may be explained by the complex interplay of biological variabilities in cardiac functional remodelling, role of sex hormones, different socioeconomic characteristics in women across geographical locations, as well as different adjustments used in studies worldwide.

On the contrary, our study showed that DM was a potent disease modifier of outcomes in HFmrEF. Distinct sex-specific differences were noted with higher

risk of overall mortality in men and a higher risk of combined HF rehospitalisations/CV death in women. This finding is corroborated by contemporary studies evaluating the effects of DM on sex differences. Malmberg et al. recently reported that the relative rate of first-time cardiovascular complications associated with DM such as myocardial infarction, HF, ischaemic stroke, or cardiovascular death composite outcomes were higher in women than in men across all ages in a large Danish cohort.²⁰ In a meta-analysis of 47 cohorts totalling 12,142,998 HF patients, DM was also shown to increase the risk of incident HF in both men and women, with a 47% and 9% excess risk of HF in type 1 diabetes mellitus and type 2 diabetes mellitus, respectively, for women when compared to their male counterparts.²¹

In terms of HF pharmacotherapy prescription, the presence and severity of chronic kidney disease (CKD) could potentially limit the initiation of guideline-directed medical therapy such as ACEi/ARB. In our cohort, the mean serum creatinine levels in our study were in the range of 126.5–177.1mmol/L, which puts the average CKD severity as stage 3. Despite this,

Table 2. Association of diabetes mellitus with different group of outcomes: (A) all-cause mortality, (B) cardiovascular mortality, (C) heart failure rehospitalisation, and (D) heart failure rehospitalisation or cardiovascular mortality in men and women

	Age-adjusted			Men			Women		
	<i>P</i> interaction with sex	Number at risk	Number of events (%)	Adjusted HR (95% CI)	<i>P</i> -value	Number at risk	Number of events (%)	Adjusted HR (95% CI)	<i>P</i> value
All-cause mortality ^a									
Diabetes	<0.001*	704	415 (58.9)	1.290 (1.094–1.522)	0.003*	602	387 (64.3)	1.234 (1.032–1.476)	0.021*
No diabetes		571	287 (50.3)	1.000 (reference)		395	227 (57.5)	1.000 (reference)	
Cardiovascular mortality ^b									
Diabetes	0.131	704	221 (31.4)	1.431 (1.148–1.783)	0.001*	602	183 (30.4)	1.423 (1.103–1.837)	0.007*
No diabetes		571	130 (22.8)	1.000 (reference)		395	96 (24.3)	1.000 (reference)	
Heart failure rehospitalisation ^c									
Diabetes	0.054	704	341 (48.4)	1.254 (1.060–1.485)	0.008*	602	275 (45.7)	1.480 (1.196–1.830)	<0.001*
No diabetes		571	244 (42.7)	1.000 (reference)		395	132 (33.4)	1.000 (reference)	
Cardiovascular mortality or heart failure rehospitalisation ^d									
Diabetes	0.027*	704	443 (62.9)	1.317 (1.137–1.526)	<0.001*	602	360 (59.8)	1.429 (1.195–1.710)	<0.001*
No diabetes		571	303 (53.1)	1.000 (reference)		395	193 (48.9)	1.000 (reference)	

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CI: confidence interval; HR: hazard ratio

^a HR adjusted for age, race, creatinine, sodium, haemoglobin, stroke, peripheral vascular disease, ACEi or ARB, beta-blockers, anticoagulants and lipid lowering.^b HR adjusted for age, prior myocardial infarction, systolic blood pressure, QRS duration and sodium.^c HR adjusted for age, prior coronary artery disease, diastolic blood pressure, QRS duration and creatinine.^d HR adjusted for prior coronary artery disease, ever smoker, QRS duration and spironolactone/aldosterone antagonist.* Values were considered to be statistically significant when $P < 0.05$.

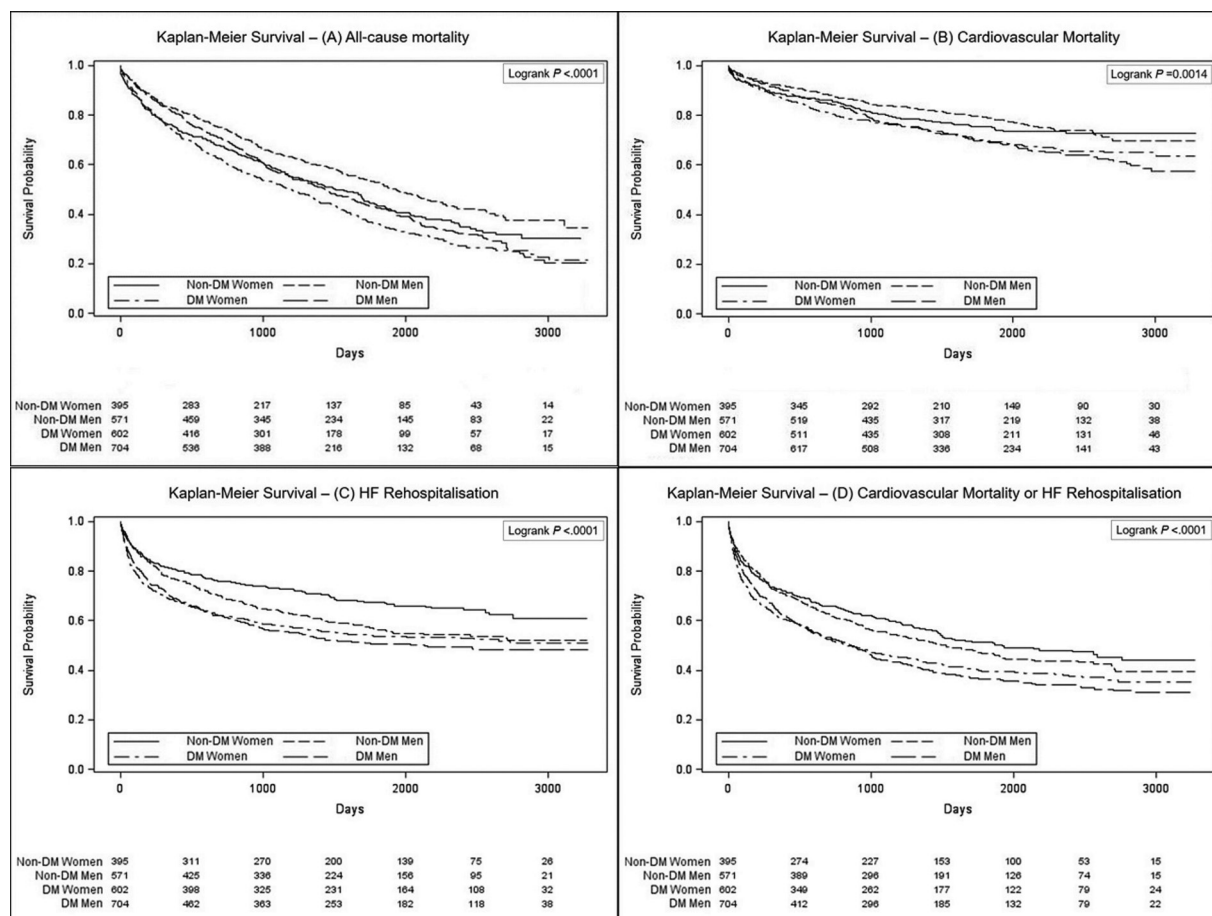


Fig. 2. Relationship between diabetes mellitus (DM) and (A) all-cause mortality (B) cardiovascular mortality, (C) heart failure (HF) rehospitalisation, and (D) cardiovascular mortality or HF rehospitalisation for men and women
DM: diabetes mellitus; HF: heart failure

the overall prescription of ACEi/ARB in our study was 67.8%, which was comparable to that of contemporary HFmrEF studies (58.8–86%).^{17,22–24}

We did, however, note subtle sex-specific differences in HF pharmacotherapy prescription in our cohort. Non-DM females were less likely to be prescribed ACEi/ARB and BB than non-DM males although there were no significant differences in baseline haemodynamic (systolic/diastolic blood pressure and heart rate) as well as mean LVEF. A possible explanation could be the older mean age of non-DM females compared to males in our cohort (75.2 vs 69.3 years) and thus physicians were less likely to prescribe medications with antihypertensive effects. In terms of CKD severity, non-DM females in our cohort had comparable mean serum creatinine to non-DM men (126.5 vs 132.4 mmol/L, $P=0.421$), and even lower creatinine compared to females with DM (126.5 vs 147.2 mmol/L, $P=0.007$), suggesting that CKD severity is less likely to be the contributing factor for this discrepant practice.

In addition, there were no specific guideline recommendations on pharmacotherapy in patients with HFmrEF until recently in 2021.²⁵ In fact, this phenomenon of guideline-directed medical therapy under-prescription in females is not new and has been reported by previous studies across all types of cardiovascular diseases.^{26–28} Specific to HF patients, Tamargo et al. reviewed contemporary studies and discussed potential factors leading to this phenomenon such as sex differences in pharmacokinetics/pharmacodynamics, as well as the paucity of data on drug efficacy and safety, given female under-representation in HF clinical trials. In addition, women were found to experience adverse drug reactions either more frequently or at greater severity despite similar HF drug dosages compared to their male counterpart.²⁸ It is crucial to address this discordance in the sex-specific prescription of HF medications since ACEi/ARB and BB have shown some evidence of benefit in the HFmrEF population. From the same cohort, we recently demonstrated that ACEi/ARB and BB had a

relative risk reduction of 16% and 18%, respectively⁹ on cardiovascular mortality in this group of patients. Randomised trials on ACEi/ARB and BB have also shown reduction in cardiovascular mortality for both, as well as overall survival for BB.^{29,30}

A major challenge with analysing sex-specific data in HF patients is the under-representation of women in clinical trials due to low recruitment rates previously. Women constitute 43.9% of our cohort, which is comparatively higher than in previous studies. Since the inception of major randomised HF trials such as the CONSENSUS trial to the more recent PARADIGM-HF trial, women only represent 11–40% of these trial populations.³¹ However, distinct sex differences have been shown to exist. For example, in a post hoc analysis of BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSAT-CHF) study followed by a validation cohort in the ASIAN-HF registry, Santema et al. highlighted that women derive the greatest benefit of ACEi/ARB and BB at a lower percentage of recommended doses, with not only no incremental benefit but increased risk of developing adverse effects at higher doses.²⁶ It is thus critical that future HF clinical trials recruit an equal proportion of women such that more robust data on sex differences can be generated to guide sex-specific HF pharmacotherapy trials as we head towards an era of targeted and personalised medicine.

Limitations

While the strengths of our study hinge upon an ethnically diverse Asian HFmrEF population with an almost proportionate sex distribution, several limitations do exist. Inherent to any observational study, despite robust adjustment for confounders, there may be variables not evaluated that may influence the results. Secondly, this study included mainly hospitalised patients. Thirdly, data on haemoglobin A1c and diabetes control, as well as detailed echocardiographic data, were not available within the registry and these will be work for future studies. Lastly, the cohort was recruited up to 2016 with the impact of newer medications such as sodium-glucose transport protein 2 inhibitors on sex differences not evaluated.

CONCLUSION

In our Asian HFmrEF cohort, women with HFmrEF have a higher prevalence of DM, with differences in clinical characteristics, compared to men. While diabetes confers poor outcomes regardless of sex, there are distinct differences between the sexes. These highlight the need for sex-specific management strategies for HFmrEF patients with DM to improve outcomes.

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