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Sex Differences in the Mortality Risk of Elderly Patients with Systolic Heart Failure in Taiwan

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on behalf of the Taiwan Society of Cardiology (TSOC) Heart Failure with Reduced Ejection Fraction (HFrEF) Registry Investigators and Committee

Background: Sex differences in heart failure mortality might be affected by age, race, and treatment response. Many large studies in Western countries have shown conflicting results, however few studies have been conducted in Asian patients.

Objectives: We prospectively investigated the mortality risk in a multicenter cohort of 1,093 male and 416 female heart failure patients with reduced ejection fraction (HFrEF) hospitalized for worsening symptoms in Taiwan between 2013 and 2015.

Methods: Kaplan-Meier curve and Cox proportional regression analyses were used to determine the one-year mortality risk by sex.

Results: There were no significant differences in major adverse cardiovascular events, re-admission rate, and mortality between sexes in the overall cohort and the young subgroup during one-year of follow-up. In the elderly subgroup, the overall and cardiac mortality rate of the male patients were higher than those of the female patients ($p = 0.035$, $p = 0.049$, respectively). We found that the prognostic effect of old age on overall mortality rate appeared to be stronger in the male patients ($p < 0.0001$) than in the female patients ($p = 0.69$) in Cox regression analysis and Kaplan-Meier survival curves. Male sex was a risk factor for all-cause mortality in the elderly (hazard ratio: 1.50, 95% confidence interval 1.02-2.25) independently of systolic blood pressure, diabetes mellitus, hemoglobin concentration, kidney function, and medications.

Conclusions: In the Taiwan HFrEF registry, the highest mortality risk was observed in male patients aged 65 years or more. Clinicians need to pay more attention to these patients.

Key Words: Age • Heart failure • Mortality • Sex difference

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INTRODUCTION

Heart failure (HF) is a growing public health issue worldwide with significant prevalence and mortality, both of which increase with advancing age.[1] Although public awareness and survival have improved along with advances in evidence-based treatment guidelines, HF remains a major cause of hospitalization in elderly populations.[2-4] How sex affects the outcomes of HF has long been of interest. Some observational registries have demonstrated that compared with men, women with HF were older and had higher blood pressure, more non-

ischemic etiology, more severe New York Heart Association (NYHA) functional classes, and comorbidities such as diabetes and chronic kidney disease.[5-7] With regards to cardiovascular disease (CVD), women have been reported to have higher serum concentrations of adipokines and D-dimer, and lower levels of biomarkers for endothelial dysfunction.[8] All of these biological findings may translate to a clinical profile in which women have a better prognosis of HF than men.

In the United States, the number of annual CVD deaths in women exceeded that of men in 1984 and still remained higher until 2007.[9] However, the age-adjusted CVD death rate in women fell from 263.3 to 134.4, whereas the rate in men fell from 542.9 to 266.8 deaths per 100,000 population from 1980 through 2000.[10] Several studies have discussed the impact of sex differences on HF mortality, however a definite conclusion has yet to be made. A Dutch cohort study conducted by Vaartjes et al. comprising 29,053 patients showed significantly better outcomes for women at 28 days, 1 year, and 5 years post HF hospitalization.[11] The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) database including 41,929 patients showed that women had a better prognosis, especially in those with a non-ischemic heart failure etiology and in patients without diabetes.[12] Moreover, similar trends favoring women were reported in the Acute Decompensated Heart Failure National Registry (ADHERE) database, the American Heart Association Get With The Guidelines-Heart Failure (GWTG-HF) registry, and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial. In contrast, a recent Asian study carried out in Japan comprising 354 women and 696 men indicated that female sex was an independent risk factor for 2-year CVD death in patients older than 79 years.[13] Since the prognosis of HF can be affected by age, sex, and ethnicity, the aim of this study was to investigate one-year mortality risk stratified by age and sex in a prospective study of southeastern Asian patients admitted for acute decompensated HF in Taiwan.[14,15]

MATERIALS AND METHODS

Study design and patients

The Taiwan Society of Cardiology (TSOC)-Heart Failure with reduced Ejection Fraction (HFrEF) registry was a prospective observational study conducted in 21 medical centers in Taiwan, that aimed to investigate the prognosis of patients with HFrEF.[14,15] This registry enrolled patients who were hospitalized for new onset heart failure or acute worsening chronic heart failure. All patients had an echocardiographic left ventricular systolic ejection fraction < 40%. Data collection of demographics, cause of HF, comorbidities, electrocardiographic and echocardiographic findings, laboratory data, and medical treatments were obtained on admission and discharge. The elderly group included those aged 65 years or older. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or receiving anti-hypertensive therapy at discharge. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dl or receiving antidiabetic therapy. Dyslipidemia was defined as fasting total cholesterol ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 130 mg/dl, or high-density lipoprotein cholesterol < 40 mg/dl in men or < 50 mg/dl in women, or receiving lipid-lowering therapy. Echocardiographic left ventricular mass (LVM) was adjusted for body height in meters with an allometric exponent of 1.7 (LVM/height$^{1.7}$).[16] Severe HF was defined as a NYHA functional class of III or IV at admission, discharge, or follow-up. Improved NYHA functional class was defined as a downstage by more than 1 during the index hospitalization. Re-hospitalizations and outpatient follow-up for evaluating clinical conditions, laboratory and imaging studies were obtained at 6 months and 12 months after the index hospitalization. Cardiovascular mortality was defined as sudden cardiac death and death due to ischemic heart disease, stroke, refractory HF, and lethal arrhythmias. The etiologies and issued dates of mortality were verified according to the medical records. This study was approved by all participating sites' institutional review boards, provided with written informed consent of all enrolled patients.

Statistical analysis

The baseline characteristics of the male and female patients were reported as mean ± standard deviations (SD) for continuous variables and numbers (%) for categorical variables. The continuous variables were compared using two-tailed t tests. The Wilcoxon signed-rank test was used if the normality test was not met. In addi-

tion, the categorical variables were compared using the chi square test. The analysis used the time for follow-up at the patients' first enrollment between May 2013 and October 2014 with censoring at the occurrence of mortality or the end of follow-up (February 1, 2015). Kaplan-Meier (K-M) survival curves were used to assess sex-specific mortality rates and were compared using the log-rank test. Cox proportional hazard regression analyses were used to assess the association between male sex and mortality. Any factor having a significant univariate test was selected as a candidate for the multivariate analysis. All of the statistical analyses were performed using SPSS software (IBM version 22.0). A p value of < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of 1,509 patients with HFrEF, of whom 72.4% were men. On average, the men were 8.6 years younger than the women (61.0 ± 16.0 versus 69.6 ± 15.3 years; $p < 0.001$). In addition, 740 patients were older than 65 years of age (hereafter referred to as the elderly subgroup), of whom men were still dominant (61.8%) and modestly younger than the women (76.8 ± 7.34 versus 78.65 ± 7.11 years; $p < 0.001$). In the 769 patients who were younger than 65 years (hereafter referred to as the younger subgroup), there was no difference in age.

Table 1. Baseline characteristics of men and women with heart failure with reduced ejection fraction in Taiwan

Characteristics	Men	Women	p value	Men ≥ 65 y	Women ≥ 65 y	p value	Men < 65 y	Women < 65 y	p value
Numbers, n (%)	1093 (72.4)	416 (36.3)		457 (61.8)	283 (38.2)		636 (82.7%)	133 (17.3)	
Age (±SD), y	60.97 (±16.0)	69.57 (±15.3)	< 0.001	76.80 (±7.34)	78.65 (±7.11)	< 0.001	50.58 (±10.4)	51.88 (±11.9)	0.20
Cause of HF, n (%)									
Ischemic	511 (46.3)	168 (40.4)	0.026	265 (58)	126 (44.5)	< 0.001	246 (38.7)	42 (31.6)	0.12
DCM	384 (35.1)	123 (29.6)	0.041	109 (23.9)	73 (25.8)	0.55	275 (43.2)	50 (37.6)	0.23
HCVD	64 (5.9)	45 (10.8)	< 0.001	23 (5)	34 (12)	< 0.001	41 (6.4)	11 (8.3)	0.45
VHD	80 (7.3)	43 (10.3)	0.056	44 (9.6)	33 (11.7)	0.29	36 (5.7)	10 (7.5)	0.41
Current smoking, n (%)	336 (30.7)	14 (3.4)	< 0.001	78 (17.1)	5 (1.8)	< 0.001	258 (40.6)	9 (6.8)	< 0.001
Current alcohol, n (%)	303 (27.7)	19 (4.6)	< 0.001	94 (20.6)	7 (2.5)	< 0.001	209 (32.9)	12 (9.0)	< 0.001
Comorbidity, n (%)									
HTN	455 (41.6)	184 (44.2)	0.36	188 (41.1)	125 (44.2)	0.417	267 (42.0)	59 (44.4)	0.08
DM	458 (41.9)	200 (48.1)	0.031	215 (47)	137 (48.4)	0.72	243 (38.2)	63 (47.4)	0.05
Dyslipidemia	221 (20.2)	86 (20.7)	0.85	86 (18.8)	56 (19.8)	0.75	135 (21.2)	30 (22.6)	0.54
COPD/Asthma	133 (12.2)	33 (7.9)	0.019	99 (21.7)	30 (10.6)	< 0.001	34 (5.3)	3 (2.3)	0.13
CAD	490 (44.8)	141 (33.9)	< 0.001	258 (56.5)	110 (38.9)	< 0.001	232 (36.5)	31 (23.3)	0.004
CAD with previous MI	285 (26.1)	87 (20.9)	0.45	150 (32.8)	72 (25.4)	0.033	135 (21.2)	15 (11.3)	0.008
Prior HF admission, n (%)	443 (40.5)	167 (40.1)	0.89	188 (41.1)	116 (41.0)	0.97	255 (40.1)	51 (38.3)	0.71

Table 1. Continued

Characteristics	Men	Women	p value	Men ≥ 65 y	Women ≥ 65 y	p value	Men < 65 y	Women < 65 y	p value
NYHA Fc (admission)									
I or II, n (%)	129 (11.8)	50 (12)	0.91	49 (10.7)	31 (11)	0.92	80 (12.6)	19 (14.3)	0.39
III or IV, n (%)	964 (88.2)	366 (88)		408 (89.3)	252 (89)		556 (87.4)	114 (85.7)	
NYHA Fc (discharge)									
I or II, n (%)	789 (72.2)	282 (67.8)	0.093	293 (64.1)	179 (63.3)	0.81	496 (78.0)	103 (77.4)	0.89
III or IV, n (%)	304 (27.8)	134 (32.2)		164 (35.9)	104 (36.7)		140 (22.0)	30 (22.6)	
Improved NYHA Fc	781 (71.5)	289 (69.5)	0.45	307 (67.2)	191 (67.5)	0.93	474 (74.5)	98 (73.7)	0.84
SBP (±SD) at admission, mmHg	129.7 (±28)	132.9 (±27.2)	0.27	132.0 (±48.8)	133.8 (±25.2)	0.57	129.3 (±28.7)	131.0 (±31.0)	0.54
eGFR (±SD) at admission, ml/min/m^2	55.6 (±35.3)	47.1 (±30.2)	< 0.001	45.7 (±28.2)	42.1 (±24.8)	0.081	62.7 (±38.1)	57.6 (±37.2)	0.17
Hb (±SD) at admission, g/dL	13.5 (±4.8)	11.6 (±2.1)	< 0.001	12.5 (±2.3)	11.2 (±2.0)	< 0.001	14.0 (±2.2)	12.4 (±2.2)	< 0.001
LVEF, 2D (±SD), %	27.4 (±8.5)	30 (±8.5)	< 0.001	29.0 (±8.8)	30.3 (±8.4)	0.086	26.2 (±8.1)	29.1 (±8.7)	0.001
LV mass / $height^{1.7}$ (±SD), $g/m^{1.7}$	131.2 (±47.7)	121.0 (±43.4)	0.03	116.80 (±36.2)	121.41 (±42.6)	0.377	141.0 (±52.0)	120.3 (±45.4)	0.01
Medication at discharge									
ACEi/ARB, n (%)	668 (63.2)	234 (57.8)	0.15	241 (52.7)	146 (51.6)	0.76	427 (67.1)	88 (66.2)	0.83
Beta-blocker, n (%)	634 (60)	238 (58.8)	0.67	235 (54)	142 (52)	0.60	399 (64.1)	96 (72.7)	0.06
CCB, n (%)	118 (11.2)	61 (15.1)	0.042	49 (11.3)	41 (15)	0.14	69 (11.1)	20 (15.2)	0.19
Diuretics, n (%)	874 (82.7)	328 (81)	0.45	346 (79.5)	221 (81)	0.65	528 (84.9)	101 (81.1)	0.27
MRA, n (%)	443 (40.5)	145 (34.9)	0.043	144 (31.5)	93 (32.9)	0.70	299 (47.0)	52 (39.1)	0.10
One year follow-up									
MACE, n (%)	315 (38.4)	126 (39.5)	0.46	127 (39.7)	96 (44)	0.30	188 (29.6)	30 (22.6)	0.10
Frequent re-admission, n (%)	154 (18.8)	56 (17.6)	0.89	56 (17.5)	37 (17.0)	0.99	98 (19.6)	19 (18.8)	0.98
Overall mortality, n (%)	171 (15.6)	65 (15.6)	0.99	101 (22.1)	46 (16.3)	0.053	70 (11.0)	19 (14.3)	0.28
Cardiac mortality, n (%)	117 (10.7)	38 (9.1)	0.37	65 (14.2)	28 (9.9)	0.084	52 (8.2)	10 (7.5)	0.80

Data are mean ± SD. ≥ 65 y, aged 65 years or older; < 65 y, aged younger than 65 years; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Frequent Readmission, more than twice; Hb, hemoglobin; HCVD, hypertensive cardiovascular disease; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; MRA, mineralocorticoid-receptor antagonist; NYHA Fc, New York Heart Association Functional Classification; SBP, systolic blood pressure; SD, standard deviation; VHD, mitral valvular heart disease.

Ischemic heart disease was more prevalent in men than in women and caused the most HF hospitalization events in both sexes of the overall cohort and the elderly subgroup. Hypertensive cardiovascular disease caused twice as many HF hospitalizations in women than in men of the overall cohort (10.8% versus 5.8%; $p < 0.001$), and in the elderly subgroup (12% versus 5%; $p < 0.001$). Meanwhile, men presented with more comorbidities such as coronary artery disease (CAD) with or without previous myocardial infarction, chronic lung disease, and unhealthy habits such as cigarette smoking and alcohol intake (Table 1). The prevalence of diabetes mellitus was significantly higher in the women of the overall cohort and the younger subgroup, but not in the elderly subgroup.

Both sexes had similar HF severity at admission or discharge of the index hospitalization. Hemodynamically, there was no difference in blood pressure level at index hospitalization. The men had a higher estimated glomerular filtration rate (eGFR) than the women (55.6 $\pm$ 35.3 versus 47.1 $\pm$ 30.2 ml/min/m^2, $p < 0.001$) in the overall cohort. A greater LVM index was seen in the men than in the women in the overall cohort (131.2 $\pm$ 7.7 versus 121.0 $\pm$ 43.4 g/$m^{1.7}$, $p = 0.03$) and in the younger subgroup (141.0 $\pm$ 52.0 versus 120.3 $\pm$ 45.4 g/$m^{1.7}$, $p = 0.01$), but was similar between the men and women in the elderly subgroup. Medications at discharge were similar in the men and women, and diuretics were the most prescribed drugs (82.7% versus 81%, respectively), followed by renin-angiotensin antagonists (63.2% versus 57.8%, respectively), beta-blockers (60% versus 58.8%, respectively), mineralocorticoid receptor antagonists (MRA) (mainly spironolactone, 40.5% versus 34.9%, respectively) and calcium-channel blockers (11.2% versus 15.1%, respectively). A similar pattern was noted in the men and women in the elderly subgroup.

One-year mortality

During a follow-up period of one year, there were no significant differences in major adverse cardiovascular events (MACE), frequent re-admission rate, overall, cardiac, and non-cardiac mortality between the men and women in the overall cohort and the younger subgroup (Table 1). The K-M survival analysis revealed no difference in mortality in the overall cohort (Figure 1A). In the elderly subgroup, the overall mortality rate of the men was higher than that of the women (N = 101, 22.1% versus N = 46, 16.3%, $p = 0.035$), as was the cardiac mortality rate (N = 65, 14.2% versus N = 28, 9.9%, $p = 0.049$) (Figure 1B). We further examined the effect of age on mortality by sex, and found that the prognostic effect of old age on overall mortality rate appeared to be stronger in the male patients [hazard ratio (HR) = 2.14, 95% confidence intervals (CI) 1.58-2.90, $p < 0.0001$], than in the female patients (HR = 1.12, 95% CI 0.65-1.91, $p = 0.69$) in Cox regression analysis (Figure 2). Based on the above findings, we focused on the elderly subgroup. Table 2 shows the multivariate Cox regression model results for the elderly subgroup, in which male sex (HR = 1.50, 95% CI 1.02-2.25) and diabetes (HR = 1.55, 95% CI 1.06-2.27) were independently associated with a higher risk of overall mortality. In contrast, improved NYHA functional class during the index hospitalization (HR = 0.58, 95% CI 0.39-0.85), beta-blocker use at discharge (HR = 0.62, 95% CI 0.43-0.90), and MRA use at discharge (HR = 0.61, 95% CI 0.40-0.95) were independently associated with a lower risk of overall mortality.

DISCUSSION

In this prospective multicenter registry in Taiwan, we found that age contributed differentially to sex differences in the overall mortality risk in patients with HFrEF. During the follow-up period of over one year, significantly higher overall and cardiac mortality rates were observed in the men of the elderly subgroup. In addition to male sex, diabetes was also associated with a higher risk of overall mortality. In contrast, improved NYHA functional class during the index hospitalization and the use of beta-blockers and MRA were associated with better outcomes.

With respect to sex differences in heart failure outcomes, women have long been under-represented in studies of HF in the past. With the recognition of HF being a major cause of death in women in the United States, the American Heart Association launched the first campaign for women between 1997 and 2009. Consequently, awareness of the impact of heart disease in women doubled and the death rate from CVD during this period nearly halved according to their annual nationwide statistical updates.[9,10,17,19] The extent of risk reduction was

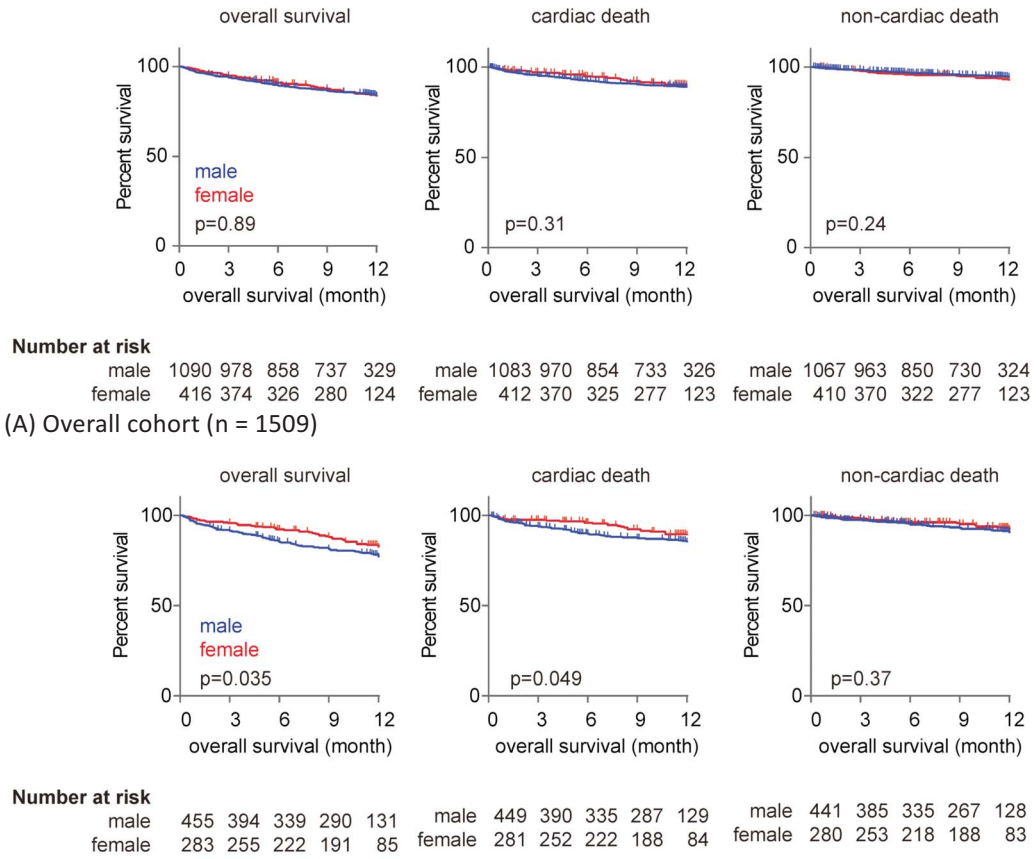

Figure 1. *(A) Kaplan-Meier survival curves for men and women showed no difference in overall survival, cardiac, and non-cardiac death during an average period of one-year follow-up. (B) In the elderly subgroup, Kaplan-Meier survival curves showed that the overall mortality rate of men was higher than that of women (22.1% versus 16.3%, p = 0.035), the cardiac death was also higher in men (p = 0.049), but no difference in non-cardiac death (p = 0.37) during an average period of one-year follow-up.*

affected by age, etiology, and comorbidities.[12,18] In a Norwegian nationwide heart failure registry, 70% of the participants were male, and they had an unremarkable mortality hazard ratio of 1.09 for those with an ejection fraction < 50%.[5] Israeli registries with 55% male participants showed that men had a significantly increased risk of late (> 6 months) mortality (HR: 1.25, 95% CI 1.09-1.43; p < 0.001).[6] In a Japanese single-center study, Nozaki et al. found an increased mortality risk by 3.2% per one year increment in age in women (N = 354, 33.7%), and that very old women aged (> 79 years) had a worse prognosis than men (157 men versus 188 women).[19] In our TSOC HFrEF registry (40% women), ageing in women with HFrEF after menopause was not associated with overall mortality (Figure 2). Similar to the findings in a recent study published by Dewan et al., women were older but lived longer than men.[20] The higher comorbi-

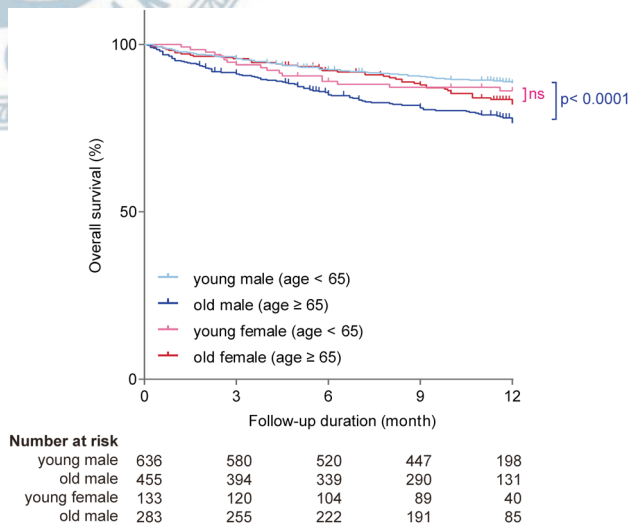

Figure 2. *For men, there was a significantly higher overall mortality rate for those aged 65 years or older than those younger than 65 years (p < 0.001), whereas for women the finding did not exist.*

Table 2. Factors of one-year all-cause mortality in the patients older than 65 years

Characteristics	Univariate		Multi-variates	
	HR (95% CI)	p value	HR (95% CI)	p value
Men	1.46 (1.02-2.07)	0.036	1.50 (1.02-2.25)	0.049
Age	1.01 (0.99-1.03)	0.37		
Cause of HF				
Ischemic	0.96 (0.69-1.32)	0.79		
DCM	0.92 (0.63-1.35)	0.67		
HCVD	0.82 (0.43-1.57)	0.56		
DM	1.46 (1.05-2.03)	0.023	1.55 (1.06-2.27)	0.025
COPD/asthma	1.41 (0.96-2.09)	0.084		
CAD with old MI	1.17 (0.83-1.65)	0.38		
NYHA Fc III/IV at discharge	2.51 (1.81-3.48)	< 0.001		
Improved NYHA	0.46 (0.33-0.64)	< 0.001	0.58 (0.39-0.85)	0.005
Smoking	0.92 (0.55-1.55)	0.75		
Alcohol	1.11 (0.70-1.76)	0.67		
ACEi/ARB at dis	0.57 (0.41-0.79)	< 0.001	1.04 (0.71-1.52)	0.86
BB	0.62(0.43-0.89)	0.0092	0.62 (0.43-0.90)	0.012
MRA	0.43 (0.29-0.65)	< 0.001	0.61 (0.40-0.95)	0.028
LVEF	0.98 (0.96-1.00)	0.11		
SBP	0.99 (0.98-1.0)	0.002	0.99 (0.99-1.001)	0.11
eGFR	0.99 (0.98-1.0)	0.001	1.00 (0.99-1.005)	0.932
Hemoglobin	0.92 (0.86-0.99)	0.03	0.92 (0.83-1.01)	0.069
NT-proBNP[#]	1.00 (1.00-1.00)	0.73		

CI, confident interval; HR, hazard ratio.

* $p < 0.05$ to normal value.

Data are adjusted for covariates: sex, DM, improved NYHA Fc, ACEi/ARB at discharge, beta-blockers at discharge, mineralocorticoid receptor antagonists at discharge, SBP, eGFR, and hemoglobin. Other abbreviations as in Table 1. [#] N = 125.

dities and worse NYHA functional classes found in our study imply a poor quality of the rest of their lives.

The mechanisms of sex difference in HF mortality can be explained in part by the etiologies or risk factors of HF such as coronary heart disease (CHD), diabetes, and smoking. A meta-analysis of 64 cohorts demonstrated that women with diabetes had higher risks of incident CHD and cardiac mortality than men.[21-23] Smoking may also have a greater impact on CVD in women. A meta-analysis of 86 cohort studies showed an adjusted female-to-male relative risk reduction of smoking versus non-smoking on CHD of 1.25.[24] Several factors for the sex difference in smoking on CHD have been discussed, including increased insulin resistance,[25] higher plasma arginine vasopressin,[26] arterial hypertension and endothelial dysfunction.[27] In the current study, few of our elderly women smoked. In contrast, with regards to sex differences in cardiac adaptation to chronic pressure overload, women have been reported to have a higher prevalence of cardiac hypertrophy and greater left ventricular ejection fraction than men.[28,29] This chronic cardiac adaptations to hypertension in women who gradually develop HF at an older age may contribute to better survival than men with the same etiology of HF at an older age.

It is well known that diabetes and more advanced NYHA functional class at admission are risk factors of mortality.[14,15] DM was found to be associated with a nearly 2- to 4-fold increase in the risk of incident HF in the Framingham Heart Study, and concomitant DM was shown to worsen clinical outcomes and increase the risk of death in both hospitalized and ambulatory patients with HF.[30-34] Improved HF symptoms at discharge has been associated with higher survival benefits in both young and older patients with HF.[35,36] However, only a few studies have reported the prognosis of mortality in elderly patients with HFrEF on renin-angiotensin antagonist therapy.[37] One previous study using a multicenter

database of patients in Japan, with an average age of 65 to 67 years, investigated the long-term prognostic impacts of renin-angiotensin antagonist therapy after acute myocardial infarction. Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) treatment was associated with better 5-year survival compared with patients who did not receive either drug. This study confirmed the clinical importance of renin-angiotensin system inhibition in CHD which is consistent with our results.[38,39] Recently, the Swedish Heart Failure Registry found that in very old patients with HFrEF aged ≥ 80 years, those receiving renin-angiotensin antagonist therapy had a 20% lower risk of overall mortality than those without the therapy.[40]

The strengths of our study include that the TSOC-HFrEF registry was a prospective multicenter study, so that selection bias was avoided. In addition, all of the patients were recruited from large cardiovascular medical centers providing guideline-based treatment for HF. This study also has some limitations. First, the average follow-up period was only one year, and whether the sex difference remained over a longer follow-up time was unknown. Second, some information such as physical fitness, troponin levels, and natriuretic peptides levels were unavailable at discharge in the study, which may have led to potential bias. Lastly, owning to the nature of the patient cohort, the number of female patients was lower compared to male patients, which may have limited the power of the statistical analysis. Therefore, further investigations including more female patients are needed.

CONCLUSIONS

Our findings suggested that male sex was an independent risk factor for overall and cardiac mortality in elderly patients with HFrEF in Taiwan during a one-year follow-up period. The sex difference may in part be due to varied effects of competing risks and survival bias in the etiologies between elderly men and women with HFrEF.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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