



## Original Article

# Association of preexisting hypertension with the morality in patients with systolic heart failure in Taiwan: The TSOC-HFrEF registry



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## ABSTRACT

**Purpose:** To investigate the association of preexisting hypertension at admission with the mortality in patients with systolic heart failure (HF).

**Method:** We prospectively investigated the association of preexisting hypertension with the mortality among 1351 patients with HF in Taiwan during an average 12 months (range: 8 months–18 months) follow-up period. A multivariate cox regression analysis for the overall cohort and a subgroup analysis by age were performed.

**Results:** After adjustment for all potential risk factors, the associations of preexisting hypertension with cardiovascular mortality were significantly reduced in the overall cohort and those aged less than 65 years (hazard ratios (HR): 0.53, 95% confidence intervals (CI): 0.33–0.84, and 0.28, 95% CI: 0.11–0.67, respectively). However, the associations with all-cause mortality were not significantly different in these two groups (HR: 0.77, 95% CI: 0.54–1.09, and 0.59, 95% CI: 0.32–1.07, respectively). Furthermore, the associations were all nonsignificant in the patients aged older than 65 years.

**Conclusion:** Preexisting hypertension have an inverse association with cardiovascular mortality in the Asian patients with systolic HF, particularly for those with younger ages.

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## 1. Introduction

Reverse epidemiology of preexisting hypertension at admission with all-cause mortality within 5-years follow-up in patients with systolic heart failure (HF) has been well known in the Western world.<sup>1</sup> However, this finding was not consistent across researches performed in the Asian countries. For instance, Lee et al have shown that systolic blood pressure rather than preexisting hypertension were associated with mortality in a Korean cohort with systolic HF.<sup>2</sup> Whether these conflicting results came from ethnical difference or the moderator such as age and obesity was unknown. Therefore we investigated the association between preexisting hypertension and the mortality in a large sample of patients with systolic HF in Taiwan.

## 2. Methods

The Taiwan Society of Cardiology-Heart Failure with Reduced Ejection Fraction (TSOC-HFrEF) registry was a multicenter study aimed to prospectively investigate the prognosis of patients with systolic HF in Taiwan from May, 2013 to October, 2015. The study design for TSOC-HFrEF has been published elsewhere.<sup>3,4</sup> In brief, the registry included 1509 patients admitted for acute worsening HF, whose echocardiographic left ventricular ejection fraction was less than 40%. Preexisting hypertension was defined as a history of systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg ever recorded, or the use of antihypertensive medications prior to this study. We excluded those with missing data on relevant variables, leaving a sample of 1351 (93.2%) for analysis. Outcomes of interest were 1) all-cause mortality, 2) cardiovascular mortality, defined as death of sudden cardiac death, ischemic heart disease, stroke, refractory HF, and lethal arrhythmia, and 3) non-cardiovascular mortality. The analysis used the time for follow-up at the patients' first enrollment (May, 2013–October, 2014) with censoring at the occurrence of mortality, or

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end of follow-up (October 31, 2015). The origin and the issue date of mortality were verified according to the medical record. The jointed ethics committee has approved the protocol and that informed consent has been obtained from the subjects. Cox proportional hazard regression analyses were used to assess the multivariable association of preexisting hypertension with mortality, adjusting for potential confounders at baseline including age, sex, body mass index, old myocardial infarction, diabetes, dyslipidemia, current smoking status, current alcohol intake, chronic obstructive pulmonary disease, New York Heart Association function class, and medications. These covariates for the adjustments were chosen based on prior published data related to HF mortality.<sup>3,4</sup> Stratified analyses exploring the association between preexisting hypertension and the mortality within age <65 (n = 693) and ≥65 (n = 658) years, and a formal test for interaction between these two age groups were performed. A 2-

tailed value of  $p < 0.05$  was considered significant. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

### 3. Results

Table 1 shows the baseline characteristics of participants younger and those older than 65 years of age. There were 293 (42.3%) and 259 (39.4%) hypertensives in the younger and the older groups. As compared with the younger ones, the elderly with HF had more proportion of female sex, ischemic origin, diabetes mellitus, chronic pulmonary disease, and presented worse kidney function and clinical symptoms.

Table 2 shows the associations of preexisting hypertension with all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality in the overall cohort (hazard ratios (HR): 0.62, 0.47,

**Table 1**  
Baseline Characteristics of Patients with Systolic Heart Failure By Age Group.

	Age Group		P-value
	Age <65 years N = 693	Age ≥65 years N = 658	
Hypertension	293 (42.3)	259 (39.4)	0.45
Demographic			
Age, years	53.2 ± 10.6	79.9 ± 7.3	<0.001
Sex (male), %	82.9	62.0	<0.001
Current smoker, %	35.1	11.2	<0.001
Current alcoholic, %	21.3	12.1	<0.001
Cause of heart failure, %			<0.001
Ischemic	39.8	54.4	
Dilated cardiomyopathy	43.7	23.9	
Hypertensive	7.3	8.6	
Valvular	9.2	13.1	
Comorbidities, %			
Diabetes	41.3	47.8	0.016
Dyslipidemia	25.3	20.8	0.05
COPD	4.6	16.9	<0.001
Prior MI	20.1	30.0	<0.001
Procedures, %			<0.001
PCI	19.6	10.1	
CABG	7.8	31.1	
Valvular surgery	3.7	5.5	
CIED	3.7	3.8	
Vital signs at discharge			
NYHA functional class	2.0 ± 0.7	2.3 ± 0.7	<0.001
Cardiogenic shock%	2.7	2.3	0.63
In-hospital mortality%	1.1	1.7	0.39
Heart rate, beats/min	81.9 ± 14.8	78.2 ± 14.6	<0.001
SBP, mmHg	118.8 ± 19.6	120.6 ± 17.8	0.09
DBP, mmHg	75.7 ± 13.1	68.7 ± 12.7	<0.001
Laboratory data at discharge			
eGFR, ml min <sup>-1</sup> 1.73m <sup>2</sup>	65.4 ± 41.0	47.7 ± 28.4	<0.001
Hemoglobin, g/dl	11.5 ± 2.1	12.2 ± 6.6	0.21
Echocardiographic parameters at discharge			
LVEDD, mm	63.3 ± 14.9	61.9 ± 27.0	0.22
LVSD, mm	53.9 ± 12.8	50.7 ± 19.4	<0.001
LVEF, %	26.6 ± 8.3	29.5 ± 8.6	<0.001
Medication use at discharge, %			
ACE inhibitors	32.2	21.8	<0.001
ARBs	35.9	32.8	<0.001
Beta-blockers	65.9	53.3	<0.001
Calcium-channel blockers	12.2	12.7	0.79
Nitrates	31.4	40.4	<0.001
Digitalis	31.4	20.5	<0.001
Diuretics	84.9	80.1	0.019
Anti-platelets	56.6	64.2	0.005
Anti-coagulants	22.2	20.5	0.45
Anti-arrhythmic agents	16.6	14.6	0.29

Abbreviations: COPD, chronic obstructive pulmonary disease; MI, myocardial infarction, TIA, transient ischemic accident; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CIED, cardiac implantable electronic devices; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

**Table 2**

Association between preexisting hypertension at admission and the mortality stratified by age in patients with systolic heart failure, 2013–2015.

	The overall cohort (n = 1351)	Age <65 years (n = 693)	Age ≥65 years (n = 658)
All-cause mortality			
Crude	0.77 (0.54–1.09)	0.59 (0.32–1.07)	0.91 (0.37–1.40)
Adjustment	0.77 (0.54–1.09)	0.59 (0.32–1.07)	0.91 (0.37–1.40)
CV mortality			
Crude	0.53 (0.33–0.84) <sup>*,§</sup>	0.28 (0.11–0.67) <sup>*,§</sup>	0.76 (0.46–1.26)
Adjustment	0.53 (0.33–0.84) <sup>*,§</sup>	0.28 (0.11–0.67) <sup>*,§</sup>	0.76 (0.46–1.26)
Non-CV mortality			
Crude	1.41 (0.82–2.41)	2.05 (0.79–5.36)	1.22 (0.66–2.28)
Adjustment	1.41 (0.82–2.41)	2.05 (0.79–5.36)	1.22 (0.66–2.28)

Cox regression model was used in the analysis adjusting for the covariates including age, sex, history of prior myocardial infarction, body mass index, diabetes, dyslipidemia, current smoking status, current alcohol intake, chronic obstructive pulmonary disease, NYHA functional class, and medications with angiotensin-II receptor blockers, beta-blockers, loop diuretics, spironolactone, anti-platelet agents (aspirin or clopidogrel), and anti-coagulation agents (warfarin or dabigatran).

Data was presented as hazard ratio (95% confidence interval).

<sup>\*</sup>P-value < 0.05.

<sup>§</sup>P for interaction of cause of mortality < 0.05.

and 0.98, respectively) during an average 12 months (range: 8 months–18 months) follow-up period. Similarly, the associations of preexisting hypertension with the mortalities in patients ages less than 65 years were compatible with that in the overall cohort (HR: 0.61, 0.44, 1.25, respectively). After adjustment for all potential risk factors, the associations of preexisting hypertension with all-cause and cardiovascular mortality were reduced in the overall cohort (0.77, 0.53, and 1.41 respectively), and those aged less than 65 years (0.59, 0.28, and 2.05 respectively). Notably, preexisting hypertension was only inversely associated with cardiovascular mortality. By contrast, the associations of preexisting hypertension with the mortality were nonsignificant in the patients ages older than 65 years. There were differences between the risk of cardiovascular and non-cardiovascular mortality in the overall cohort and the patients aged younger than 65 years (p for interaction < 0.05).

Table 3 shows the results of the associations between each medication use and mortality. We found that merely beta-blockers use was associated with lower risk of all-cause and cardiovascular mortality in the elderly patients with HF (0.61 and 0.58, respectively).

#### 4. Discussion

Our principal finding in Taiwan showed that preexisting hypertension was not associated with 1-year all-cause mortality in patients with systolic HF. However, there was an inverse association of preexisting hypertension with cardiovascular mortality.

In previous findings from TSOC-HFrEF and the eastern Taiwan integrated health care delivery system of Coronary Heart Disease (ET-CHD) registry,<sup>4,5</sup> we have shown that the obesity paradox phenomenon was present in patients with established cardiovascular disease, particularly in the elderly patients. In addition, several studies also have identified that elevated blood pressure was associated with greater survival in patients with HF.<sup>1,6</sup> These findings might suggest that increased body weight and blood pressure reflect the status of better circulatory power, a strong predictor of survival in systolic HF.<sup>7,8</sup>

Our findings were consistent to the Korean study results by Lee et al that pre-existing hypertension was not associated with all-cause mortality.<sup>2</sup> In contrast, the reverse epidemiology was only present in patients younger than 65 years of age. This was probably due to a higher prevalence of comorbidities in the elderly HF patients that reduced the effect of some protective factors such as elevated blood pressure on mortality. In addition, beta-blockers which could inhibit sympathetic nervous activation to decrease

blood pressure levels had remarkable protective effect on mortality in merely the elderly HF patients, indicating that the benefits and hazards of hypertension may be neutralized in this setting.

The strengths of our study were that the TSOC-HFrEF registry was conducted strictly in a nationwide spectrum and prospectively followed up the mortality events. The limitation of our study included that blood pressure levels were not adjusted at baseline for a high correlation with preexisting hypertension that could not be compared with previous study results.

In conclusion, an inverse relationship between preexisting hypertension and cardiovascular mortality was observed in the Asian patients with systolic HF, particularly for younger individuals.

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#### Disclosures

The authors have no conflicts of interest to disclose.

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