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Original article

## The prognostic impact of gender in patients with acute heart failure – An evaluation of the age of female patients with severely decompensated acute heart failure

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### ABSTRACT

**Background:** The gender differences in the prognosis of Asian patients with acute heart failure (AHF) remain to be elucidated.

**Methods and results:** One thousand fifty AHF patients were enrolled. The patients were assigned to a female group ( $n = 354$ ) and a male group ( $n = 696$ ). A Kaplan–Meier curve showed that the cardiovascular survival rate of the female group was significantly lower than that of the male group ( $p = 0.005$ ). A multivariate Cox regression model identified female gender [hazard ratio (HR): 1.381, 95% CI: 1.018–1.872] as an independent predictor of 730-day cardiovascular death. In subgroup analysis by age, in patients over 79 years, female gender significantly increased the cardiovascular death (HR: 1.715, 95% CI: 1.088–2.074,  $p < 0.001$ ) with a significant interaction ( $p$ -value for interaction  $< 0.001$ ). The prognosis, including cardiovascular death, was significantly poorer among elderly female patients ( $\geq 79$  years) than among elderly male patients ( $p = 0.019$ ). The multivariate Cox regression model identified female gender as an independent predictor of 730-day cardiovascular death in patients who were older than 79 years of age (HR, 1.943; 95% CI, 1.192–3.167).

**Conclusions:** Female gender was associated with poor prognosis in AHF patients. In particular, old age ( $\geq 79$  years) was associated with adverse outcomes in female patients with AHF.

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### Introduction

Some epidemiological studies have demonstrated gender differences in cardiovascular disease. Women with acute coronary syndrome are reported to be older and are more likely to have hypertension, dyslipidemia, and diabetes, and to have poor outcomes, including worse in-hospital mortality and long-term prognoses [1–4]. Meanwhile, other studies have suggested that there are no gender differences in acute coronary syndrome [5].

Cardiovascular disorders, including acute coronary syndrome, sometimes induce heart failure (HF). HF is therefore a major and

increasing problem in the cardiovascular field. Gender differences have been demonstrated in patients with chronic HF or acute HF (AHF), with women reported to have a better prognosis than men [6–9], while other studies reported that there were no differences in the prognoses of male and female patients [10–13]. These HF studies included lower numbers of female patients than male patients, and the female HF patients were characterized as being older and having a non-ischemic and valvular etiology, a preserved left ventricular ejection fraction (LVEF), and a maintained renal function.

AHF syndrome is currently defined, according to the European Society of Cardiology guidelines, as sudden life-threatening severely decompensated (HF) [14], and some investigators reported predictive factors for worse outcomes [15–17]. However, gender differences have not been evaluated in detail in AHF registries of Asian patients – in particular, in Japanese

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patients [18–20]. Furthermore, the prognostic impact of gender, especially the relationship between gender and age, has not been elucidated in Asian AHF patients. We therefore investigated the gender differences in the characteristics and the prognosis of severely decompensated AHF patients who were admitted to an intensive care unit (ICU).

## Methods

### Subjects

One thousand fifty AHF patients who were admitted to the ICU in Nippon Medical School Chiba Hokusoh Hospital between January 2000 and September 2014 were analyzed in the present study. All of the patients had a New York Heart Association (NYHA) functional class of either III or IV. The treating physician in the emergency department diagnosed AHF within 30 min of admission (based on these criteria) by filling out a form. AHF was defined as either new-onset HF or the decompensation of chronic HF with symptoms that were sufficient to warrant hospitalization [21]. HF was diagnosed according to the Framingham criteria for clinical HF, based on the patient fulfilling 2 major criteria or 1 major criterion and 2 minor criteria [22]. Patients with HF caused by acute coronary syndrome were excluded from this study. The patients who met one of the following criteria were admitted to the ICU: (1) patients who required high projectile oxygen inhalation (including mechanical support) to treat orthopnea; (2) patients who required inotrope or mechanical support due to low blood pressure; and (3) patients who required various types of diuretics to improve general or lung edema. All of the patients in the present study received either intravenous diuretics or vasodilators for the treatment of AHF after admission. The data were retrospectively reviewed from the patients' hospital medical records.

### Procedures

The patients were divided into female ( $n = 354$ ) and male ( $n = 696$ ) groups. We compared the patients' characteristics, including their age, the presence of de novo or recurrent HF, the etiology of HF, the risk factors for atherosclerosis (diabetes mellitus, hypertension, and dyslipidemia), vital signs [systolic blood pressure (SBP) and heart rate], arterial blood gas, the LVEF on echocardiograms, laboratory data [blood urea nitrogen (BUN), total bilirubin, hemoglobin, brain natriuretic peptide (BNP), C-reactive protein (CRP) and other variables], the medications that were administered during their admission to the ICU and the short-term prognosis (the duration of ICU stay, hospital stay, and in-hospital mortality).

The LVEF was calculated using the Teichholz method or modified Simpson's method on admission (Sonos 5500, Hewlett Packard, Palo Alto, CA, USA or Vivid I, GE Yokogawa Medical, Tokyo, Japan). The evaluation of LVEF was performed at emergency department on admission.

### Prognosis

The long-term prognosis, including cardiovascular death within 730 days, was evaluated. Cardiovascular death was defined as cardiac death, sudden death, cerebrovascular death, and HF death. The patients were followed-up at a routine outpatient clinic. The prognosis of the patients who were followed-up at other institutes was determined by telephone contact. The prognostic value in terms of 730-day cardiovascular mortality was evaluated using a Cox regression hazard model and a Kaplan–Meier curve.

### Statistical analysis

All of the statistical analyses were performed using the SPSS 22.0 software program (SPSS Japan Institute, Tokyo, Japan). All of the numerical data were expressed as the median and range or the median and the 25–75% interquartile range, depending on normality. Normality was assessed using the Shapiro–Wilk  $W$  test. The Mann–Whitney  $U$ -test and Kruskal–Wallis test were used for comparisons between two or more groups. The chi-squared test was used to compare proportions. Values of  $p < 0.05$  were considered to indicate statistical significance.

The prognostic value in terms of 730-day cardiovascular mortality was evaluated using a Cox regression hazard model and a Kaplan–Meier curve. All clinically relevant factors affecting the prognosis, including gender, age (per 1 year increase), SBP (per 10 mmHg increase), heart rate (per 1 bpm increase), serum creatinine level (per 0.1 mg/dl increase), total bilirubin (per 1.0 mmol/L increase), sodium (per 1.0 mmol/L increase), CRP (per 1.0 mg/dl increase), hemoglobin (per 1.0 mg/dl increase), and LVEF (per 10% increase) were selected for inclusion in the multivariate Cox regression hazard model associated with 730 days cardiovascular death in all patients cohort. Multivariate Cox regression hazard model was performed by the backward stepwise selection. We also conducted a subgroup analysis stratified by age ( $< 79$  years and  $\geq 79$  years), LVEF ( $< 41\%$  and  $\geq 41\%$ ), type of HF (de novo and re-admission), etiology (valvular disease and non-valvular disease), hemoglobin ( $\leq 12.4$  g/dl and  $> 12.4$  g/dl), and creatinine ( $\leq 1.0$  mg/dl and  $> 1.0$  mg/dl) with a formal interaction test between each group and the risk of female relative to male. The continuous variables were dichotomized by median values of female. Furthermore, the multivariate Cox regression hazard model and Kaplan–Meier curve analysis were performed again in age category ( $< 79$  years,  $\geq 79$  years).

### Ethics review

The institutional review board of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol.

## Results

### The patient characteristics and the prognosis in the female and male patients

Female patients comprised 33.7% of the study population. The median age was 74 years and the median LVEF was 35%; 354 (33.7%) patients had re-admission HF, and 846 (80.6%) patients had NYHA class IV on admission.

Table 1 shows the characteristics (on admission) of the patients in the two groups. The female patients were significantly older than the male patients. In comparison to the male patients, the female patients were less likely to be re-admitted for HF and their LVEF was significantly preserved. The female patients were less likely to have ischemic heart disease and valvular disease was more likely to be the etiology of their HF.

There were no significant differences in the history or in the arterial blood gas data of the two groups. The female patients showed significantly lower serum levels of uric acid, hemoglobin, creatinine, and CRP. There were no significant differences between the two groups regarding the length of ICU hospitalization and total hospitalization, or the in-hospital mortality rate.

Median follow-up date for long-term prognosis was 556 days in the overall population. All-cause deaths occurred in 225 patients (22.4%), and cardiovascular deaths occurred in 203 patients (19.3%) of the 1020 patients within 730 days. In 825 survival patients, 463 patients (56.1%) were followed-up for 730 days.

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