12-month mortality and hospitalizations in patients with heart failure with preserved ejection fraction and comorbid hypertension and type 2 diabetes mellitus

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▶ Received: 10 October 2023
Accepted: 15 November 2023
Published online: 30 November 2023

To cite: Nguyen NTV, Truong QB, Chau NH. *J Vietnam Cardiol 2023*;**107E**:37-41

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) carries a high risk of mortality and hospitalization, especially in patients with comorbid hypertension and type 2 diabetes mellitus. Little is known about the prognosis of hypertensive-diabetic HFpEF in Vietnam.

Objective: To examine the 12-month mortality, hospitalization, and combined outcome of all-cause mortality or heart failure hospitalization in hypertensive-diabetic HFpEF patients.

Methods and Materials: A 12-month prospective cohort study conducted in University Medical Center, HCMC and Nhan Dan Gia Dinh hospital. Recruiting period started in January 2021 and ended in April 2022.

Results: 233 patients were recruited. During 12-month, 6.9% died (n=16), in which 50% were due to cardiovascular cause. Hospital admission was reported in 62.2% of patients (n=145). 23.5% (n =55) were hospitalized at least 3 times. During the first hospitalization, 57.3% were due to cardiovascular reasons, most often heart failure (24.2%) and acute myocardial infarction (9%). Among non-cardiovascular admissions (42.7%), infection was the leading cause (22.1%). Combined outcome was observed in 24.9% (n=58).

Conclusions: Hypertensive-diabetic HFpEF patients experienced high rates of adverse events during a 12-month period, which were not restricted to cardiovascular causes, but also triggered by non-cardiovascular diseases. Comprehensive management should be taken into consideration to reduce both cardiovascular and non-cardiovascular events.

Keywords: Heart Failure with Preserved Ejection Fraction, Hypertension, Type 2 Diabetes Mellitus, All-cause Mortality, All-cause Hospitalization.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) accounts for roughly 50% of heart failure population, with similar risk of all-cause mortality compared to those with reduced ejection fraction [1]. While heart failure with reduced ejection fraction had multiple foundational therapies to improve survival, SGLT2 inhibitor was the only treatment with proven cardiovascular protection in HFpEF [2]. Therefore, HFpEF is becoming

a research priority in recent years.

The last two decades have seen major advancement in both the diagnosis and management of HFpEF. The development and validation of scoring systems as well as practical guidelines on early detection of HFpEF contributed to an increasing prevalence of HFpEF. In fact, due to the high comorbidity burden, the first point of contact for many HFpEF patients were non-cardiovascular facilities. Even after HFpEF diagnosis, non-cardiovascular comorbidity remained to be an issue of top concern in HFpEF patients. Since the ARIC trial, an increasing trend in non-cardiovascular mortality and hospitalization were observed in many HFpEF population [3]. Regardless of etiologies, an episode of hospitalization increased the risk of all-cause mortality in HFpEF individuals [4].

Among HFpEF patients, those with diabetes were subject to higher rates of adverse events [5]. As hypertension was present in most HFpEF patients, diabetic HFpEF frequently had concurrent hypertension. Not only does the combination of hypertension and diabetes increased the risk of incident HFpEF, they also heightened the risk for other HFpEF comorbidities, such as cornary syndrome or chronic kidney disease. These comorbidities in turn predisposed patients to further adverse events. Therefore, the coprevalence of hypertension and diabetes in HFpEF was expected to be associated with worse prognosis.

Most HFpEF studies focused on cardiovascular outcomes rather than non-cardiovascular events. In Asia, cardiovascular causes accounted for roughly half of all-cause mortality and hospitalization[6]. However, this registry (ASIAN-HF) excluded Vietnam. As data in Vietnamese HFpEF patients were lacking, we conducted the first multicentered prospective cohort study to evaluate the 12-month cardiovascular and non-cardiovascular events, including mortality, hospitalization and combined endpoint of all-cause mortality or heart failure hospitalization in hypertensive-diabeteic HFpEF patients.

METHODS

A 12-month multicentered, prospective cohort study was conducted in University Medical Center, HCMC and Nhan Dan Gia Dinh hospital. Patient enrolment started in January 2021 and ended in April 2022. The study adhered to Declaration of Helsinski and received approval from Ethics Committee of Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh city prior to initial patient recruitment. The study was registered in clinicaltrial.gov in 2021 (NCT: 04835194).

Inclusion criteria included hypertensive-diabetic adults with HFpEF. Exclusion criteria included prior cardiovascular admission within 30 days, acute heart failure, <1 year of life-expectancy due to other causes, unrepaired congenital heart disease, stage D primary valvular disease or prosthetic valve, severe pericardial diseases or cardiomyopathies (hypertrophic, restrictive, stress-induced, chemo-induced, amyloidosis, sarcoidosis), implantation with ICD, PM or CRT, Child C cirrhosis, end stage renal disease, severe COPD or asthma requiring home oxygen, pregnancy or lactation or active enrolment in interventional trial.

After giving informed consent, each patient was collected data on demographics, comorbidities, investigations and medications. For the next 12 months, data on all-cause hospitalization or mortality were collected at each follow-up and adjudicated by the main investigators.

For calculation of sample size, we employed the 12-month all-cause mortality or heart failure hospitalization rate from ASIAN-HF trial. The formula was as follow.

$$n = Z^2_{1-\alpha/2} \frac{p(1-p)}{d^2}$$

With $\alpha = 0.05$, $Z_{0.975} = 1.96$, d= 0.05, p=0.121, the minimal number of patients required was 162.

Python 3.11 was used for data analysis. Numerical variables were presented as mean (normal distribution) or median (skewed distribution). Categorial variables were presented as percentage. T-test or Wilcoxon range sum test was used to compare means of 2 groups. Chi square test was

performed to compare the difference between the categorial variables.

RESULTS

A total of 233 patients were recruited, 3.9% of which (n=9) were lost to follow-up. Mean age was 73. The ratio of women to men was 2.1. Apart from hypertension and diabetes, 82% had at least two other comorbidities. The proportion of patients with concurrent dyslipidemia, chronic coronary artery synfrom, anemia, chronic kidney disease and atrial fibrillation were 99.6%, 77.3%, 64%, 38.2% and 29.2% respectively. Prior myocardial infarction was documented in 38.2% of patients.

12-month Mortality

During a 12-month period, there were 16 dealths, 8 of which were attributed to cardiovascular causes. The remaining were due to non-cardiovascular etiologies.

12-month Hospitalization

62.2% of patients were admitted at least once (n=145). The proportion of patients with one, two, three and at least 4 admissions were 23.2%, 15.5%, 9.4% and 14.1% respectively (Figure 1).

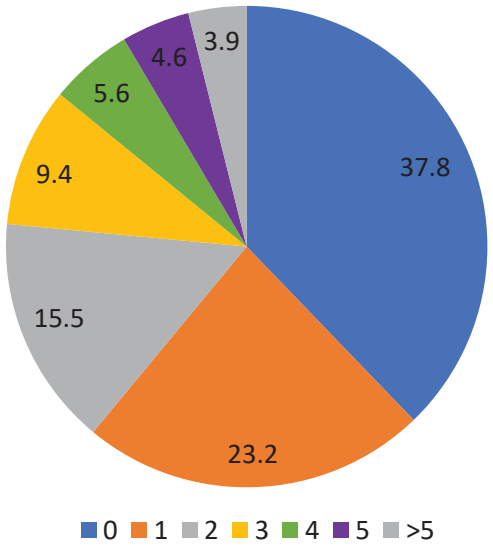

***Figure 1**. Number of hospital admissions during 12 months*

For the first hospitalization, 57.3% of patients got admitted because of cardiovascular disease, with the two most common causes being heart failure (24.2%), and acute myocardial infarction (9%). For non-cardiovascular admissions (42.7%) of all hospitalizations), the most frequent trigger was infection, accounting for 22.1% of cases. Details on triggers of the first admission were demonstrated in Figure 2.

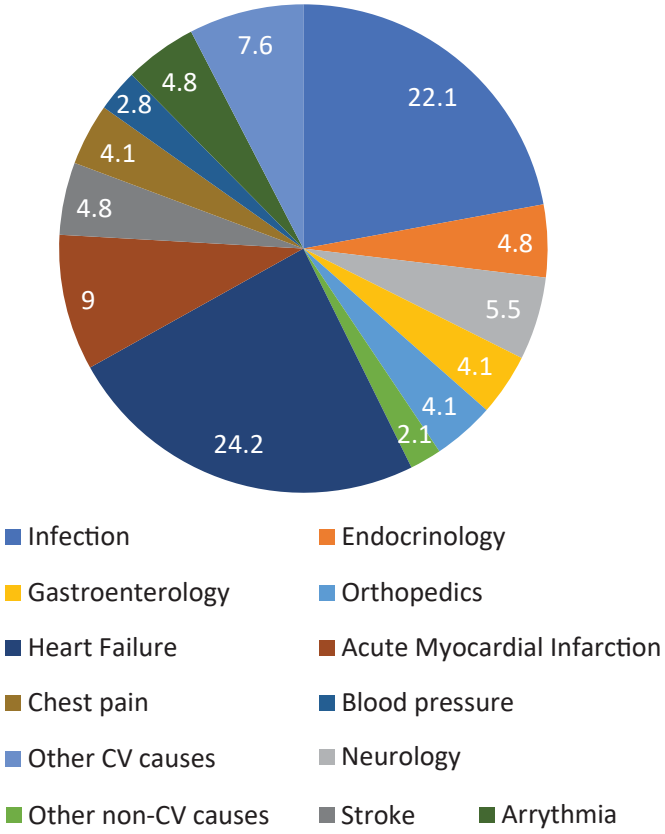

***Figure 2**. Main causes of First Admission*

12-month combined outcome

Combined outcome of all-cause mortality or heart failure hospitalization was reported in 24.9% of patients (n=58). Specifically, 46 patients (19.7%) experienced heart failure hospitalization.

DISCUSSIONS

12-month Hospitalizations

The percentage of patients with at least one admission in our study was higher than that of I-PRESERVE trial (62.2% versus 55%), but the proportion of cardiovascular causes were similar (57.3% versus 53.8%) [4]. For the first admission, our study demonstrated higher rates of heart failure hospitalization or acute myocardial infarction

(24.2% and 9% respectively) compared to those of I-PRESERVE trial (17.6% and 3.3%).

The difference between our study and I-PRESERVE trial could be explained by the study population. All of our patients had concurrent hypertension and type 2 diabetes mellitus, whereas in the I-PRESERVE trial, hypertension and diabetes were presented in 88.4% and 25.1% of patients respectively. The combination of hypertension and diabetes increase the risk of acute myocardial infarction and heart failure hospitalization.

In HFpEF patients, apart from mortality and heart failure hospitalization, incident acute myocardial infarction is associated with prognosis. In a meta-analysis from CHARM-Preserved, I-PRESERVE and TOPCAT, 3.8% of patients had incident myocardial infarction [7]. In these patients, the risk of cardiovascular death was highest in the first 30 days (HR=31, 95% CI 22-44), then gradually decreased during the next 12 months (HR=3.6, 95% CI 2.6-5.1). This heightened risk persisted even after 12 months (HR=1.58, 95% CI 1.03-2.43). There was similar risk for cardiovascular death between first and recurrent myocardial infarction, highlighting the importance of primary and secondary prevention of myocardial infarction in HFpEF patients. In our study, 9% of patients reported incident myocardial infarction, almost trippled that of the meta-analysis of CHARM-Preserved, I-PRESERVE and TOPCAT (3.8%). Thus, our hypertensive-diabetic HFpEF patients with high rates myocardial infarction were at an increased risk for more adverse events compared to other HFpEF population.

In the first admission, there was striking similarity between our study and I-PRESERVE trial in terms of heart failure hospitalization (24.2% and 17.6%) and non-cardiovascular hospitalizations (42.7% and 43.8%) [4]. These findings were in contrast to studies on heart failure patients with reduced ejection fraction (HFrEF). In HFrEF patients, heart failure was the most common cause of hospitalization, accounting for 46% of all admissions in EVEREST trial and 56% in COPERNICUS trial. Taken together, these data illustrated the difference in causes of hospitalization across ejection fraction spectrum, with non-cardiovascular causes being more frequent in HFpEF patients. In a recent analysis from SwedeHF registry, an increasing trend in non-cardiovascular admission was noted in HFpEF population. When HFpEF is accompanied by diabetes, the most common non-cardiovascular etiology was infection [8]. The same pattern was observed in our study, with infection being the leadning cause of non-cardiovascular infection (22.1%).

Regardless of the cause, all-cause mortality significantly increased in HFpEF patients post hospitalization, especially in the first 30 days [4]. All-cause hospitalization was higher in our study (62.2%) compared to I-PRESERVE trial (55%), inferring a higher-risk population.

12-month Mortality

In regard to mortality, 6.9% (n=16) of the study population died within 12 months. Among these cases, 50% (n=8) was attributed to cardiovascular diseases. Our result was in accordance with other HFpEF registries, such as GWTG-HF (52%), ESC-HF-LT (47%), ASIAN-HF (53%) and Olmsted County (51%). However, our finding was lower than HFpEF randomized controlled trials (I-PRESERVE, TOPCAT, CHARM-Preserved, PEP-CHF, and ASCEND-HF), in which cardiovascular mortality accounted for roughly 60-70% of cases. In both registries and RCTs, HFpEF patients experienced more non-cardiovascular mortality as opposed to HFrEF counterparts [9]. High rates of non-cardiovascular causes may explain the difficulties in improving all-cause mortality of HFpEF population.

12-month combined outcome

During the 12-month follow-up, 24.9% of patients reported either mortality (6.9%) or first hospitalization for heart failure (19.7%). Compared to diabetic HFpEF population from ASIAN-HF registry, our patients experienced higher rates of combined endpoint (24.9% versus 14.8%) [5]. The difference was mostly attributed to heart failure hospitalization (19.7% versus 10.6%), rather than all-cause mortality (6.9% versus 5.7%). ASIAN-HF registry was conducted in 47 centers from 11 Asian nations. These representative

sites were carefully chosen, depending on the population size, geographic features, patient volume and standardized echocardiogram protocol. Due to their high-quality healthcare delivery, adverse events in ASIAN-HF registry was expected to be lower than the general population. Specifically, marked regional variation in combined endpoint was noted in the ASIAN-HF registry with highest events observed in South East Asian (25.4%). This was similar to our study at 24.9%.

CONCLUSION

We described a modern-day population of heart failure with preserved ejection fraction and concurrent hypertension, diabetes, who experienced high rates of mortality and admissions during a 12-month period. Non-cardiovascular causes was responsible for about half of all adverse events, including both mortality and hospitalization. Three most common causes of first hospital admission were heart failure, infection and acute myocardial infarction. These findings warrant the need for comprehensive risk management in hypertensive-diabetic HFpEF patients, taking into account other non-cardiovascular events in addition to hospitalization for heart failure.

Conflictcs of interest: The authors declared no conflicts of interest.

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