# Impact of diabetes mellitus on mortality in patients with acute heart failure: a prospective cohort study

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# Abstract

Background

Although more than one third of the patients with acute heart failure (AHF) have diabetes mellitus (DM), it is unclear whether DM exerts adverse impact on clinical outcomes. This study aimed to compare the outcomes in patients hospitalized for AHF in accordance with DM and left ventricular ejection fraction (LVEF).

Methods

The Korean Acute Heart Failure registry prospectively enrolled and completed follow-up of 5,625 patients from March 2011 to February 2019. Primary endpoints were in-hospital and overall all-cause mortality. We evaluated the impact of DM on these mortalities according to HF subtypes and glycemic control.

Results

DM was significantly associated with increased long-term mortality (adjusted hazard ratio [HR], 1.12; 95% confidence interval [CI], 1.02-1.22) even after adjusting for potential confounders. In subgroup analysis according to LVEF, DM was associated with higher long-term mortality in only HF with reduced ejection fraction (HFrEF) (adjusted HR, 1.14; 95% CI, 1.02-1.27). Inadequate glycemic control defined by HbA1c ≥ 7.0% within 1 year after discharge was significantly associated with higher long-term mortality compared to adequate glycemic control (HbA1c <7.0%) (44.0% vs. 36.8%; Log-rank p =0.016).

Conclusions

This large registry data showed that DM and inadequate glycemic control were significantly associated with increased long-term mortality in AHF, especially HFrEF. Tight glucose control is required to mitigate long-term mortality.


# Background

More than 26 million people worldwide suffer from heart failure (HF) and the prevalence is increasing due to aging societies, increased prevalence of risk factors, and longer survival in patients with cardiovascular diseases [1, 2]. HF is the primary cause of hospitalization in patients over the age of 65 in the United States [3]. Hospitalization for HF is associated with high mortality and rehospitalization rates [4, 5]. About 75% of HF patients suffer from at least 1 comorbidity, and the comorbidity is likely to worsen the patient's overall clinical outcomes [6]. Diabetes mellitus (DM) is present in nearly 35% of patients admitted to hospital with acute HF [7]. Multiple factors such as ischemia, hypertension, and extracellular fluid volume expansion are involved in the pathogenesis of HF in DM [8, 9]. While DM is associated with increased cardiovascular morbidity and mortality in patients with chronic HF with reduced left ventricular systolic function (HFrEF) [10, 11], its impact as an independent predictor of in-hospital and long-term outcomes after HF hospitalization is not consistently apparent. Some large registries and clinical trials

demonstrated that DM was associated with poor in-hospital and post-discharge mortality outcomes in patients with acute HF [12–17]. On the contrary, other studies could not verify any significant association with DM and mortality in hospitalized HF patients after adjusting confounding factors [18–21]. Thus, the association of DM, per se, with mortality in patients with HF still remains uncertain. Another question is whether DM exerts adverse impact across HF subtypes such as HFrEF, HF with preserved left ventricular ejection fraction (HFpEF) or mid-range EF (HFmrEF).

This study evaluated all-cause mortality both in-hospital and long-term, in acute HF patients with and without DM based on the Korean Acute Heart Failure Registry (KorAHF) [22]. We also analyzed the differences in association of mortality with DM according to HF subtypes.

## Methods

# Study population

We analyzed the acute HF patients enrolled in the KorAHF registry (ClinicalTrial.gov identifier, NCT01389843) [22]. Briefly, the KorAHF registry is a prospective multicenter cohort study enrolling 5,625 patients who were admitted for AHF from one of 10 tertiary university hospitals between March 2011 and February 2014 and have been followed for more than 5 years until February 2019. Patients who had signs or symptoms of HF and met one of the following criteria were enrolled for this registry: 1) lung congestion or 2) objective findings of left ventricle (LV) systolic dysfunction or 3) structural heart disease.

We excluded 21 patients who were lost to follow up and 210 patients without information of LV ejection fraction (LVEF) during the follow-up period. Finally, 5,394 AHF patients with information on DM status and LVEF were enrolled for analysis (Fig. 1).

# Data Collection And Outcome Definition

Data were collected by each hospital and entered into a web-based case-report form in the web-based Clinical Research and Trial (iCReaT) system form the Korea National Institute of Health. Detailed information was collected at admission, and follow-up data were collected from patients by the attending physician at 30 days and 3, 6, 12, 24, 36, 48, and 60 months after discharge. The information including patient demographics, medical history, physical signs, laboratory test results, electrocardiography, echocardiography, medications and outcomes was collected.

The mortality data for patients lost to follow-up was detected from the National Insurance data or National Death Records.

# Definition Of DM And Glycemic Control

DM was defined as self-reported, history of anti-hyperglycemic agent use, or newly diagnosed during hospitalization [16]. Newly diagnosed DM was defined as a glycated hemoglobin (HbA1c) ≥ 6.5% when measured after a random glucose level ≥ 200 mg/dl at enrollment.

We additionally classified DM patients based on HbA1c levels measured at the follow-up visit within 1 year from discharge. We defined well-controlled and uncontrolled DM groups by HbA1c < 7.0% and ≥ 7.0% at the follow-up visit, respectively.

According to LVEF, we categorized AHF patients into three groups as EF < 40% (HFrEF), 40%≤ EF < 50% (HFmrEF) and EF ≥ 50% (HFpEF).

# Statistical analysis

Comparison of baseline characteristics in accordance with DM was carried out using the $\chi^2$ test for categorical variable and the unpaired Student t test for continuous variable. Kaplan-Meier survival curves in accordance with DM status were compared using log-rank test. We used the multivariable Cox proportional hazard regression to evaluate association between DM and mortality in AHF patients. Potential confounders which demonstrated the difference in their baseline characteristics between patients with and without DM, or were considered clinically significant including age, sex, body mass index (BMI), etiology of HF (ischemic or non-ischemic), prior admission history due to HF, parenteral inotropic agents usage, serum creatinine concentration (< 2.0 or ≥ 2.0 mg/dL), and elevated brain natriuretic peptides (BNP) (≥ 500 pg/mL) or N-terminal pro-brain natriuretic peptides (NT-proBNP) (≥ 1000 pg/mL) were adjusted. Interaction between DM and potential confounders was assessed by adding interaction term in the Cox proportional hazard regression model. All p-values were two-sided, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.0 with packages (“survival”, and “survminer”).

## Results

# Baseline characteristics

Among the study population, 2,321 patients with AHF had DM (43.0%) (Table 1). Patients with DM frequently had other risk factors including old age, obesity, hypertension as well as ischemic heart disease, chronic kidney disease, and cerebrovascular disease. Moreover, patients with DM had a higher proportion of BNP ≥ 500 pg/mL or NT-proBNP ≥ 1000 pg/mL, NYHA class III-IV on admission acute pulmonary edema on chest x-ray, higher level of systolic blood pressure, C-reactive protein, potassium, creatinine concentration, lower level of sodium, and lower LVEF compared to those without DM. As a result, patients with DM were prescribed more parenteral diuretics, inotropic agents, and vasodilators. However, aldosterone antagonists were prescribed less frequently in patients with DM.

Table 1

Baseline clinical characteristics according to diabetes mellitus (DM)

| Variables | All patients (N = 5,394) | Non-DM (N = 3,073) | DM (N = 2,321) | P-value |
|---|---|---|---|---|
| Age | 68.5 ± 14.5 | 67.6 ± 15.9 | 69.6 ± 12.3 | < 0.001 |
| Body mass index (kg/m$^2$) | 23.0 ± 3.9 | 23.0 ± 3.9 | 23.7 ± 3.8 | < 0.001 |
| Male, N (%) | 2,872 (53.2) | 1,596 (51.9) | 1,277 (55.0) | 0.023 |
| Current smoker, N (%) | 961 (17.8) | 546 (17.8) | 415 (17.9) | 0.086 |
| Risk factors, N (%) | | | | |
| Hypertension | 3,183 (59.0) | 1,554 (50.6) | 1,629 (70.2) | < 0.001 |
| Ischemic heart disease | 1,501 (27.8) | 636 (20.7) | 865 (37.2) | < 0.001 |
| Atrial fibrillation | 1,523 (28.2) | 921 (30.0) | 602 (25.9) | 0.001 |
| Chronic lung disease | 608 (11.3) | 350 (11.4) | 258 (11.1) | 0.492 |
| Chronic kidney disease | 756 (14.0) | 277 (9.0) | 479 (20.6) | < 0.001 |
| Cerebrovascular disease | 807 (15.0) | 405 (13.2) | 402 (17.3) | < 0.001 |
| Previous heart failure | 2,539 (47.1) | 1,380 (44.9) | 1,159 (49.9) | < 0.001 |
| Physical & laboratory Findings | | | | |
| SBP, mmHg | 131.4 ± 30.1 | 130.4 ± 29.4 | 132.8 ± 30.9 | 0.003 |
| DBP, mmHg | 78.7 ± 18.7 | 79.2 ± 18.8 | 78.1 ± 18.6 | 0.028 |
| Heart rate, beats/minute | 92.8 ± 25.9 | 92.5 ± 26.4 | 93.1 ± 25.2 | 0.379 |
| Glucose, mg/dL | 155.3 ± 76.7 | 129.6 ± 47.8 | 189.1 ± 94.1 | < 0.001 |
| Total Cholesterol, mg/dL | 151.8 ± 43.2 | 153.9 ± 42.2 | 149.2 ± 44.4 | < 0.001 |
| BNP ≥ 500 pg/mL or NT-proBNP ≥ 1000 pg/mL | 4,047 (75.0) | 2,267 (73.8) | 1,780 (76.7) | 0.014 |
| CRP, mg/dL | 2.4 ± 4.3 | 2.1 ± 3.5 | 2.9 ± 5.0 | < 0.001 |

Values are presented as mean ± standard deviation, or n (%).

Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptides; NT-proBNP, N-terminal pro-brain natriuretic peptides; hsCRP, high sensitivity C-reactive protein; CRP, C-reactive protein; BUN, blood urea nitrogen; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LA, left atrium; RVSP, right ventricular systolic pressure; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AAs, aldosterone antagonists

| Variables | All patients (N = 5,394) | Non-DM (N = 3,073) | DM (N = 2,321) | P-value |
|---|---|---|---|---|
| hsCRP, mg/dL | 2.3 ± 4.2 | 2.0 ± 3.8 | 2.6 ± 4.6 | < 0.001 |
| Sodium, mmol/L | 137.5 ± 4.8 | 138.0 ± 4.6 | 136.8 ± 5.0 | < 0.001 |
| Potassium, mmol/L | 4.4 ± 0.7 | 4.3 ± 0.6 | 4.5 ± 0.8 | < 0.001 |
| BUN, mg/dL | 26.1 ± 16.3 | 23.7 ± 14.3 | 29.2 ± 18.3 | < 0.001 |
| Creatinine, mg/dL | 1.5 ± 1.5 | 1.3 ± 1.3 | 1.7 ± 1.6 | < 0.001 |
| NYHA class III-IV, N (%) | 4,582 (84.9) | 2,558 (83.2) | 2,024 (87.2) | < 0.001 |
| Acute pulmonary edema on chest X-ray, N (%) | 1,039 (19.3) | 502 (16.3) | 537 (23.1) | < 0.001 |
| Echocardiographic Findings | | | | |
| LVEDD, mm | 57.4 ± 10.1 | 57.5 ± 10.6 | 57.4 ± 9.3 | 0.863 |
| LVESD, mm | 45.2 ± 12.3 | 45.1 ± 12.8 | 45.4 ± 11.7 | 0.302 |
| LVEF (%) | 37.8 ± 15.6 | 38.5 ± 15.9 | 36.7 ± 15.0 | < 0.001 |
| LA volume index, mL/m2 | 63.8 ± 42.1 | 66.7 ± 41.9 | 59.6 ± 42.0 | < 0.001 |
| E', cm/sec | 5.0 ± 2.3 | 5.2 ± 2.1 | 4.8 ± 2.5 | < 0.001 |
| S', cm/sec | 5.1 ± 2.0 | 5.1 ± 2.1 | 5.0 ± 1.9 | 0.026 |
| E/E' | 21.2 ± 11.5 | 20.1 ± 10.8 | 22.7 ± 12.2 | < 0.001 |
| RVSP | 43.9 ± 15.1 | 43.2 ± 14.9 | 44.9 ± 15.4 | < 0.001 |
| Management, N (%) | | | | |
| Parenteral diuretics | 4,062 (75.3) | 2,222 (72.3) | 1,840 (79.3) | < 0.001 |
| Parenteral inotropics | 1,672 (31.0) | 760 (24.7) | 912 (39.3) | < 0.001 |
| Parenteral vasodilators | 2,231 (41.4) | 1,105 (36.0) | 1,126 (48.5) | < 0.001 |
| ACEIs/ARBs at admission | 3,383 (62.7) | 1,977 (64.3) | 1,406 (60.6) | 0.001 |
| ACEIs/ARBs at discharge | 3,601 (66.8) | 2,117 (68.9) | 1,484 (63.9) | < 0.001 |

Values are presented as mean ± standard deviation, or n (%).

Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptides; NT-proBNP, N-terminal pro-brain natriuretic peptides; hsCRP, high sensitivity C-reactive protein; CRP, C-reactive protein; BUN, blood urea nitrogen; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LA, left atrium; RVSP, right ventricular systolic pressure; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AAs, aldosterone antagonists

| Variables | All patients (N = 5,394) | Non-DM (N = 3,073) | DM (N = 2,321) | P-value |
|---|---|---|---|---|
| Beta-blockers at admission | 2,054 (38.1) | 1,183 (38.5) | 871 (37.5) | 0.001 |
| Beta-blockers at discharge | 2,725 (50.5) | 1,533 (49.9) | 1,192 (51.4) | 0.285 |
| AAs at admission | 2,206 (40.9) | 1,379 (44.9) | 827 (35.6) | < 0.001 |
| AAs at discharge | 2,443 (45.3) | 1,472 (47.9) | 971 (41.8) | < 0.001 |
| Warfarin at discharge | 1,531 (28.4) | 965 (31.4) | 566 (24.4) | < 0.001 |
| Heart transplantation | 69 (1.3) | 13 (0.4) | 56 (2.4) | < 0.001 |
| Values are presented as mean ± standard deviation, or n (%). | | | | |
| Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptides; NT-proBNP, N-terminal pro-brain natriuretic peptides; hsCRP, high sensitivity C-reactive protein; CRP, C-reactive protein; BUN, blood urea nitrogen; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LA, left atrium; RVSP, right ventricular systolic pressure; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AAs, aldosterone antagonists | | | | |

All patients underwent echocardiography during the index admission (Table 1). There were no significant differences in LV end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD) between DM group and non-DM group. However, there was significant difference in LVEF (38.5 ± 15.9% vs. 36.7 ± 15.0%, $p < 0.001$). Furthermore, parameters such as E/e' (20.1 ± 10.8 vs. 22.7 ± 12.2, $p < 0.001$), and right ventricular (RV) systolic pressure (43.2 ± 14.9 mmHg vs. 44.9 ± 15.4 mmHg, $p < 0.001$) reflecting LV diastolic function were more impaired in patients with DM. Conversely, patients without DM had larger LA volume index (66.7 ± 41.9 mL/$m^2$ vs. 59.6 ± 42.0 mL/$m^2$, $p < 0.001$).

# In-hospital And Long-term Mortality According To DM

The median follow-up duration was 3.5 years. During the follow-up period, 235 (4.4%) patients died in during the index hospitalization and 2,500 (46.3%) patients died in overall during follow-up. Patients with DM had a higher incidence of in-hospital mortality and long-term mortality compared to patients without DM (Fig. 2). After adjusting for potential confounders including age, sex, BMI, etiology of heart failure (ischemic vs. non-ischemic), prior admission history due to HF, parenteral inotropics usage, creatinine concentration, and elevated BNP/NT-proBNP (≥ 1000), DM was still independently associated with long-term mortality (adjusted HR 1.12, 95% CI 1.03–1.22).

# Independent Predictors Of In-hospital And Long-term Mortality

Results of multivariable Cox proportional hazard regression on in-hospital and long-term all-cause mortality are reported in Table 2. DM, by itself, was not significantly associated with an increased in-hospital mortality (HR 0.81; 95% CI 0.61–1.06, p = 0.127). Parenteral inotropic usage, age, ischemic origin, and higher level of serum creatinine were other strong independent predictors for in-hospital mortality.

Table 2

Independent predictors of in-hospital and long-term mortality on multivariable Cox proportional hazard regression model

| Variables | Adjusted HR[1] | p value |
|---|---|---|
| In-hospital mortality | | |
| Diabetes | 0.81 (0.61–1.06) | 0.127 |
| Age (years) | 1.03 (1.02–1.04) | < 0.001 |
| Ischemic cause (vs non-ischemic cause) | 1.40 (1.06–1.85) | 0.017 |
| Parenteral inotropics usage | 5.16 (3.45–7.72) | < 0.001 |
| Serum creatinine ≧ 2.0 (vs < 2.0 mg/dL) | 1.54 (1.15–2.06) | 0.015 |
| Long-term mortality | | |
| Diabetes | 1.12 (1.03–1.22) | 0.009 |
| Age (years) | 1.04 (1.04–1.05) | < 0.001 |
| Sex (male) | 1.24 (1.14–1.34) | < 0.001 |
| Body mass index (kg/m$^2$) | | |
| Underweight vs. Normal | 1.66 (1.47–1.87) | < 0.001 |
| Overweight or obese vs. Normal | 0.81 (0.73–0.89) | < 0.001 |
| Ischemic cause (vs non-ischemic cause) | 1.16 (1.07–1.26) | < 0.001 |
| Prior admission history due to HF | 1.52 (1.40–1.65) | < 0.001 |
| Parenteral inotropics usage | 1.42 (1.30–1.55) | < 0.001 |

1. Adjusted for age, sex, body mass index, etiology of heart failure (ischemic vs. non-ischemic), prior admission history due to HF, parenteral inotropics usage, creatinine concentration (< 2.0 vs. ≥2.0 mg/dL), and elevated BNP (≧ 500) or NT-proBNP (≧ 1000)

| Variables | Adjusted HR[1] | p value |
|---|---|---|
| Serum creatinine ≥ 2.0 (vs < 2.0 mg/dL) | 1.66 (1.50–1.83) | < 0.001 |
| Higher BNP (≥ 500), or NT-proBNP (≥ 1000) during index hospitalization | 1.35 (1.21–1.49) | < 0.001 |

1. Adjusted for age, sex, body mass index, etiology of heart failure (ischemic vs. non-ischemic), prior admission history due to HF, parenteral inotropics usage, creatinine concentration (< 2.0 vs. ≥2.0 mg/dL), and elevated BNP (≥ 500) or NT-proBNP (≥ 1000)

Of note, DM was an independent predictor for long-term mortality (HR 1.12; 95% CI 1.03–1.22, p = 0.009). Other variables, such as old age, male, high BMI, ischemic origin, acute decompensated HF, parenteral inotropic usage, and high concentrations of serum creatinine and higher BNP or NT-proBNP during index hospitalization were also independent predictors for high long-term mortality.

# In-hospital and long-term mortality according to DM in subgroup by LVEF

Patients with DM had a higher in-hospital mortality rate in all the LVEF subgroups compared to patients without DM (3.4% vs. 7.1%; 3.2% vs. 4.3%, 2.7% vs. 3.8%, respectively), However, there were no significant associations after adjusting for potential confounders (HFrEF, adjusted HR 0.96, 95% CI 0.68–1.34; HFmrEF, adjusted HR 0.71, 95% CI 0.33–1.53; HFpEF, adjusted HR 0.78, 95% CI 0.41–1.49) (Table 3).

Table 3
In-hospital and long-term mortality according to diabetes in 3 subtypes of HF

| Diabetes mellitus (DM) | Unadjusted HR (95% CI) | Adjusted HR (95% CI)[1] |
|---|---|---|
| In-hospital mortality | | |
| LVEF < 40% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 1.28 (0.92–1.77) | 0.96 (0.68–1.34) |
| 40%≤LVEF < 50% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 0.83 (0.41–1.68) | 0.71 (0.33–1.53) |
| LVEF ≥ 50% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 0.94 (0.50–1.77) | 0.78 (0.41–1.49) |
| Long-term mortality | | |
| LVEF < 40% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 1.48 (1.33–1.64) | 1.14 (1.02–1.27) |
| 40%≤LVEF < 50% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 1.19 (0.98–1.44) | 0.99 (0.80–1.23) |
| LVEF ≥ 50% | | |
| Non-diabetes | 1.00 | 1.00 |
| Diabetes | 1.15 (0.98–1.35) | 1.16 (0.98–1.38) |

1. Adjusted for age, sex, body mass index, etiology of heart failure (ischemic vs. non-ischemic), prior admission history due to HF, parenteral inotropics usage, creatinine concentration (< 2.0 vs. ≥2.0 mg/dL), and elevated BNP (≥ 500) or NTproBNP (≥ 1000)

In contrast, during follow-up, the presence of DM had different impacts on long-term mortality according to LVEF. In HFrEF, DM was significantly associated with increased long-term mortality even after adjusting for potential confounders (adjusted HR 1.14; 95% CI 1.02–1.27). However, DM did not have significant associations with long-term mortality in patients with HFmrEF (adjusted HR 0.99; 95% CI 0.80–1.23), or HFpEF (adjusted HR 1.16; 95% CI 0.98–1.38) (Table 3). The Kaplan-Meier analysis also revealed

significant worse long-term mortality in patients with HFrEF and DM compared with patients with HFrEF but without DM (40.2% vs. 52.7%; Log-rank $p < 0.001$) (Fig. 3).

# Long-term Mortality, According To Prespecified Subgroup And Glycemic Control

Figure 4 presents the association between DM and long-term mortality in stratified group according to potential confounders including age, sex, ischemic origin, hypertension, chronic kidney disease, and de novo HF. The impact of DM on the long-term mortality was generally consistent across stratified subgroups (p for interaction $\geq 0.05$). However, there was a significant difference in the impact of DM on long-term mortality between patients with LVEF $\geq 40\%$ (adjusted HR 1.09; 95% CI 0.95–1.25) and LVEF $< 40\%$ (adjusted HR 1.27; 95% CI 1.13–1.43) (p for interaction $< 0.001$).

Figure 5 demonstrated that patients with uncontrolled DM (HbA1c $\geq 7.0\%$) had significantly higher long-term mortality compared to patients with well-controlled DM (HbA1c $< 7.0\%$) by the Kaplan-Meier analysis (44.0% vs. 36.8%; Log-rank $p = 0.016$).

## Discussion

The main findings of our study are as follows: (1) patients with DM-AHF had significantly higher in-hospital and long-term mortality compared to those without; (2) Even when potential confounding factors including age, sex, BMI, HF etiology, renal function, and HF severity were adjusted, DM was still significantly associated with high long-term mortality; (3) In HFrEF, DM had a significant association with higher long-term mortality, whereas DM was not significantly associated with increased long-term mortality in HFmrEF and HFpEF; (4) Patients with poor glycemic control after discharge (HbA1c $\geq 7.0\%$) had higher long-term mortality compared to those with adequate glycemic control (HbA1c $< 7.0\%$).

Previously, a number of studies compared the clinical characteristics and outcomes in patients with and without DM in HF. However, there were only two reports comparing clinical outcomes with and without DM in HFpEF [11, 23]. Moreover, there is no data from large registry or trials with patients with HFmrEF. One study on HFpEF from the CHARM program demonstrated that DM was significantly associated with higher mortality and morbidity in HFrEF and HFpEF [11]. However, detailed echocardiographic data were not provided in the report from CHARM program. The other large scaled study from the I-PRESERVE trial (Irbesartan in Heart Failure With Preserved Ejection Fraction) showed that patients with DM had greater structural and functional echocardiographic abnormalities, and worse clinical outcomes than non-DM patients in HFpEF [23]. This study used an LVEF cut point of 45%, and echocardiographic data were shown in < 20% of whole study population. These two studies similarly demonstrated the significant associations of DM and higher mortality in HFpEF. However, the cut-off points of LVEF were different from the current updated guidelines for the diagnosis and treatment of HF, which were accepted and used generally in clinical practice [24]. Unlike these two studies, our study did not show a significant

association between DM and overall mortality in HFpEF. However, this result should be interpreted cautiously. In general, patients with DM had higher long-term mortality rate, but there was no statistical significance only in HFpEF after adjusting for risk factors such as old age, ischemic origin, and severity of initial presentation.

Comparing patients according to HF subtypes, patients with HFmrEF had clinical characteristics that were similar to those of HFpEF [25–28]. For prognosis, recent studies have demonstrated that mortality rates in HFmrEF are more similar to those in HFpEF [26–29]. Although there were no studies that elucidated the association of DM with mortality in patients with HFmrEF, our study showed that the impact of DM on mortality in HFmrEF was different from other two groups. Whether HFmrEF is in itself a distinct clinical syndrome or whether patients with HFmrEF are “in transition” between HFrEF and HFpEF is unknown yet [30]. Despite cautious interpretation needed because of numbers of patients with HFmrEF not being large enough in our study, our results provide a significant clue to the nature of HFmrEF.

Our study has several important implications. First, we analyzed one of the largest prospective cohorts comparing the characteristics and clinical outcomes in patients with AHF with and without DM. Second, our study analyzed baseline echocardiographic findings in all patients, which is unique and difficult to obtain in large scaled HF registries. Third, we evaluated both in-hospital and overall all-cause mortality. Thereby, we were able to estimate the impact of DM on short and long-term mortality in patients with AHF. Fourth, we compared mortality according to three subtypes of HF based on LVEF. This is the first report that evaluated the association of DM with mortality in HFrEF, HFmrEF, and HFpEF. Because the characteristics and prognosis of HFpEF, and HFmrEF is still unclear and unknown, our study results might be able to contribute to understanding of clinical implication of HFpEF and HFmrEF. Lastly, we demonstrated that adequate glycemic control during follow-up was linked to improvement of long-term prognosis in DM-AHF patients.

# Limitations

There are several limitations in this study. First, our study is an observational study. To evaluate the effect of glycemic control, it has intrinsic limitations of nonrandomized comparisons such as different distribution of other clinical risk factors, and the possibility for influence of unmeasured confounding factors. Second, our endpoint was only all-cause mortality. If we can estimate other clinical outcomes such as cardiovascular death, and rehospitalization for HF, it may have been more helpful to understand the impact of DM on outcomes in AHF.

# Conclusions

The present study using large registry data with echocardiographic information from all participant showed that DM were significantly associated with increased long-term mortality in AHF, especially HFrEF. Given poor glycemic control was independently associated with long-term mortality, tight glucose control is required to mitigate worse outcome in this population.

# Abbreviations

AHF: Acute heart failure; CI: Confidence interval; DM: Diabetes mellitus; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HR: Hazard ratio; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association

# Declarations

### Ethics approval and consent to participate

The study protocol was approved by Institutional review board or ethics committee at each participating hospital. All patients provided written informed consent for participation in the registry.

### Consent for publication

The authors have reviewed the manuscript and consent for publication.

### Availability of data and materials

The data of this study may be available on reasonable request to the Korean Acute Heart Failure

(KorAHF) Registry.

### Competing interests

The authors have no competing of interests.


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### Author's contributions

MGK, SYJ wrote the first draft of the manuscript. MGK, HJC, SL, SKP and H-YL designed, interpreted the results and edited the manuscript. JJ, SL and SKP performed statistical analysis of this study. SYJ, SEL, KHK, BSY, SMK, SHB, DJC, ESJ, JJK, MCC, SCC and BHO recruited participants in the KorAHF registry and collected data. All authors read and approved the final manuscript.


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# References


1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017; 135: e146-e603.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.
3. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure–associated hospitalizations in the United States. J Am Coll Cardiol 2013; 61: 1259-67.
4. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol 2013; 61: 391-403.
5. Lee SE, Cho HJ, Lee HY Yang HM, Choi JO, Jeon ES, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J Heart Fail 2014; 16: 700-8.
6. Van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014; 16: 103-11.
7. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006; 27: 2725-36.
8. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care 2004; 27: 1879-84.
9. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015; 3: 136-45.
10. De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, Bauters C. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. Eur Heart J 2004; 25: 656-62.
11. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J 2008; 29: 1377-85.
12. Gustafsson I, Brendorp B, Seibæk M, Burchardt H, Hildebrandt P, Køber L. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. J Am Coll Cardiol 2004; 43: 771-7.
13. MacDonald MR, Jhund PS, Petrie MC, Lewsey JD, Hawkins NM, Bhagra S, et al. Discordant short- and long-term outcomes associated with diabetes in patients with heart failure: importance of age

and sex: a population study of 5.1 million people in Scotland. Circ Heart Fail 2008; 1: 234-41.

14. Mebazaa A, Gayat E, Lassus J, Meas T, Mueller C, Maggioni A, et al. Association between elevated blood glucose and outcome in acute heart failure: results from an international observational cohort. J Am Coll Cardiol 2013; 61: 820-9.
15. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. Eur J Heart Fail 2013; 15: 194-202.
16. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, et al. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail 2017; 19: 54-65.
17. Parissis JT, Rafouli-Stergiou P, Mebazaa A, Ikonomidis I, Bistola V, Nikolaou M, et al. Acute heart failure in patients with diabetes mellitus: clinical characteristics and predictors of in-hospital mortality. Int J Cardiol 2012; 157: 108-13.
18. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2007; 154: 277. e1-8.
19. Kosiborod M, Inzucchi SE, Spertus JA, Wang Y, Masoudi FA, Havranek EP, Krumholz HM. Elevated admission glucose and mortality in elderly patients hospitalized with heart failure. Circulation 2009; 119: 1899-907.
20. Targher G, Dauriz M, Tavazzi L, Temporelli PL, Lucci D, Urso R, et al. Prognostic impact of in-hospital hyperglycemia in hospitalized patients with acute heart failure: Results of the IN-HF (Italian Network on Heart Failure) Outcome registry. Int J Cardiol 2016; 203: 587-93.
21. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, et al. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. Circ Heart Fail 2014; 7: 76-87.
22. Lee SE, Lee HY, Cho HJ, Choe WS1, Kim H1, Choi JO, et al. Clinical Characteristics and Outcome of Acute Heart Failure in Korea: Results from the Korean Acute Heart Failure Registry (KorAHF). Korean Circ J 2017; 47: 341-53.
23. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC1, Preiss D1, Win S, et al. Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes According to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction: A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation 2017; 135: 724-35.
24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and

treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.

25. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007; 50: 768-77.
26. Cheng RK, Cox M, Neely ML, Heidenreich PA3, Bhatt DL4, Eapen ZJ, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J 2014; 168: 721-30.
27. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017; 19: 1586-96.
28. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017; 19: 1258-69.
29. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260-9.
30. Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail 2017; 5: 763-71.

# Figures

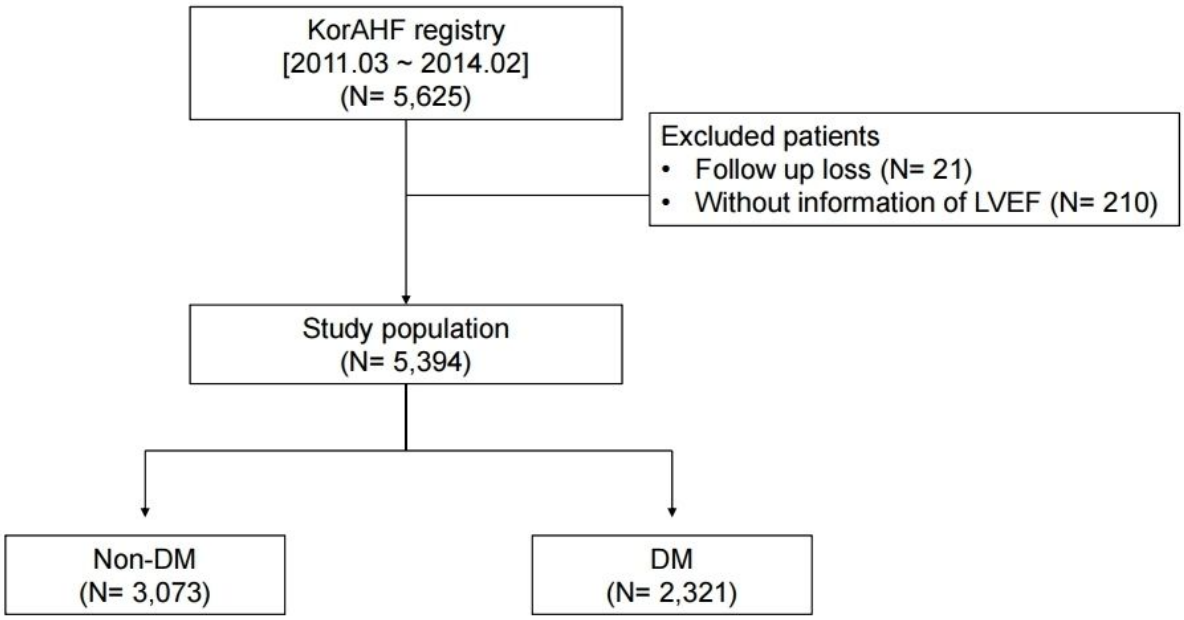


**Figure 1**

## Figure 1

Flow chart of the study. KorAHF registry, Korean Acute Heart Failure registry.

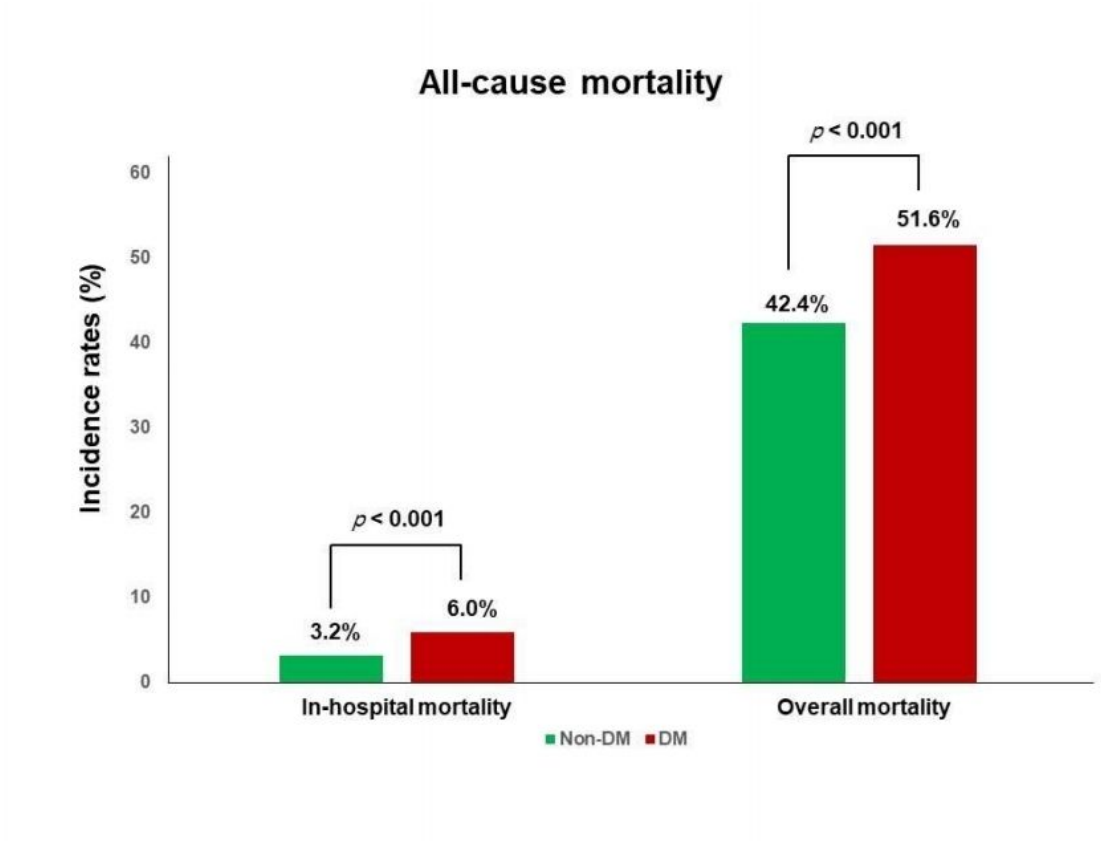


**Figure 2**

## Figure 2

Comparison of in-hospital and long-term all-cause mortality according to DM.

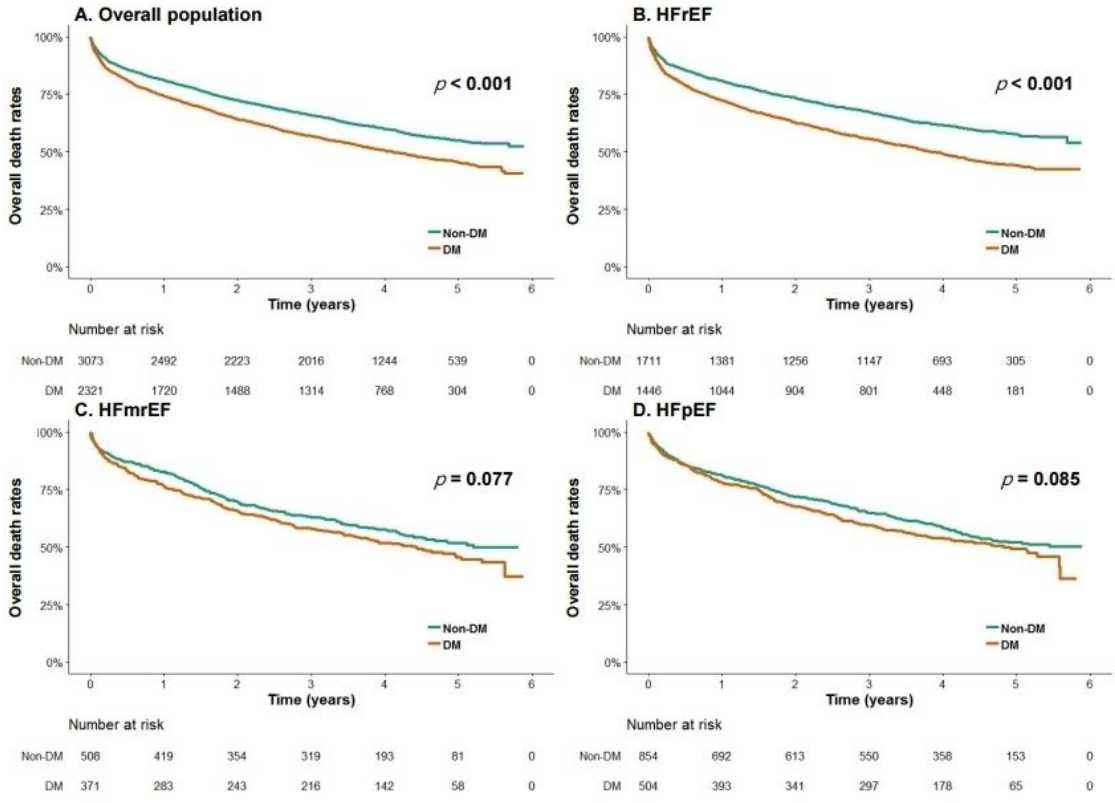


**Figure 3**

## Figure 3

Kaplan-Meier curves of all-cause mortality in DM and non-DM patients according to LVEF.

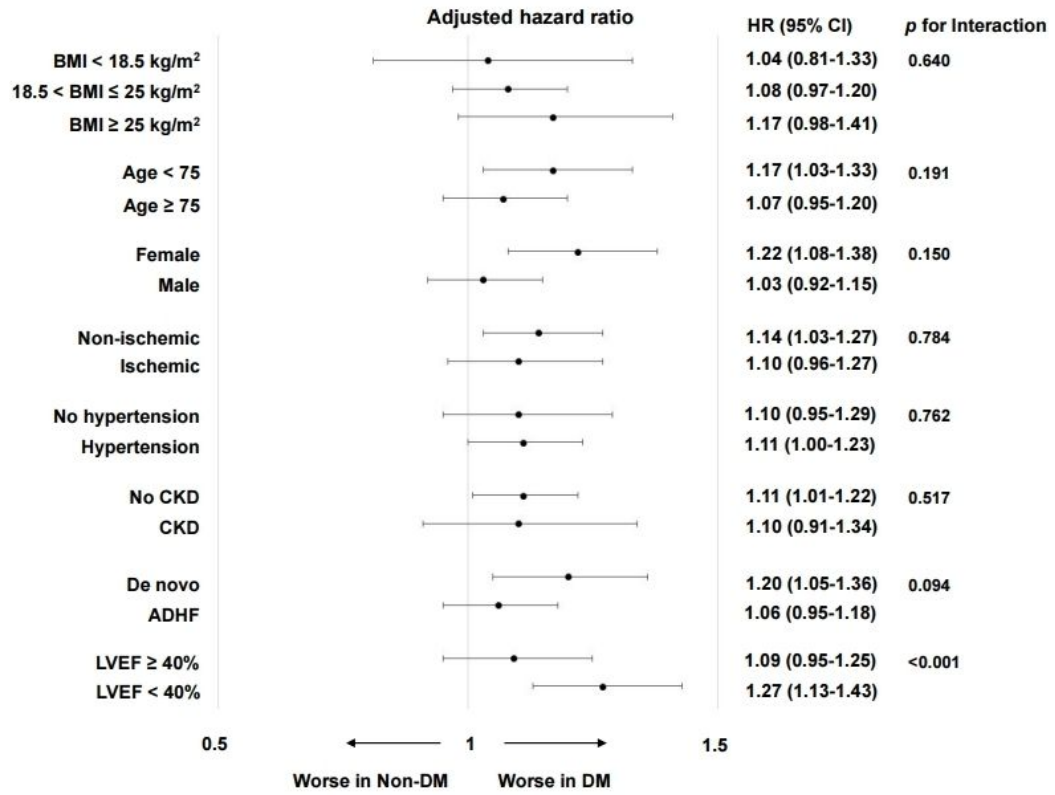


**Figure 4**

## Figure 4

Long-term all-cause mortality in prespecified subgroups.

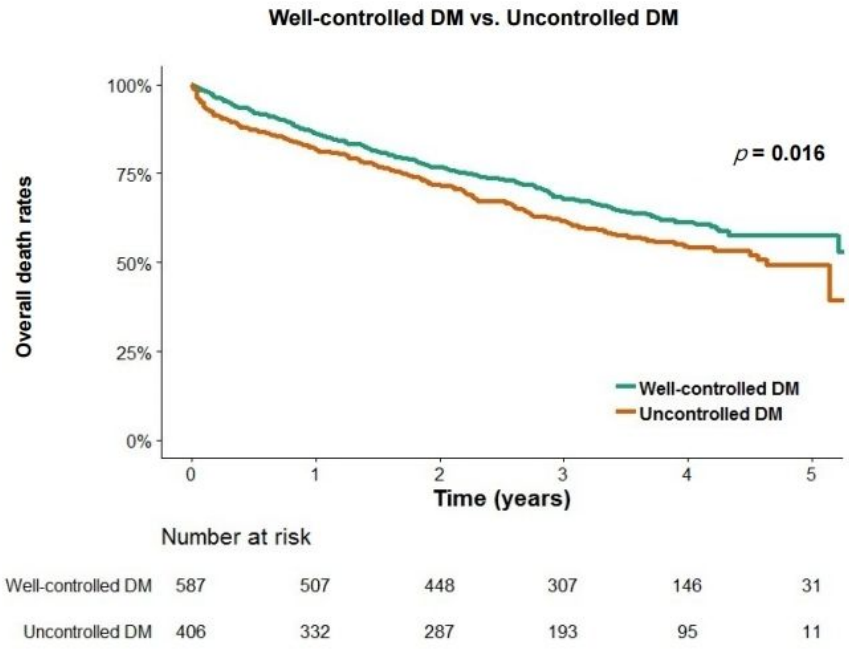


**Figure 5**

## Figure 5

Comparison of overall all-cause mortality according to glycemic control after discharge in DM patients. * Well-controlled DM as a HbA1c <7.0% at follow-up visit within 1 year after discharge; Uncontrolled DM as a HbA1c ≥7.0%.