Role of diabetes mellitus in acute coronary syndrome patients with heart failure with mid-range ejection fraction underwent percutaneous coronary intervention: a 3-year case series follow-up retrospective study

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Abstract

Background Data are limited about the effect of diabetes mellitus (DM) on prognosis of acute coronary syndrome (ACS) patients with heart failure with mid-range ejection fraction (HFmrEF) underwent percutaneous coronary intervention (PCI). This study aimed to investigate the relationship between type 2 diabetes mellitus (T2DM) and the 3-year outcomes in such population.

Methods 377 ACS patients with HFmrEF (left ventricular EF 40–49%) underwent PCI (132 diabetic and 245 nondiabetic patients) were included into analysis. The primary outcome was a composite endpoint of all-cause death or HF rehospitalization. Cox proportional-hazards regression analysis and Kaplan–Meier test were used to assess the effect of diabetes on the primary outcome. Sensitivity analysis was conducted with propensity score-matching analysis.

Results During a follow-up of three years, diabetic patients had a higher incidence rate of the primary outcome than nondiabetic patients (96.1 vs. 44.6 per 1000 patient-years, incidence rate ratio 2.301, 95% confidence interval 1.334–3.969; P=0.002). Multivariate analysis showed that diabetes mellitus was associated with a significant increase in the composite outcome of all-cause death or HF rehospitalization (adjusted hazard ratio 2.080, 95% confidence interval 1.115–3.878, P=0.021). Sensitivity analysis further confirmed that diabetes mellitus was an independent prognostic factor of long-term adverse outcome for ACS patients with HFmrHF who underwent PCI (adjusted hazard ratio 3.792, 95% confidence interval 1.802–7.980, P<0.001).

Conclusions Among ACS patients with HFmrEF underwent PCI, complicating with T2DM was significantly associated with worse long-term outcomes.

Keywords: Diabetes mellitus; Acute coronary syndrome; Heart failure with mid-range ejection fraction; Percutaneous coronary intervention; Outcome

Background

Acute coronary syndrome (ACS) is the acute manifestation of ischemic heart disease. Despite receiving optimal antithrombotic therapies and timely revascularization, ACS remains a major cause of morbidity and mortality worldwide, and can lead to the development of de novo acute heart failure (HF) or worsening of chronic HF[1]. Diabetes mellitus (DM) as a complex, chronic metabolic disease, often complicated with coronary artery disease (CAD) and other atherosclerosis-related cardiovascular diseases, and is also a major risk factor of HF, especially for ACS patients. Epidemiologic and clinical data from past two decades have proven that diabetes increased the mortality of patients with heart failure with reduced ejection fraction.
fraction (HFrEF)[2]. Heart failure with a mid-range ejection fraction (HFmrEF), as a distinctive phenotype, was first defined as left ventricular ejection fraction (LVEF) 40%-49% in 2016 European Society of Cardiology (ESC) HF guidelines[3,4]. Recent observational studies only focused on description of its characteristics and prognosis of HFmrEF, and patients enrolled in these clinical trials covered different aetiology of HF. In view of above-mentioned facts that previous studies have no selectivity on aetiology, our study concentrated on ACS patients and presented a 3-year retrospective analysis to investigate the role of diabetes mellitus (DM) in ACS patients with HFmrEF underwent percutaneous coronary intervention (PCI).

Methods
Patients selection
The ACS patients with HFmrEF underwent PCI was retrospectively screened from the Coronary Angiography and Angioplasty Registry Database of Fujian Medical University Union Hospital, registered from January 2014 to June 2017. The inclusion criteria were as followed: 1) Patients was hospitalized for ACS and underwent PCI, survived to discharge during their first admission; 2) Patients met HFmrEF diagnostic criteria according to the 2016 ESC guidelines[4], reviewed by an expert cardiologist during their hospitalization: a) The presence of symptoms and/or signs of HF; b) LVEF ranged from 40 to 49%; c) Elevated levels of BNP > 35 and/or NT-proBNP > 125pg/ml; d) Objective evidence of other cardiac functional and structural alterations underly HF; 3) a 3-year follow-up completed at least. The patients were excluded according to the following procedure: 1) echocardiography data or other clinical information no available; 2) echocardiography confirmed left ventricular ejection fraction (LVEF) ≥50% or < 40%; 3) patients lost to follow-up; 4) HF due to non-ischaemic heart disease (such as valvular heart disease, alcoholic cardiomyopathy, etc.). Through the screening process mentioned above, 377 HFmrEF patients were successfully enrolled in this analysis. The flowchart was showed in Figure 1.

![Figure 1](image.png)

**Figure 1.** Patient selection and study scheme. ACS: acute coronary syndrome; LVEF, left ventricular ejection fraction; HFmrEF, heart failure with mid-range ejection fraction.

**Definition of type 2 diabetes mellitus**
Patients were considered as having type 2 diabetes mellitus if they had been previously
informed of the diagnosis by a physician or were at a status of glucose-lowering therapy, i.e. insulin, oral hypoglycemic agents, diet and exercise. Patients without previously diagnosed T2MD who required initiation of antihyperglycemic therapy during hospital stay were also considered to have diabetes[5].

Data collection
Patient information and coronary angiography procedural details were collected by an independent trained reviewers blinded to group assignment from hospital databases and recorded in a computerized database. The baseline data include (i) demography; (ii) clinical status; (iii) complications; (iv) comorbidities; (v) electrocardiographic findings; (vi) angiographic and intervention status; (vii) treatment including discharge medications. These patients were divided into diabetic group and nondiabetic group at discharge from the index hospitalization.

Follow-up and Endpoints
All patients were followed up and clinical endpoint events happened within the first 3-year was registered and recorded after the index admission, and follow-up data was collected from the review of hospital charts, or discharge summary review, clinical visits or telephone interviews, which were conducted by independent trained reviewers. The primary outcome was a composite of all-cause death or rehospitalization for HF. Secondary endpoints were a composite of cardiovascular death or rehospitalization for HF, all-cause death, cardiovascular (CV) death, rehospitalization for HF and unplanned revascularization[6]. Cardiovascular death was defined as death due to heart failure, myocardial infarction, cardiogenic shock, sudden cardiac death (SCD), death related to stroke or other cardiac causes. Unexplained death was also regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Rehospitalization for HF was defined as an admission for decompensated HF after discharge from the index hospitalization, decompensated HF was defined on the basis of symptoms and signs, such as dyspnea, rales, and ankle edema, and the need for intravenous drug therapy, hemodialysis, mechanical circulatory or respiratory support[7]. Unplanned revascularization was repeat PCI or coronary artery bypass grafting of any vessels excluding staged PCI[8].

Statistical analysis
Continuous variables were presented as mean ± standard deviation or median with interquartile range (IQR), and differences were assessed by Student’s t-test, or Wilcoxon rank sum test. Categorical variables were described as percentage (%), and differences were analyzed by Pearson $\chi^2$ or Fisher exact test. For analysis of associations between diabetes mellitus and outcomes, incidence rates per 1000 patient-years and incidence rate ratio were calculated for each outcome. Cumulative incidence of outcomes was estimated by using regression estimates from a Cox proportional hazards model including covariates that were either statistically significant($P<0.20$) on univariate analysis or clinically relevant. Adjusted hazard ratios (HRs) were estimated by Cox regression model and were presented with 95% confidence interval (CI). The following covariates were taken into adjusted hazard ratios (HRs) analysis: age, gender, hypertension, history of prior myocardial infarction (MI), Killip functional class (III–IV vs. I–II), atrial fibrillation or atrial flutter (AF), diagnosis at admission (STEMI vs. NSTEMI–ACS), coronary disease status (multivessel vs. single vessel disease), complete revascularization, statin, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonist (MRA). Survival curves were
constructed using Kaplan–Meier estimates for time to the first event and compared using a log-rank test.

For the purpose of the sensitivity analysis, a propensity score was estimated by fitting a logistic-regression model that adjusted for age, gender, Killip functional class (III–IV vs. I–II), hypertension, AF, coronary disease status (multivessel vs. single vessel disease), complete revascularization, ACEI or ARB, calcium channel blocker (CCB). 1:1 pair matching between the two groups was performed by nearest neighbor matching without replacement. The same analysis was performed for the propensity matched cohorts. All tests were two tailed, and P < 0.05 was considered to be statistically significant. All analyses were performed with the SPSS statistical software (version 23.0, IBM, Chicago, USA).

**Table 1 Baseline characteristics**

| Variables                  | Before PSM | After PSM | P-value |
|----------------------------|------------|-----------|---------|
|                            | No diabetes (245) | Diabetes (132) | P-value | No diabetes (130) | Diabetes (130) | P-value |
| Demographics               |            |           |         |                   |                   |         |
| Age, years                 | 62.89±11.07 | 63.83±11.29 | 0.025   | 62.85±10.33       | 63.89±11.36       | 0.442   |
| Male                       | 217(88.6%) | 107(81.1%) | 0.061   | 112(86.2%)        | 107(82.3%)        | 0.496   |
| BMI, kg/m²                 | 23.91±3.16 | 24.69±3.13 | 0.439   | 24.39±2.91        | 24.68±3.14        | 0.436   |
| Smoking                    | 167(68.2%) | 81(61.4%)  | 0.211   | 79(60.8%)         | 81(62.3%)         | 0.899   |
| Co-morbidities             |            |           |         |                   |                   |         |
| Hypertension               | 133(54.3%) | 100(75.8%) | 0.000   | 94(72.3%)         | 98(75.4%)         | 0.672   |
| Chronic kidney disease     | 3(1.2%)    | 5(3.8%)   | 0.134   | 6(4.6%)           | 15(11.5%)         | 0.066   |
| Hyperuricemia              | 87(35.5%)  | 48(36.4%)  | 0.91    | 45(34.61%)        | 47(36.15%)        | 0.795   |
| Atrial Fibrillation        | 22(9.0%)   | 15(11.4%)  | 0.472   | 14(10.8%)         | 15(11.5%)         | 1.000   |
| Echocardiography data      |            |           |         |                   |                   |         |
| LVDD, mm                   | 52.67±5.70 | 53.1±6.09  | 0.426   | 53(50.0, 57.5)    | 53(48.95, 57.6)   | 0.713   |
| LVEDs, mm                  | 40.89±4.49 | 42.43±5.04 | 0.339   | 41.3(38.42,44.07) | 41.0(38.1,45.05)  | 0.714   |
| LVEF, %                    | 44.96(42.10,46.65) | 44.10(42.10,46.68) | 0.290 | 44.85(42.3,46.66) | 44.10(42.15,46.60) | 0.690   |
| FS, %                      | 22.40(20.80,23.50) | 21.80(20.7,23.40) | 0.190 | 22.40(20.92,23.50) | 21.80(20.80,23.35) | 0.581   |
| E/e’                       | 12.40(10.10,16.70) | 13.65(11.60,18.73) | 0.009 | 13.45(10.40,17.05) | 13.60(11.60, 18.90) | 0.122   |
| e’                         | 0.05(0.04,0.06) | 0.05(0.04,0.06) | 0.854 | 0.05(0.04, 0.06)  | 0.05(0.04 , 0.06)  | 0.840   |
| Clinical status            |            |           |         |                   |                   |         |
| Previous MI                | 204(83.3%) | 100(75.8%) | 0.101   | 108(83.1%)        | 99(76.2%)         | 0.218   |
| proBNP at admission, pg/mL | 1133.0(336.0,2693.5) | 959.0(301.5,2013.0) | 0.307 | 733.50 (253.0, 2207.5) | 745.50 (306.25, 2007.2) | 0.052   |
| Diagnosis at admission     | 0.731      |           |         |                   |                   | 0.599   |
| STEMI                      | 80(32.7%)  | 46(34.8%)  | 0.414   | 41(31.5%)         | 46(35.4%)         | 0.468   |
Table 1 Incidence rate and incidence rate ratio

|                        | Diabetes group(132) | No diabetes group(245) |
|------------------------|---------------------|------------------------|
| Patient with events,n | Incidence/1000       | Patient with events,n  |
|                        | person-years at risk | person-years at risk   |
| All-cause death or     | 33(25.0%)            | 31(12.6%)              |
|                        | 96.1                 | 44.6                   |

Table 2 Incidence rate and incidence rate ratio

|                        | Diabetes group(132) | No diabetes group(245) |
|------------------------|---------------------|------------------------|
|                        | Incidence/1000       | Incidence/1000         |
|                        | person-years at risk | person-years at risk   |
|                        | 2.301(1.334,3.969)   | 0.002                  |
### HF rehospitalization

- CV death or HF rehospitalization: 31(23.5%) 88.6 28(11.4%) 41.6 2.055(1.291,3.272) 0.003
- All-cause death: 17(12.9%) 49.5 14(5.7) 20.8 2.254(1.148,4.260) 0.019
- CV death: 15(11.4%) 43.7 10(4.1) 14.9 2.784(1.287,6.023) 0.009
- HF rehospitalization: 30(25.0%) 82.4 24(9.8) 35.7 2.320(1.417,3.800) 0.001
- Unplanned revascularization: 32(24.2%) 92.9 33(13.5) 48.4 2.056(1.196,3.532) 0.010

### CV death or HF rehospitalization

Table 3 Unadjusted and adjusted hazard ratio for primary outcome

| Variables                               | Univariate analysis          | Multivariate analysis         |
|-----------------------------------------|------------------------------|-------------------------------|
|                                         | Hazard ratio | 95% CI  | P value | Hazard ratio | 95% CI  | P value |
| Diabetes mellitus                       | 2.666        | 1.618,4.390 | 0.000   | 2.080        | 1.115,3.878 | 0.021   |
| Age                                     | 1.045        | 1.017,1.073 | 0.001   | 1.038        | 1.007,1.069 | 0.015   |
| Male                                    | 1.050        | 1.023,1.078 | 0.000   | 0.943        | 0.416,2.140 | 0.889   |
| Previous MI                             | 1.034        | 0.952,1.122 | 0.432   |              |           |         |
| Killip III-VI at admission              | 2.824        | 1.428,5.844 | 0.003   | 1.268        | 1.062,2.133 | 0.032   |
| Smoking                                 | 0.907        | 0.545,1.507 | 0.706   |              |           |         |
| LVDD,mm                                 | 1.023        | 0.980,1.068 | 0.292   |              |           |         |
| LVDs,mm                                 | 1.036        | 0.982,1.094 | 0.196   | 1.201        | 0.879,1.640 | 0.250   |
| Hypertension                            | 1.589        | 0.917,2.755 | 0.099   | 1.391        | 0.712,2.721 | 0.334   |
| Chronic kidney disease                  | 1.378        | 0.334,5.679 | 0.657   |              |           |         |
| Hyperuricemia                           | 1.173        | 0.919,1.497 | 0.201   |              |           |         |
| STEMI vs. NSTEMI-ACS                    | 0.902        | 0.622,1.060 | 0.514   | 0.899        | 0.696,1.160 | 0.414   |
| Multi- vs. single vessel                | 1.528        | 0.887,2.631 | 0.126   | 3.146        | 1.210,8.185 | 0.019   |
| Complete vs. incomplete revascularization | 0.208   | 0.093,0.465 | 0.000   | 0.149        | 0.057,0.391 | 0.000   |

### Revascularization

- Atrial fibrillation: 3.138 1.753,5.618 0.000 3.411 1.510,7.702 0.003
- Anti-platelet: 0.991 0.599,1.637 0.971
- Statin: 0.534 0.254,1.126 0.099 1.327 0.434,4.060 0.620
- ACEI or ARB: 1.176 0.685,2.02 0.556 1.002 0.524,1.917 0.995
- Beta-blocker: 0.945 0.519,1.722 0.854 0.648 0.321,1.309 0.226
- CCB: 0.706 0.283,1.761 0.455
- Loop diuretics: 0.783 0.448,1.366 0.389
- MRA: 0.932 0.563,1.542 0.784 1.709 0.927,3.148 0.086

LVDD, left ventricular end diastolic diameter; LVDs, left ventricular end systolic diameter; CCB, calcium channel blocker.
Figure 2. Comparison of estimated event rates including: (A) All cause death and heart failure rehospitalization, (B) CV death and heart failure rehospitalization, (C) all-cause death, (D) CV death, (E) heart failure rehospitalization, (F) unplanned revascularization between diabetes group (red line) and no diabetes group (blue line) underwent PCI in the overall population.
Figure 3. Comparative unadjusted odds ratios of the primary outcome between the diabetes group and the no diabetes group for each subgroup in the overall population. CI, confidence interval; OR, odds ratio; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex artery.

Table 4 Unadjusted and adjusted hazard ratio for primary outcome in propensity score-matched cohorts

| Variables                          | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | Hazard ratio 95%CI  | P value               | Hazard ratio 95%CI  | P value               |
| Diabetes mellitus                 | 4.481 2.047,9.810   | 0.000                 | 3.792 1.802,7.980   | 0.000                 |
| Age                               | 1.054 1.019,1.091   | 0.003                 | 1.039 1.007,1.073   | 0.016                 |
| Male                              | 1.244 0.531,2.912   | 0.615                 |                       |                       |
| Previous MI                       | 0.943 0.421,2.112   | 0.886                 |                       |                       |
| Killip III-VI at admission        | 2.710 1.480,4.960   | 0.001                 | 1.878 0.963,3.659   | 0.064                 |
| Smoking                           | 0.654 0.336,1.270   | 0.21                  |                       |                       |
| Alcohol                           | 1.225 0.333,4.500   | 0.76                  |                       |                       |
| LVDD,mm                           | 1.024 0.969,1.082   | 0.406                 |                       |                       |
| LVDs,mm                           | 1.043 0.973,1.118   | 0.233                 |                       |                       |
| Hypertension                      | 1.918 0.809,4.549   | 0.139                 |                       |                       |
| Chronic kidney disease            | 1.764 0.179,17.381  | 0.627                 |                       |                       |
| Hyperuricemia                     | 1.088 0.809,1.890   | 0.130                 |                       |                       |
| STEMI vs. NSTE-ACS                | 0.702 0.523,1.256   | 0.654                 |                       |                       |
| Multi- vs. single vessels         | 1.300 0.389,4.344   | 0.670                 |                       |                       |
| Complete vs. incomplete revascularization | 1.235 0.395,3.855 | 0.717               |                       |                       |
| Atrial fibrillation               | 3.306 1.411,7.748   | 0.006                 | 2.988 1.432,6.236   | 0.004                 |
| Anti-platelet                     | 1.046 0.739,1.480   | 0.801                 |                       |                       |
| Statin                            | 0.864 0.309,2.417   | 0.781                 |                       |                       |
ACEI or ARB  0.808  0.411, 1.587  0.536  
Beta-blocker  0.543  0.265, 1.114  0.096  0.613  0.306, 1.231  0.613  
CCB  0.692  0.198, 2.427  0.566  
Diuretics  1.002  0.491, 2.046  0.996  
MRA  1.111  0.574, 2.152  0.755  

LVEDd, left ventricular end diastolic diameter; LVEDs, left ventricular end systolic diameter;  

**Figure 4** Comparison of estimated event rates including: (A) All cause death and heart failure rehospitalization, (B) CV death and heart failure rehospitalization, (C) all-cause death, (D) CV death, (E) heart failure rehospitalization, (F) unplanned revascularization between diabetes group (red line) and no diabetes group (blue line) underwent PCI in propensity score-matched cohorts.
Figure 5. Comparative unadjusted odds ratios of the primary outcome between the diabetes group and the no diabetes group for each subgroup in propensity score-matched cohorts. CI, confidence interval; OR, odds ratio; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex artery.

Figure 6. Comparison of estimated event rates of all cause death and heart failure rehospitalization in diabetes patients stratified by HbA1c ≥7.5% tested at baseline and after 1-year follow-up.

Results

Patient’s baseline characteristics

377 ACS patients with HFmrEF underwent PCI who survived to discharge were enrolled, all subjects were divided into diabetic group and non-diabetic group. Baseline characteristics are shown in Table 1. The mean age was 63.2-year and 85.9% patients were male. Diabetic patients is elder than non-diabetic patients (63.83±11.29 vs. 62.89±11.07, P<0.025). Co-morbidities were comparable except for higher prevalence of hypertension (75.8% vs. 54.3%, P=0.000) in the diabetic group. However, the value of NT-proBNP at admission between two groups was not significant (959.0 [301.5, 2013.0] vs. 1133.0 [336.0, 2693.5]; P = 0.307). As regard to medication at discharge, ACEI or ARB, and CCB were more frequently prescribed in the non-diabetic group (57.6% vs. 70.2%, P = 0.017; 6.1% vs. 13.5%, P=0.036, respectively).
Compared with nondiabetic patients, diabetic patients have a higher prevalence of multivessel disease (57.6% vs. 47.5%, P=0.015), and required longer total stent length (43.5[29.0,69.75] vs. 33[24.0,60.0]; P=0.038). However, they received less complete revascularization (47.0% vs. 62.0%, P=0.006). In addition, there was no significant difference between groups with respect to the proportion of drug-eluting stent use, stent number and minimal stent diameter. Because of baseline characteristics of patients was disequilibrium, so we used 1:1 propensity score matching, after which, no statistical difference was observed between two groups, especially in the aspect of medication at discharge, as also shown in Table 1.

Comparison of 3-year outcomes between diabetic and nondiabetic patients

During a follow-up of 3 years, the incidence rate of primary outcome was higher in diabetic patients than nondiabetic patients (33 [25.0%] vs. 31 [12.6%], P=0.002). The incidence rates of composite outcome of all-cause death or HF rehospitalization, composite outcome of cardiovascular death or HF rehospitalization, all-cause death, cardiovascular death, HF rehospitalization and unplanned revascularization per 1000 patient-years were 96.1 vs. 44.6, 88.6 vs. 41.6, 49.5 vs. 20.8, 43.7 vs. 14.9, 35.7 and 92.9 vs. 48.4 for the diabetic and nondiabetic groups, respectively (Table2). The incidence odd ratios were 2.301 (95% CI 1.334-3.969; P=0.002), 2.055 (95% CI 1.291-3.272; P=0.003), 2.254 (95% CI 1.148-4.260, P=0.019), 2.784 (95% CI 1.287-6.023, P=0.009), 2.320 (95% CI 1.417-3.800, P=0.001) and 2.056 (95% CI 1.196-3.532, P=0.010) for each outcome (Table 2).

Univariate analysis for the composite of all-cause death or HF rehospitalization by Cox regression hazard model demonstrated that diabetes mellitus, age, gender, Killip functional class III–IV at admission, complete revascularization, atrial fibrillation was significantly associated with the primary outcome. Multivariate analysis including these factors showed that diabetes mellitus (adjusted HR 2.080, 95% CI 1.115-3.878; P=0.021), age (adjusted HR 1.038, 95% CI 1.007-1.069; P=0.015), Killip III–VI at admission (adjusted HR 1.268, 95% CI 1.006-2.213; P=0.032), multivessel disease (adjusted HR 3.146, 95% CI 1.210-8.185; P=0.019), complete revascularization (adjusted HR 0.149, 95% CI 0.057-0.391; P=0.000), atrial fibrillation (adjusted HR 3.411, 95% CI 1.510-7.702; P=0.003) was associated with worse prognosis (Table 3). After propensity score matching, diabetes mellitus (adjusted HR 3.792, 95% CI 1.802-7.980; P<0.001) was still significantly associated with the primary outcome in multivariate analysis (shown in Table 4).

Figure 2 demonstrates survival curves constructed using Kaplan–Meier estimates for time to the first event and compared the cumulative incidence of each outcome. The cumulative incidence of the composite of all-cause death or HF rehospitalization (P=0.0023; Figure 2A), the composite of cardiovascular death or HF rehospitalization (P=0.0028; Figure 2B), all cause death (P=0.0163; Figure 2C), cardiovascular death (P=0.0071; Figure 2D), heart failure hospitalization (P<0.0006, Figure 2E) and unplanned revascularization (P=0.0081; Figure 2F) were significantly higher in the diabetic patients. After adjusted by propensity score matching, diabetes still increased the cumulative incidence of the composite of all-cause death or HF rehospitalization (P=0.0001; Figure 4A), the composite of CV death or HF rehospitalization (P = 0.0004; Figure 4B), all cause death (P=0.0004;Figure 4C), CV death (P= 0.0004; Figure 4D) and HF rehospitalization (P= 0.0003; Figure 4E), but not significant association was found.
between diabetes and the cumulative incidence of unplanned revascularization (P=0.1189; Figure 4F).

**Subgroup Analysis**

To confirm the association between diabetes and the composite of all cause death or heart failure rehospitalization across various sub-groups, we performed post hoc subgroup analyses. As Figure 3 showed, despite of complete revascularization had been done, diabetes patients still suffered higher risk of composite of primary endpoint (OR 0.24, 95% CI 0.10-0.59, P<0.05), no difference between groups has been found in patients with incomplete revascularization. Subgroup analysis in propensity score-matched cohorts also demonstrated that whether complete revascularization or not, diabetes increased the risk of the composite of endpoint.

To further study the effect of glycemic control status on the prognosis, we divided diabetic patients into two groups: well-controlled group (HbA1c<7.5%) and poorly-controlled group (HbA1c≥7.5%), according to the level of glycosylated hemoglobin tested at baseline and at the end of 1-year follow-up. As the survival curves showed in Figure 6, compared with well-controlled diabetic patients, the cumulative incidence of the composite of all-cause death or HF rehospitalization was significantly higher in poorly-controlled diabetic patients (all P<0.05).

**Discussion**

HF with LVEF ranged from 40 to 49% is a grey area exists between HFrEF and HFpEF, which the 2016 ESC HF guidelines term it HFmrEF[4]. In view of the facts that previous studies only focus on description of its characteristics and have no selectivity on aetiology[9-11]. Our study concentrates on ACS patients, and presented a 3-year retrospective analysis to further investigate the relationship between diabetes mellitus and the long-term outcomes in the ACS patients with HFmrEF underwent PCI. The major finding of the present study was that diabetes mellitus significantly increased the risk of composite of all-cause death or HF rehospitalization among such population, especially in ACS patients with poorly-controlled glycemic status. This is the first report to identify such a relationship between diabetes mellitus and ACS patients with HFmrEF underwent PCI.

It has reached a consensus that patients with heart failure often had a higher prevalence of diabetes mellitus. The proportion of T2DM in chronic HF patients was about 30%, irrespective of HF phenotype (i.e. HFrEF and HFpEF)[12-14], and the percentage is 30-40% in clinical trials of acute HF. Our research reported the similar result that approximately 35.0% of HFmrEF patients suffered diabetes mellitus, which is in accordance with the data mentioned before.

Although the majority of data in the past suggested that diabetes significantly increased the higher risk of heart failure secondary to coronary artery disease, most of the data were limited to patients with heart failure whose EF was reduced or preserved up to now[15-17]. Maybe our research provided some data to fill the lack of knowledge on HFmrEF and attempted to explore the pathophysiological mechanism of diabetes mellitus increasing the risk of adverse prognosis of HFmrEF.

Knowledge about pathophysiological aspects of myocardial dysfunction in type 2 diabetes mellitus has increased enormously in recent years. First, the widest accepted mechanism is
that DM patients are easier to develop coronary artery disease, and suffer more diffuse coronary disease. As showed in table 1, compared with the nondiabetic group, the proportion of multi-vessel disease in the diabetic group was higher, the total stent length was longer, demonstrating T2DM caused accelerated atherosclerosis and more diffuse atherosclerosis in the coronary arteries, which may partly explained why diabetes was associated with adverse prognosis. In addition, the present study found the proportion of complete revascularization in diabetic patients was lower (47.0% vs. 62.0%, P<0.05), appear to complete revascularization may help to protect HF patients from adverse events. Actually, evidence-based data regarding to the importance of complete revascularization to HF are limited, but some randomized data still provided favorable evidence supporting CAD patients with HF may benefit from complete revascularization, which derived from the SYNTAX and FAME trials[18,19]. However, worse prognosis of diabetic patients has not been changed in propensity score-matched cohort after difference in complete revascularization was balanced. Subgroup analysis also demonstrated that no matter complete revascularization or not, diabetes patients still suffered the higher risk of adverse outcome, suggesting that revascularization alone is not enough to change the prognosis of diabetic patients.

In addition, neuro-hormonal antagonists (ACEIs, MRAs and beta-blockers) are recommended and have been proved to improve survival for patients with HF. However, little differences have been observed between the diabetic and non-diabetic group in respect to the medication at discharge (i.e., MRAs and beta-blocker, except for ACEI/ARB) for HF in this study, especially in propensity score-matched cohorts. In other words, HF patients with diabetes have not received individualized or optimal treatment different from those without diabetes, which may be one of the reasons for the worse prognosis of diabetic patients. Thus far, there were no clinical trials of HF treatment that included only patients with T2DM, and available evidence is derived from sub-group analysis of mixed populations. The embarrassing situation that no specific recommends to HF treatment in T2DM patients is urgent to be solved.

Many clinical trials have observed that T2DM-related processes can cause myocardial dysfunction in certain diabetic patients, but in the absence of coronary artery disease. Rubler et al came up with a new theory named “diabetic cardiomyopathy” to explain such a phenomenon[20]. Hyperglycemia and insulin resistance are the 2 major consequences of diabetes mellitus responsible for cardiovascular disorders in patients with diabetes mellitus[21]. Their detrimental effect interact each other and exert a potentiating effect, leading to several maladaptive responses and resulting in myocyte alteration, a common element was involved in these chains that reactive oxygen species (ROS) production increases in diabetic cardiomyocyte. Hyperglycemia and insulin resistance affect myocardial function by breaking the balance of ROS production in cardiomyocyte, leading to impaired cellular function and cardiovascular pathology[22]. As figure 6 showed, compared with diabetic patients with well controlled glycemic status (HbA1c < 7.5%), diabetic patients with poorly-controlled glycemic status (HbA1c ≥ 7.5%) has a higher risk of composite endpoint events, demonstrating that hyperglycemia itself has an important impact on the prognosis of HF patients with diabetes mellitus, indirectly indicating that optimized antidiabetic treatment and strict blood glucose control is of great significance to improve the prognosis. However, old antidiabetic drugs widely used such as insulin and sulphonylureas have not been proved safe in HF patients with T2DM[23,24], some drugs have been shown to increase the risk of HF hospitalizations (i.e.
rosiglitazone, pioglitazone and saxagliptin)]25-28. Inappropriate antidiabetic treatment not only failed to benefit the patients, it may lead to the opposite result. Fortunately, some new antidiabetic drugs such as glucagon-like peptide-1 (GLP1) receptor agonists and dipeptidyl peptidase-4 (DPP4) inhibitor, have a neutral effect on the risk of HF hospitalisations[29-33]. In addition, sodium-glucose cotransporter(SGLT) 2 inhibitors (e.g. empagliflozin and canagliflozin) demonstrated a significant reduction in the risk of HF hospitalizations in patients with T2DM and are currently being investigated as a potential addition to the optimal medical treatment of HF, especially in patients with T2DM[34,35]. Therefore, based on the facts mentioned above, we speculated that combination use of optimized hypoglycemic drugs and anti-heart failure drugs may bring the greatest improvement to HF patients with diabetes in prognosis.

Limitations Several limitations of this study should be acknowledged. Firstly, This study is a single-center, retrospective, observational study, the sample capacity is limited, the number of subjects with diabetes was modest (132), but it still provides meaningful evidence for clinical practice; Secondly, our study attempted to explore the impact of complete revascularization on the prognosis of ACS patients with HFmrEF, and found that it may be one of the factors affecting the prognosis, but not the only one. In view of this, we tried to study whether the optimization of drug treatment, including anti-heart failure and antidiabetic drugs, may be more important for the prognosis of such population, but limited data is not enough to support our conjecture. More large-scale, randomized controlled trials are required to verify such conjecture; Thirdly, the details of antidiabetic therapy were not collected in the study, so the effects of antidiabetic therapy on the prognosis of HFmrEF complicated with diabetes wasn’t completed.

Conclusion Taken together, our data suggested that T2DM was associated with adverse outcomes in ACS patients with HFmrEF underwent PCI, and significantly increased the risk of mortality and HF rehospitalization, compared to HF patients without T2DM. In regard of the management of such population, in addition to effective revascularization, the optimal medication including the optimization of hypoglycemic therapy and anti-heart failure therapy was probably more significant.

Abbreviations
T2DM: type 2 diabetes mellitus; ACS: acute coronary syndrome; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; PCI: percutaneous coronary intervention; CAD: coronary artery disease; HR: hazard ratio; CI: confidence interval; MI: myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB: calcium channel blocker; MRA: mineralocorticoid receptor antagonist.

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Authors’ contributions
The original idea came from LF, LLY, GYL, ZHF, HC, YFC and LZ performed the acquisition of data and made contribution to endpoints adjudication; LYL, GYL and SML performed analysis, and interpretation of the data. LYL and LF wrote the manuscript, LLC and other authors critically revised the manuscript. All authors read and approved the final manuscript.
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics of approval and consent to participate
The present study was approved by the Clinical Research Ethics Committee of Union Hospital, Fujian Medical University, Fuzhou, Fujian province, China. Informed consent was exempt by the committee.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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