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Type 2 diabetes increases the risk of mortality and cardiovascular events in ischemic HFmrEF patients: a retrospective cohort study

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Abstract

Background Type 2 diabetes mellitus (T2DM) is known to worsen the prognosis of heart failure (HF), but its specific impact on patients with ischemic versus non-ischemic heart failure with mildly reduced ejection fraction (HFmrEF) remains unclear due to limited research and conflicting evidence.

Methods We conducted a retrospective study of 1,691 HFmrEF patients at Xiangtan Central Hospital. Participants were divided into four groups: ischemic with T2DM (467 patients), ischemic without T2DM (856 patients), non-ischemic with T2DM (87 patients), and non-ischemic without T2DM (281 patients). We utilized the Cox proportional hazards model to analyze differences in all-cause mortality and cardiovascular events among the groups.

Results After adjusting for multiple confounding factors using the Cox proportional hazards model, the ischemic heart disease and T2DM group had a significantly higher risk of all-cause mortality compared to the ischemic group without T2DM (HR = 1.5, 95% CI = 1.2–1.9, $P = 0.001$). The risk of cardiovascular events was also significantly increased (HR = 1.3, 95% CI = 1.1–1.5, $P = 0.001$). In non-ischemic HFmrEF patients, T2DM was not associated with a significantly increased risk of all-cause mortality (HR = 1.0, 95% CI = 0.6–1.7, $P = 0.957$) or cardiovascular events (HR = 1.3, 95% CI = 0.9–1.9, $P = 0.113$).

Conclusion T2DM significantly increases the risk of all-cause mortality and cardiovascular events in ischemic HFmrEF patients, while its impact on non-ischemic HFmrEF patients is limited. These findings underscore the importance of managing T2DM in patients with ischemic HFmrEF.

Keywords Type 2 diabetes Mellitus (T2DM), Heart failure with mildly reduced ejection fraction (HFmrEF), Ischemic, All cause death, Cardiovascular events

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Introduction

T2DM is a significant risk factor for cardiovascular diseases, including heart failure (HF) [1–6]. However, its role in heart failure with mildly reduced ejection fraction (HFmrEF), particularly in distinguishing between ischemic and non-ischemic subtypes, remains unclear. While ischemic heart failure (IHF) patients with T2DM experience worse outcomes, the impact of T2DM on non-ischemic HFmrEF requires further investigation [1, 7–9]. Ischemic heart disease is a leading cause of heart failure [10, 11], with T2DM playing a central role in accelerating its progression by inducing vascular changes and myocardial ischemia [12, 13]. This distinction is crucial, as ischemic and non-ischemic HFmrEF may respond differently to treatments and management strategies. Patients with both ischemic heart disease and T2DM often experience more severe ischemic damage, leading to worse therapeutic outcomes [14].

Heart failure with mildly reduced ejection fraction (HFmrEF) is a distinct clinical phenotype that has garnered increasing attention due to its unique pathophysiology and presentation [15–17]. While T2DM is known to influence the prognosis of ischemic heart failure (IHF) patients, its role in HFmrEF, particularly in the context of ischemic versus non-ischemic HFmrEF, remains unclear. Most existing studies have primarily focused on patients with heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), leaving a critical knowledge gap regarding the impact of T2DM on the HFmrEF subgroup [18].

Hypothesis and novel contribution

This study hypothesizes that T2DM exacerbates the risk of mortality and cardiovascular events more significantly in ischemic HFmrEF patients compared to non-ischemic HFmrEF patients. By exploring this difference, the study aims to inform clinical management strategies for HFmrEF patients with T2DM, tailoring interventions based on ischemic or non-ischemic etiology. To address this gap, we aim to compare the outcomes of ischemic and non-ischemic HFmrEF patients with and without T2DM. The novel aspect of this study lies in its direct comparison of ischemic and non-ischemic HFmrEF patients, a group that has been largely underexplored in the context of T2DM's impact on heart failure outcomes. Moreover, common comorbidities in HFmrEF populations, such as chronic kidney disease (CKD) and hypertension [19, 20], are significant factors that may influence prognosis and outcomes in these patients. By providing insights into the differential effects of T2DM in these two distinct HFmrEF subgroups, while accounting for other relevant comorbidities, this research will offer valuable knowledge to guide more personalized clinical management strategies for HFmrEF patients with T2DM, ultimately improving patient outcomes.

Methods

Study design and population

We conducted a retrospective cohort study at Xiangtan Central Hospital, including 1,691 HFmrEF patients diagnosed between January 1, 2015, and August 31, 2020. To ensure data consistency, all patient data were validated using multiple sources, including medical records, diagnostic imaging results, and laboratory reports. Regular audits of the hospital's electronic medical records were performed to address potential discrepancies or missing data. Exclusion criteria included severe valvular pathologies, acute pulmonary edema primarily due to acute coronary syndrome, renal insufficiency with an eGFR < 30 mL/min/1.73 m^2, specific HF subcategories, isolated right-sided HF, patients with life-threatening conditions anticipating a lifespan of less than 1 year, and those younger than 18 years. Although the exclusion criteria are comprehensive, we recognize that the criteria for severe valvular disease and renal insufficiency may limit generalizability. These criteria were selected to ensure the homogeneity of the study population and reduce confounding factors; however, we acknowledge that including patients with milder forms of these conditions might provide broader insights. The study population was stratified based on ischemic status and the presence of Type 2 Diabetes Mellitus (T2DM): ischemic with T2DM ($n = 467$), ischemic without T2DM ($n = 856$), non-ischemic with T2DM ($n = 87$), and non-ischemic without T2DM ($n = 281$) (Fig. 1).

Definition of confounders

In this study, several potential confounders were considered, and their definitions are outlined below to ensure the reproducibility of the research:

Hyperlipidemia

Defined as elevated levels of cholesterol and/or triglycerides in the blood, typically assessed through total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride measurements. Hyperlipidemia is a known risk factor for cardiovascular diseases, including heart failure.

Hypertension

Refers to sustained high blood pressure, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Hypertension is a major contributor to the development and progression of heart failure.

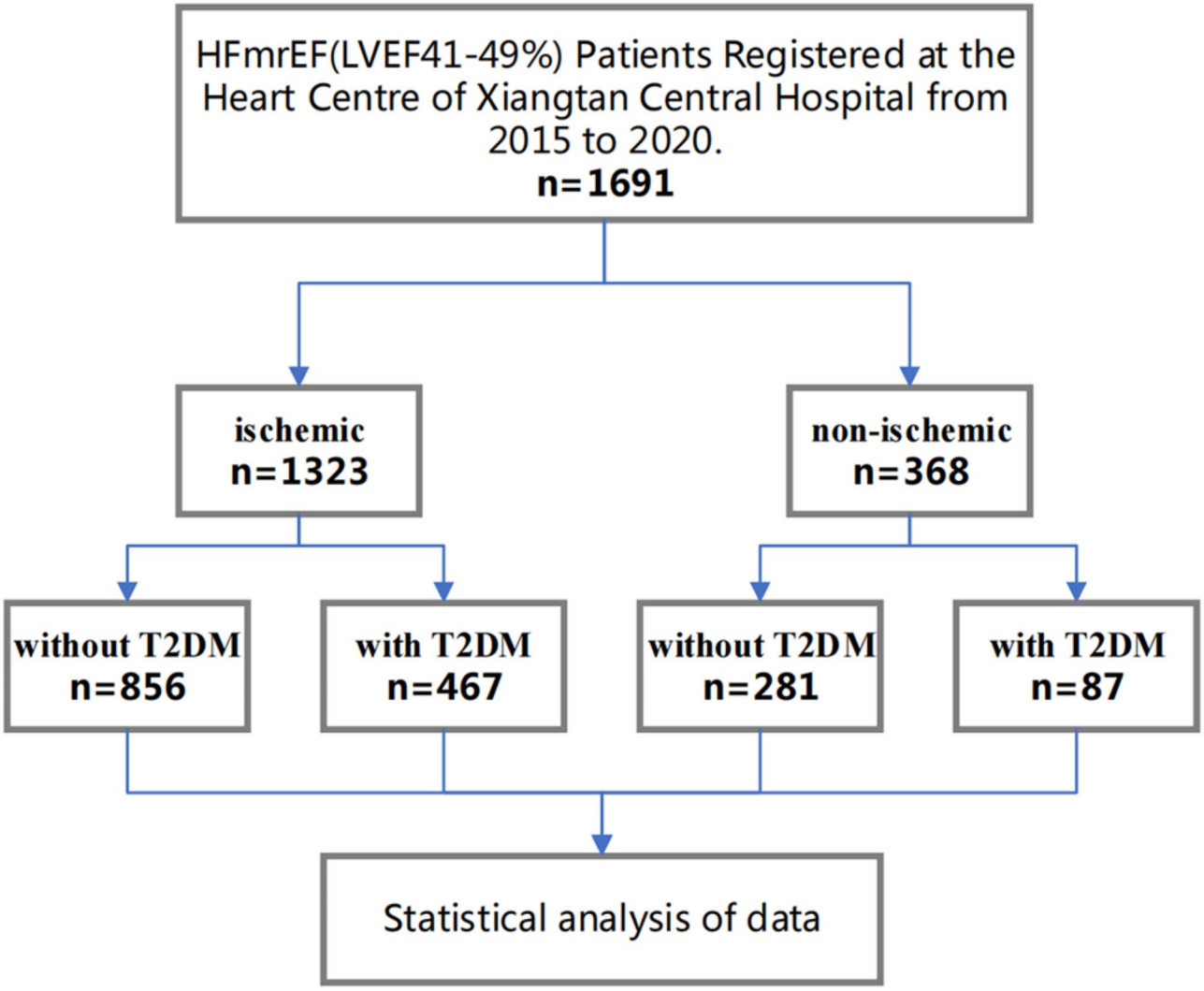


Fig. 1 Flow diagram for participant screening, eligibility and analysis

Atrial fibrillation

A common arrhythmia characterized by an irregular and often rapid heart rate, which increases the risk of stroke and exacerbates heart failure symptoms.

Renal dysfunction

Defined by impaired kidney function, typically assessed by serum creatinine, urea nitrogen, or estimated glomerular filtration rate (eGFR). Renal dysfunction is closely associated with worse outcomes in heart failure patients.

Percutaneous coronary intervention (PCI)

A procedure used to treat coronary artery disease by widening narrowed or blocked coronary arteries, typically through the use of stents. PCI is an important factor in determining cardiovascular outcomes in heart failure patients.

Stroke

Defined as a sudden interruption of blood flow to the brain, leading to neurological deficits. A history of stroke is associated with increased mortality and morbidity in heart failure patients.

NYHA class

The New York Heart Association (NYHA) functional classification system for heart failure, ranging from Class I (no symptoms) to Class IV (severe symptoms). A higher NYHA class indicates worse functional status and is associated with a poorer prognosis.

NT-proBNP

N-terminal pro B-type natriuretic peptide, a biomarker used to assess heart failure severity. Elevated NT-proBNP levels are indicative of worse heart failure outcomes.

Chronic obstructive pulmonary disease (COPD)

A group of lung diseases characterized by chronic obstruction of airflow. COPD frequently coexists with heart failure, potentially exacerbating symptoms and influencing prognosis.

Anemia

Defined by a low hemoglobin concentration, leading to inadequate oxygen delivery to tissues. Anemia is common in heart failure patients and is associated with worsened symptoms and outcomes.

Hyperuricemia

Elevated serum uric acid levels, which can lead to gout or renal impairment. In heart failure, hyperuricemia may be associated with worse clinical outcomes and increased mortality risk.

Diagnostic criteria

The diagnosis of ischemic heart disease was based on coronary angiographic findings, myocardial perfusion imaging outcomes, or documented diagnoses in patient medical records. Type 2 diabetes mellitus (T2DM) was determined according to the World Health Organization criteria [21]: a fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL) or a 2-hour postprandial glucose ≥ 11.1 mmol/L (200 mg/dL), as confirmed by an oral glucose tolerance test. A documented history of diabetes in medical records also sufficed for a T2DM diagnosis. Heart failure with mildly reduced ejection fraction (HFmrEF) was categorized according to the 2021 European Society of Cardiology (ESC) guidelines [16], which define it as a left ventricular ejection fraction between 41% and 49%.

Procedures and clinical endpoints

Demographic and clinical data were extracted from hospital archives or relevant databases. All participants were followed up until August 31, 2021. A team of seven experienced clinicians determined clinical endpoints through a thorough review of hospital documentation, supplemented by follow-up measures, including telephonic assessments and community visits. Information about primary and secondary outcomes was meticulously recorded. For each participant, the duration from initial follow-up to the occurrence of primary or secondary clinical events was calculated. The primary endpoint was all-cause mortality. Secondary endpoints included cardiovascular events, comprising cardiovascular mortality and rehospitalizations related to heart failure. Cardiovascular mortality was defined as deaths resulting from acute myocardial infarction, sudden cardiac events, heart failure, cerebrovascular events, complications from cardiovascular surgical procedures, hemorrhagic cardiovascular events, or other cardiac-related causes.

Statistical analysis

Quantitative variables were presented as mean ± standard deviation, while categorical data were represented as frequencies and percentages. The t-test was used for quantitative variables, and the chi-square test, executed via the "compareGroups" package, was applied to categorical data.

The Cox proportional hazards model was used to assess the impact of diabetes and ischemia on cardiovascular events and all-cause mortality in HFmrEF patients. This model was adjusted for confounders, including age, gender, BMI, smoking history, hypertension, hyperlipidemia, and other common comorbidities. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using the "survival::coxph" function. The Kaplan-Meier method was used to determine the cumulative incidence of events. While we performed rigorous data collection, we acknowledge that retrospective data may be subject to measurement bias. We took steps to minimize bias by cross-referencing diagnostic results and medical records with imaging findings and laboratory tests. Quality control was enforced by the clinical data management team.

To validate our Cox model findings, we incorporated propensity score matching for all adjusted variables. Of the initial 1,323 ischemic HFmrEF patients, exclusions due to missing data reduced the sample to 1,181: 417 with type 2 diabetes and 764 without. The GenMatch method in the "Matching" package was used for 1:1 matching based on the diagnosis of type 2 diabetes, with a caliper set at 0.05. The 1:1 matching ratio was chosen to maximize comparability between the two groups while maintaining a sufficient sample size. While alternative matching methods, such as inverse probability weighting, could have been considered, 1:1 matching was preferred due to its simplicity and effectiveness in reducing bias in observational studies. The choice of a 0.05 caliper was based on recommendations from previous studies [22, 23], which balance the trade-off between matching precision and sample size. A sensitivity analysis was conducted to assess the effect of varying caliper widths (0.01, 0.05, 0.1) on the matched sample size and covariate balance. This ensured that our choice of caliper did not substantially affect the reliability of our results. The matching resulted in 2,362 observations, or 1,181 matched pairs. A subsequent multivariate Cox regression analysis was performed to identify independent risk factors for outcomes in this ischemic HFmrEF cohort, particularly assessing the role of diabetes. A decision tree method was used to determine the optimal NT-proBNP threshold predictive of outcomes. Stratified analysis using the "forestplot" package was conducted to evaluate outcomes across different subgroups of ischemic HFmrEF patients. Additionally, an in-depth analysis of 467 patients with both ischemia and type 2 diabetes was conducted to explore

correlations between antidiabetic therapies and outcomes and to evaluate the impact of different treatment modalities on glycosylated hemoglobin levels.

For continuous data, *P*-values were calculated using the Kruskal-Wallis rank-sum test, while Fisher's exact test was used for categorical data. A *P*-value < 0.05 was considered statistically significant. Analyses were conducted using R software (version 4.2.0, http://www.R-project.org), EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA), and SPSS (version 26.0, SPSS Inc., Chicago, IL, USA).

Results

Patient baseline characteristics

Table 1 outlines the baseline characteristics of ischemic and non-ischemic HFmrEF patients, stratified by the presence or absence of T2DM. Among the 1,691 participants, 467 had both ischemia and T2DM, 856 had ischemia without T2DM, 87 had T2DM without ischemia, and 281 had neither ischemia nor T2DM. In the ischemic group, the non-T2DM subgroup had an average age of 70.2 years, with 68.1% being male. In contrast, the T2DM subgroup had an average age of 68.3 years, with 62.5% being male. The non-ischemic group was younger: the non-T2DM subgroup had an average age of 63.8 years, with 58.7% being male, while the T2DM subgroup had an average age of 62.1 years, with 63.2% being male.

Clinically, there were notable differences in parameters such as blood pressure, heart rate, and prevalent comorbidities—obesity, smoking habits, hypertension, anemia, and renal dysfunction—across the stratified cohorts. Each clinical metric showed significant variations between the subgroups with and without T2DM. For instance, in the ischemic cohort, the prevalence of hypertension was higher in patients with T2DM (78.2%) compared to those without T2DM (66.5%). Similarly, in the non-ischemic cohort, hypertension rates were 56.2% in the non-T2DM subgroup and 80.5% in the T2DM subgroup.

Echocardiographic metrics, including left ventricular ejection fraction (LVEF), left atrial dimensions (LAs), and left ventricular diameter (LVd), also showed intergroup differences. Regarding heart failure pharmacotherapy, there were variations in the use of ACE inhibitors (ACEi), angiotensin II receptor blockers (ARB), β-blockers, and diuretics across the cohorts. Notably, compared to the non-T2DM subgroup, there was a significant increase in calcium channel blocker (CCB) use in the T2DM subgroup, as detailed in Table 1.

Key findings

In patients with ischemic HFmrEF, the all-cause mortality for those without T2DM was observed to be 201 out of 856 (23.5%). In contrast, the T2DM cohort registered a mortality rate of 145 out of 467 (31.0%). Regarding cardiovascular events, 562 out of 856 (65.7%) events were noted in the non-T2DM group, whereas the T2DM group documented 338 out of 467 events (72.4%).

In the ischemic HFmrEF population, those diagnosed with T2DM displayed a significantly higher risk for all-cause mortality compared to their non-T2DM counterparts（Fig. 2A）. An unadjusted model yielded a hazard ratio (HR) of 1.4 (95% CI: 1.1–1.8, $P = 0.001$), indicating a 40% increased risk of death in the T2DM group. When adjusted for age and gender, this HR increased to 1.7 (95% CI: 1.4–2.1, $P < 0.001$), reflecting a 70% increased risk. After full adjustment for confounders, the HR stabilized at 1.5 (95% CI: 1.2–1.9, $P = 0.001$), suggesting that T2DM continues to confer a clinically meaningful 50% increased risk of all-cause mortality in ischemic HFmrEF patients, independent of other factors. Regarding cardiovascular events, the risk was also higher in ischemic patients with T2DM（Fig. 2A）, as evidenced by an HR of 1.2 (95% CI: 1.1–1.4, $P = 0.002$) in the crude model, and 1.3 (95% CI: 1.1–1.5, $P < 0.001$) after adjusting for age and gender. This remained consistent at an HR of 1.3 (95% CI: 1.1–1.5, $P = 0.001$) after comprehensive adjustment for confounders, indicating a clinically significant 30% increased risk of cardiovascular events in ischemic patients with T2DM.

Of the 1,323 ischemic HFmrEF patients assessed, propensity scores were assigned based on T2DM status. Following the alignment of all adjustment variables, baseline propensity scores were 0.35 ± 0.13 for non-T2DM individuals and 0.35 ± 0.14 for those with T2DM. A *P*-value of 0.5692 indicated no statistical difference, validating intergroup comparisons (for an in-depth post-PSM baseline, refer to Supplementary Table 1). Within the ischemic HFmrEF demographic, compared to non-diabetic individuals, those with T2DM had a significantly higher mortality risk, indicated by an HR of 1.40 (95% CI: 1.19–1.63, $P < 0.0001$). The risk increase also extended to cardiovascular events for T2DM individuals, marked by an HR of 1.13 (95% CI: 1.03–1.25, $P = 0.0125$) (detailed findings in Supplementary Table 2). These data align with the results from the multivariate Cox hazard model, supporting the robustness of the statistical conclusions.

Conversely, within non-ischemic HFmrEF patients, no significant associations between T2DM and the risks of all-cause mortality (HR 1.0, 95% CI: 0.6–1.7, $P = 0.957$) or cardiovascular events (HR 1.3, 95% CI: 0.9–1.9, $P = 0.113$) were observed (refer to Table 2 for specifics).

Independent risk factors in ischemic HFmrEF patients

We employed a multivariate Cox regression analysis to identify risk factors independently associated with adverse outcomes in ischemic HFmrEF patients (refer to Table 3). Variables with a significance level of $P < 0.05$ in

Table 1 Baseline characteristics of ischemic/non-ischemic HFmrEF patients stratified by the presence of T2DM

Variable	ischemic		non-ischemic	
	without T2DM	with T2DM	without T2DM	with T2DM
Demographics				
n	**856**	**467**	**281**	**87**
Age, years	70.2 ± 11.4	68.3 ± 10.6*	63.8 ± 15.0	62.1 ± 14.9
Male sex, n(%)	583 (68.1%)	292 (62.5%)*	165 (58.7%)	55 (63.2%)
Body mass index, kg/m^2	25.1 ± 4.2	25.6 ± 4.0	24.2 ± 4.2	25.4 ± 4.1*
Clinical characteristics				
Systolic BP, mmHg	134.0 ± 25.3	138.5 ± 25.9*	138.4 ± 27.2	143.4 ± 25.0
Diastolic BP, mmHg	79.5 ± 16.0	80.7 ± 15.0	81.9 ± 19.4	83.6 ± 17.1
Heart rate, bpm	81.4 ± 18.1	84.5 ± 19.1*	90.3 ± 24.1	86.9 ± 18.4
Cardiac risk factors and co-morbidities, n (%)				
Obesity[a]	208 (24.3%)	108 (23.1%)	65 (23.1%)	18 (20.7%)
Current smoker	313 (36.6%)	132 (28.3%)*	77 (27.4%)	22 (25.3%)
Current drinker	84(9.8%)	31(6.6%)	26(9.3%)	6(6.9%)
Atrial fibrillation	134 (15.7%)	66 (14.1%)	81 (28.8%)	15 (17.2%)*
Hyperlipidemia	155 (18.1%)	126 (27.0%)*	35 (12.5%)	34 (39.1%)*
Hypertension	569 (66.5%)	365 (78.2%)*	158 (56.2%)	70 (80.5%)*
Hyperuricaemia	204 (23.8%)	114 (24.4%)	88 (31.3%)	20 (23.0%)
Anaemia	271 (31.7%)	196 (42.0%)*	102 (36.3%)	37 (42.5%)
Renal dysfunction[b]	148 (17.3%)	155 (33.2%)*	70 (24.9%)	34 (39.1%)*
PCI	365 (42.6%)	196 (42.0%)	3 (1.1%)	1 (1.1%)
CABG	4 (0.5%)	4 (0.9%)	0 (0.0%)	1 (1.1%)
Stroke/transient ischaemic attack	90 (10.5%)	77 (16.5%)*	28 (10.0%)	12 (13.8%)
COPD	124 (14.5%)	43 (9.2%)*	35 (12.5%)	7 (8.0%)
ICD	3 (0.4%)	3 (0.6%)	4 (1.4%)	1 (1.1%)
CRTD	5 (0.6%)	2 (0.4%)	1 (0.4%)	0 (0.0%)
NYHA class III–IV	466 (54.4%)	275 (58.9%)	178 (63.3%)	53 (60.9%)
Serology				
HbA1c,%	–	8.0 ± 1.8	–	8.0 ± 2.3
NT-proBNP, pg/ml	2207.5 (570.0-6413.2)	3027.0 (748.0-9126.0)*	4353.5 (1400.8-14267.2)	4916.5 (1393.5-15330.8)
Low density lipoprotein, mmol/L	2.5 ± 0.9	2.5 ± 1.1	2.3 ± 0.9	2.6 ± 1.1*
Echocardiography				
LVEF, %	44.5 ± 2.8	44.4 ± 2.7	44.2 ± 2.8	44.5 ± 2.7
LAs, mm	38.2 ± 5.9	39.2 ± 5.4*	42.2 ± 7.5	40.7 ± 5.3
LVd, mm	53.3 ± 6.7	53.0 ± 6.4	57.1 ± 7.6	56.0 ± 6.0
IVSd, mm	9.9 ± 1.6	10.1 ± 1.5*	10.1 ± 1.7	10.3 ± 1.5
LVPWd, mm	9.3 ± 1.5	9.5 ± 1.6*	10.0 ± 1.6	10.1 ± 1.5
RAs, mm	36.9 ± 5.7	36.8 ± 5.5	40.7 ± 7.7	38.7 ± 6.4*
RVd, mm	20.7 ± 5.1	20.7 ± 5.2	21.4 ± 5.7	21.7 ± 5.5
HF-related medical therapy, n (%)				
ACEi	510 (59.6%)	225 (48.2%)*	96 (34.2%)	28 (32.2%)
ARB	214 (25.0%)	150 (32.1%)*	62 (22.1%)	26 (29.9%)
ARNI	36 (4.2%)	28 (6.0%)	12 (4.3%)	3 (3.4%)
Beta-blocker	707 (82.6%)	398 (85.2%)	184 (65.5%)	61 (70.1%)
Spironolactone	406 (47.4%)	207 (44.3%)	121 (43.1%)	41 (47.1%)
Digoxin	26 (3.0%)	13 (2.8%)	18 (6.4%)	7 (8.0%)
Loop diuretics	436 (50.9%)	269 (57.6%)*	146 (52.0%)	44 (50.6%)
SGLT2i	1 (0.1%)	15 (3.2%)*	0 (0.0%)	3 (3.4%)*
CCBs	301 (35.2%)	225 (48.2%)*	89 (31.7%)	46 (52.9%)*
Statins	770 (90.0%)	429 (91.9%)	156 (55.5%)	67 (77.0%)*
Nitrate	436 (50.9%)	262 (56.1%)	107 (38.1%)	45 (51.7%)*
Aspirin/antiplatelets	762 (89.0%)	426 (91.2%)	143 (50.9%)	63 (72.4%)*
T2DM treatment, n (%)				

Table 1 (continued)

Variable	ischemic		non-ischemic	
	without T2DM	with T2DM	without T2DM	with T2DM
One oral medication				
Metformin	–	55 (11.8%)	–	18 (20.7%)
SU/glinide	–	62 (13.3%)	–	12 (13.8%)
DDP-4i	–	36 (7.7%)	–	6 (6.9%)
Glucosidase inhibitor	–	150 (32.1%)	–	20 (23.0%)
≥ 2 oral medications	–	70 (15.0%)	–	15 (17.2%)
Insulin/insulin + oral drug	–	261 (55.9%)	–	48 (55.2%)

Data are presented as mean ± SD or number (%) of subjects.

aBody mass index ≥ 30 mg/m2. bEstimated glomerular filtration rate < 60 mL/min/1.73m2 by Cockcroft–Gault equation.

Abbreviations: HFmrEF: Heart failure with mildly reduced ejection fraction; T2DM: Type 2 Diabetes Mellitus; BP: Blood Pressure; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; ICD: Implantable cardioverter defibrillator; CRTD: Cardiac resynchronization therapy defibrillator; NYHA: New York Heart Association; HbA1c: Hemoglobin A1c; NT-proBNP: N-terminal pro b-type natriuretic peptide; LVEF: Left Ventricular Ejection Fraction; LAs: Left Atrial size; LVd: Left Ventricular diameter; IVSd: Interventricular Septal thickness at end-diastole; LVPWd: Left Ventricular Posterior Wall thickness at end-diastole; RAs: Right Atrial size; RVd: Right Ventricular diameter; ACEi: Angiotensin-Converting Enzyme inhibitors; ARB: Angiotensin II Receptor Blockers; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; SGLT2i: Sodium-Glucose Co-Transporter 2 inhibitors; CCBs: Calcium Channel Blockers; SU: Sulfonylureas; DDP-4i: Dipeptidyl Peptidase-4 inhibitors;

*$P < 0.05$ vs. without T2DM Group

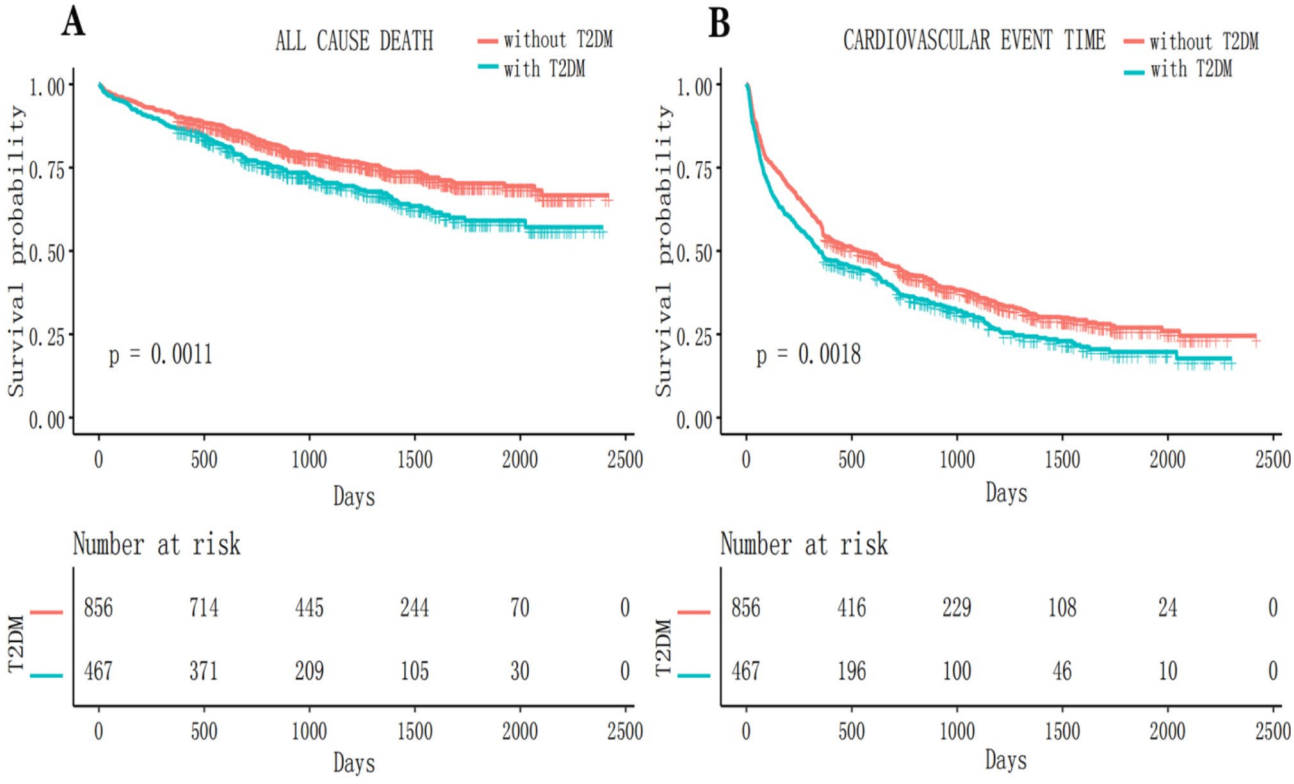


Fig. 2 Cumulative incidence of Outcome event in patients with ischemic HFmrEF. (**A**) Cumulative All-cause death. (**B**) Cumulative Cardiovascular event

the univariate Cox regression were included in the multivariate model.

Our results identified several factors independently linked to all-cause mortality: advanced age (HR 1.05, 95% CI 1.03–1.06, $P < 0.0001$), the presence of T2DM (HR 1.50, 95% CI 1.18–1.91, $P = 0.0009$), anemia (HR 1.65, 95% CI 1.28–2.12, $P < 0.0001$), undergoing PCI (HR 0.48, 95% CI 0.36–0.64, $P < 0.0001$), hyperuricemia (HR 1.37, 95% CI 1.07–1.75, $P = 0.0137$), prior stroke (HR 1.76, 95% CI 1.33–2.33, $P < 0.0001$), and elevated Log NT-proBNP levels (HR 1.16, 95% CI 1.06–1.26, $P = 0.0013$). These factors indicate a significant increase in the risk of mortality, particularly in patients with T2DM and those with elevated NT-proBNP levels.

Regarding cardiovascular events, advanced age (HR 1.01, 95% CI 1.00–1.02, $P = 0.0026$), T2DM (HR 1.29,

Table 2 Association between T2DM and clinical outcomes (all-cause death and cardiovascular events) in ischemic and non-ischemic HFmrEF patients: Cox regression models

	Events/ Total	Events rate(%)	Model A		Model B		Model C	
			Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Ischemic								
ALL CAUSE DEATH								
without T2DM	201/856	23.50%	Ref.					
with T2DM	145/467	31.00%	1.4 (1.1, 1.8)	**0.001**	1.7 (1.4, 2.1)	**< 0.001**	1.5 (1.2, 1.9)	**0.001**
CARDIOVASCULAR EVENT								
without T2DM	562/856	65.70%	Ref.					
with T2DM	338/467	72.40%	1.2 (1.1, 1.4)	**0.002**	1.3 (1.1, 1.5)	**< 0.001**	1.3 (1.1, 1.5)	**0.001**
Non-ischemic								
ALL CAUSE DEATH								
without T2DM	88/281	31.30%	Ref.					
with T2DM	23/87	26.40%	0.8 (0.5, 1.3)	0.486	0.9 (0.6, 1.4)	0.621	1.0 (0.6, 1.7)	0.957
CARDIOVASCULAR EVENT								
without T2DM	197/281	70.10%	Ref.					
with T2DM	63/87	72.40%	1.1 (0.8, 1.5)	0.471	1.1 (0.8, 1.5)	0.433	1.3 (0.9, 1.9)	0.113

Statistical significance is indicated by bold values ($p < 0.05$). Hazard ratios and confidence intervals are presented for each outcome.

Model A adjust for: None

Model B adjust for: Age; Sex

Model C adjust for: Age; Sex; Body mass index; Current smoker; Hyperlipidemia; Hypertension; Atrial fibrillation; Renal dysfunction; PCI; Stroke; NYHA class; NT-proBNP; COPD; Anaemia; Hyperuricaemia

Abbreviation: CI = confidence interval; Other abbreviations can be found in Table 1.

Table Notes:

1. All-cause Death (Ischemic): Patients with T2DM show a significantly higher risk of all-cause death compared to those without T2DM ($p = 0.001$), with hazard ratios ranging from 1.4 to 1.7 across different models.

2. Cardiovascular Events (Ischemic): T2DM is associated with an increased risk of cardiovascular events in ischemic HFmrEF patients, with hazard ratios ranging from 1.2 to 1.3 ($p < 0.05$).

3. All-cause Death (Non-ischemic): No significant association between T2DM and all-cause death in non-ischemic HFmrEF patients ($p = 0.486$).

4. Cardiovascular Events (Non-ischemic): No significant difference in cardiovascular events between T2DM and non-T2DM groups in non-ischemic HFmrEF patients ($p = 0.433$)

95% CI 1.11–1.49, $P = 0.0009$), anemia (HR 1.19, 95% CI 1.02–1.39, $P = 0.0293$), hyperuricemia (HR 1.34, 95% CI 1.14–1.58, $P = 0.0004$), atrial fibrillation (HR 1.32, 95% CI 1.09–1.59, $P = 0.0042$), hypertension (HR 1.19, 95% CI 1.01–1.40, $P = 0.0403$), and elevated Log NT-proBNP levels (HR 1.13, 95% CI 1.08–1.19, $P < 0.0001$) were independently associated with an increased risk of cardiovascular events. These findings corroborate our previous results, confirming that T2DM and elevated NT-proBNP levels are significant predictors of both all-cause mortality and cardiovascular events in ischemic HFmrEF patients.

Stratified evaluation in ischemic HFmrEF patients

Using the CHAID algorithm for decision trees, we identified NT-proBNP levels of ≤ 441, 441 to 9401.22, and > 9401.22 pg/ml as potential prognostic benchmarks for all-cause mortality among diabetic individuals (see Fig. 3A). Similarly, NT-proBNP levels of ≤ 441, 441 to 2573, and > 2573 pg/ml were identified as potential prognostic indicators for cardiovascular events (Fig. 3B). For non-diabetic subjects, the relevant thresholds are delineated in Fig. 3.

Given that the decision tree identified NT-proBNP ≤ 441 pg/ml as a consistent benchmark for both endpoints in diabetic individuals, this stratified assessment considered NT-proBNP = 441 pg/ml as the pivotal threshold.

All-Cause Mortality Risk in Ischemic HFmrEF Patients with Concomitant Diabetes Mellitus:

Ischemic HFmrEF patients with concurrent diabetes mellitus displayed a heightened risk of all-cause mortality, irrespective of gender, age, NT-proBNP concentrations, atrial fibrillation status, hyperlipidemia, hypertension, hyperuricemia, anemia, or NYHA class III + IV designation. This elevated risk persisted in non-smoking, non-obese individuals, even in the absence of renal insufficiency, previous stroke, COPD, or prior PCI interventions (Fig. 4A).

Cardiovascular Event Risk in Ischemic HFmrEF Patients with Diabetes Mellitus:

Female ischemic HFmrEF patients aged above 70 years, with NT-proBNP concentrations surpassing 441 pg/ml, and those with NYHA class III + IV, hypertension, hyperuricemia, or anemia, demonstrated an increased risk for

Table 3 Cox proportional hazards regression model analysis for outcome risks in ischemic HFmrEF patients

Variable	Univariable			Multivariable	
	Hazard ratio (95% CI)	*P*-value	Wald	Hazard ratio (95% CI)	*P*-value
ALL CAUSE DEATH					
Age per year	1.06 (1.05, 1.07)	**< 0.0001**	**112.9**	1.05 (1.03, 1.06)	**< 0.0001**
Log NT-proBNP	1.46 (1.35, 1.58)	**< 0.0001**	**87.44**	1.16 (1.06, 1.26)	**0.0013**
Anaemia	2.68 (2.17, 3.31)	**< 0.0001**	**82.92**	1.65 (1.28, 2.12)	**< 0.0001**
PCI	0.32 (0.25, 0.41)	**< 0.0001**	**75.67**	0.48 (0.36, 0.64)	**< 0.0001**
Renal dysfunction	2.27 (1.82, 2.83)	**< 0.0001**	**52.97**	1.22 (0.94, 1.57)	0.1348
Hyperuricaemia	2.03 (1.63, 2.53)	**< 0.0001**	**40.18**	1.37 (1.07, 1.75)	**0.0137**
COPD	2.04 (1.58, 2.65)	**< 0.0001**	**29.07**	1.26 (0.93, 1.69)	0.1315
NYHA class IV/III vs. II	1.82 (1.45, 2.29)	**< 0.0001**	**26.86**	1.20 (0.93, 1.54)	0.165
Stroke	1.97 (1.52, 2.55)	**< 0.0001**	**26.19**	1.76 (1.33, 2.33)	**< 0.0001**
Atrial fibrillation	1.71 (1.32, 2.21)	**< 0.0001**	**16.7**	1.23 (0.93, 1.63)	0.148
Hypertension	1.68 (1.30, 2.17)	**< 0.0001**	**15.41**	1.08 (0.82, 1.42)	0.5922
T2DM	1.42 (1.15, 1.76)	**0.0012**	**10.49**	1.50 (1.18, 1.91)	**0.0009**
Hyperlipidemia	0.64 (0.48, 0.86)	**0.0026**	**9.08**	0.78 (0.57, 1.08)	0.1312
Current smoker	0.77 (0.61, 0.97)	**0.0254**	**4.99**	1.17 (0.90, 1.51)	0.2407
Male vs. Female	0.91 (0.73, 1.13)	0.3917	0.73		
Body mass index	0.99 (0.97, 1.02)	0.5095	0.44		
CARDIOVASCULAR EVENT					
Log NT-proBNP	1.23 (1.17, 1.28)	**< 0.0001**	**66.81**	1.13 (1.08, 1.19)	**< 0.0001**
Anaemia	1.52 (1.33, 1.74)	**< 0.0001**	**37.55**	1.19 (1.02, 1.39)	**0.0293**
Age per year	1.02 (1.01, 1.02)	**< 0.0001**	**35.47**	1.01 (1.00, 1.02)	**0.0026**
Hyperuricaemia	1.53 (1.32, 1.77)	**< 0.0001**	**31.89**	1.34 (1.14, 1.58)	**0.0004**
Renal dysfunction	1.52 (1.31, 1.76)	**< 0.0001**	**30.25**	1.03 (0.86, 1.22)	0.7712
Atrial fibrillation	1.43 (1.20, 1.70)	**< 0.0001**	**16.54**	1.32 (1.09, 1.59)	**0.0042**
Hypertension	1.34 (1.16, 1.56)	**< 0.0001**	**15.37**	1.19 (1.01, 1.40)	**0.0403**
PCI	0.77 (0.67, 0.88)	**0.0001**	**15.13**	0.99 (0.85, 1.15)	0.8570
NYHA class IV/III vs. II	1.26 (1.10, 1.43)	**0.0008**	**11.34**	1.03 (0.89, 1.20)	0.6916
COPD	1.35 (1.12, 1.63)	**0.0016**	**9.96**	1.19 (0.97, 1.46)	0.099
T2DM	1.24 (1.08, 1.42)	**0.0018**	**9.71**	1.29 (1.11, 1.49)	**0.0009**
Stroke	1.31 (1.09, 1.58)	**0.0043**	**8.14**	1.19 (0.97, 1.45)	0.0902
Current smoker	0.85 (0.74, 0.98)	**0.0216**	**5.28**	0.99 (0.85, 1.17)	0.9497
Hyperlipidemia	0.90 (0.76, 1.06)	0.1872	1.74		
Body mass index	0.99 (0.97, 1.01)	0.2291	1.45		
Male vs. Female	0.93 (0.81, 1.06)	0.2793	1.17		

Bold represent significant values ($p < 0.05$). abbreviations can be found in Table 1

cardiovascular events. This observation held true regardless of their obesity status or the presence of atrial fibrillation. Furthermore, non-smokers and patients without hyperlipidemia, prior stroke, COPD, or a history of PCI also demonstrated this increased risk (Fig. 4B).

Therapeutic implications on outcomes for ischemic HFmrEF patients with T2DM

Upon adjusting for age, gender, and heart failure medication usage, ischemic HFmrEF patients treated with two or more oral hypoglycemic drugs (HR 0.4, 95% CI 0.2–0.8, $P = 0.007$) or insulin therapy (HR 0.7, 95% CI 0.5–0.9, $P = 0.020$) showed a notably reduced all-cause mortality risk compared to their counterparts not on these regimens. After similar adjustments, ischemic HFmrEF patients receiving one (HR 0.7, 95% CI 0.6–0.9, $P = 0.016$) or more (HR 0.7, 95% CI 0.5–1.0, $P = 0.039$) oral hypoglycemic agents had a lower risk of cardiovascular events. Notably, insulin therapy (HR 0.9, 95% CI 0.7–1.1, $P = 0.354$) was not significantly associated with cardiovascular event rates (Table 4). No significant difference was noted in glycated hemoglobin levels between patients on oral hypoglycemic therapy and those not on it (Fig. 5A, $P > 0.05$). Conversely, those on insulin therapy showed reduced glycated hemoglobin levels compared to those not on the regimen (Fig. 5B, $P < 0.05$).

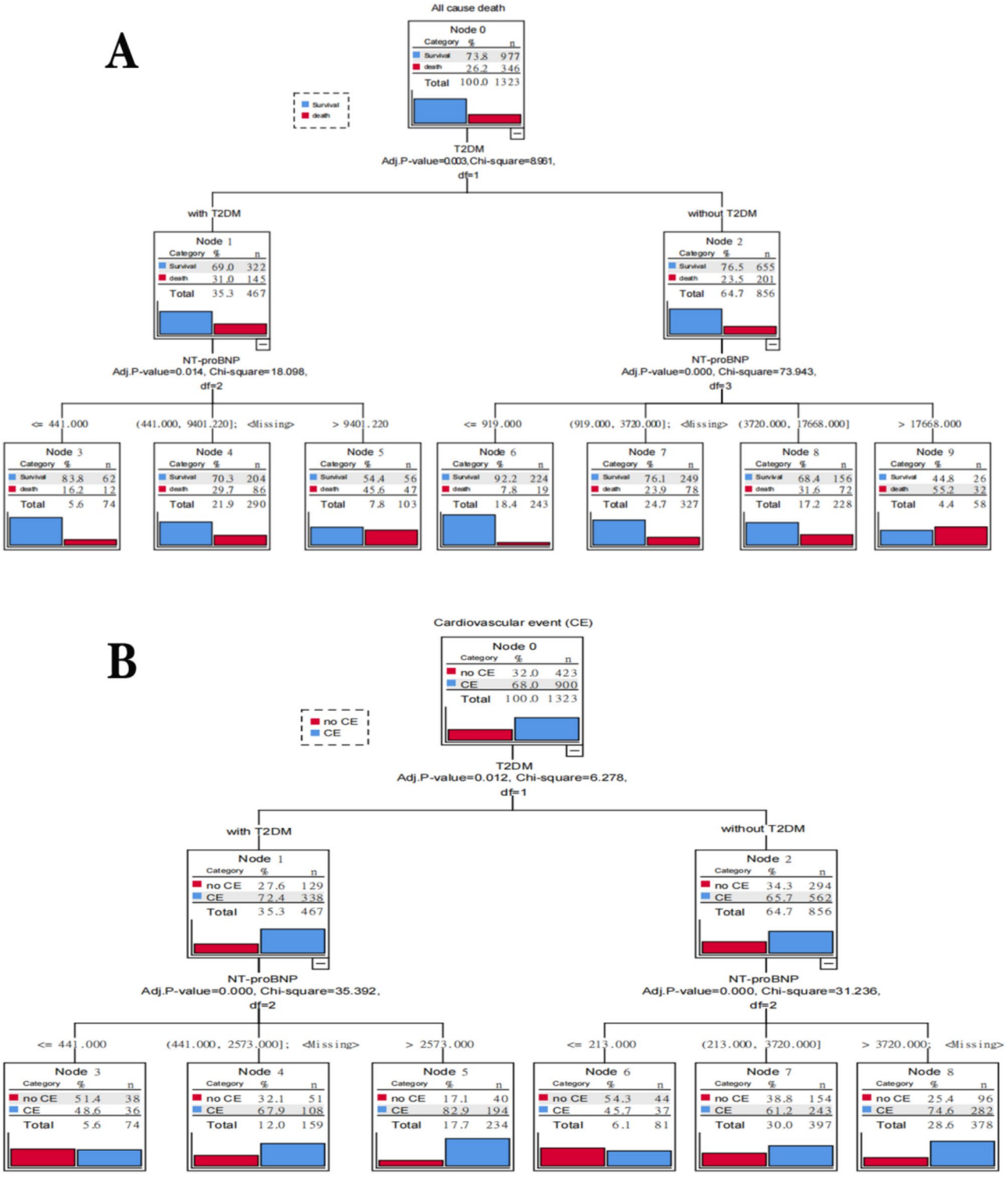
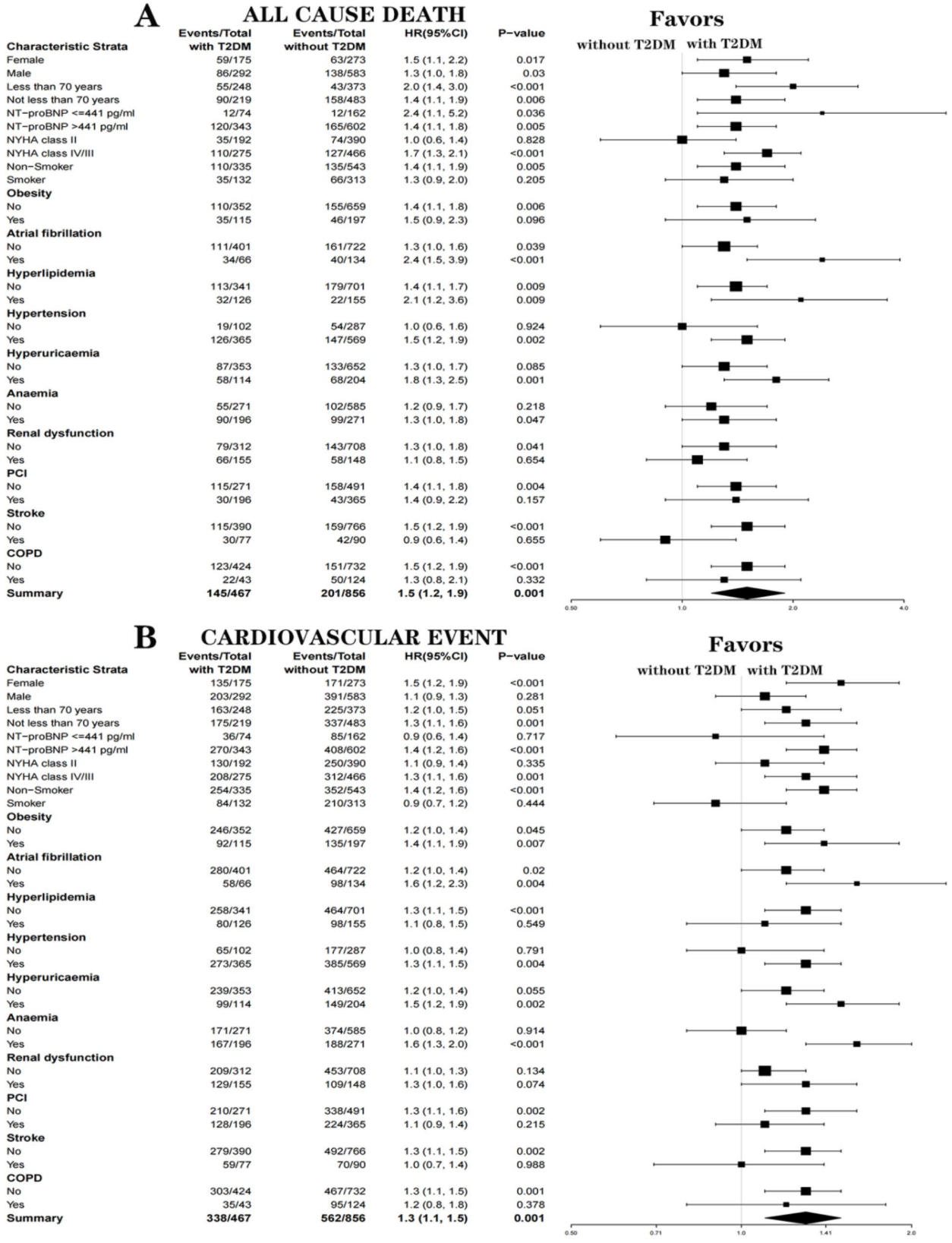


Fig. 3 For ischemic HFmrEF patients, a classification tree using the CHAID algorithm was adopted to ensure the accuracy of the model. Potential risk factors related to the outcome event are: T2DM and NT-proBNP. (**A**) Categorization with T2DM and NT-proBNP based on all-cause mortality. (**B**) Categorization with T2DM and NT-proBNP based on cardiovascular event



Characteristic Strata	Events/Total with T2DM	Events/Total without T2DM	HR(95%CI)	P−value
Female	59/175	63/273	1.5 (1.1, 2.2)	0.017
Male	86/292	138/583	1.3 (1.0, 1.8)	0.03
Less than 70 years	55/248	43/373	2.0 (1.4, 3.0)	<0.001
Not less than 70 years	90/219	158/483	1.4 (1.1, 1.9)	0.006
NT−proBNP <=441 pg/ml	12/74	12/162	2.4 (1.1, 5.2)	0.036
NT−proBNP >441 pg/ml	120/343	165/602	1.4 (1.1, 1.8)	0.005
NYHA class II	35/192	74/390	1.0 (0.6, 1.4)	0.828
NYHA class IV/III	110/275	127/466	1.7 (1.3, 2.1)	<0.001
Non−Smoker	110/335	135/543	1.4 (1.1, 1.9)	0.005
Smoker	35/132	66/313	1.3 (0.9, 2.0)	0.205
Obesity				
No	110/352	155/659	1.4 (1.1, 1.8)	0.006
Yes	35/115	46/197	1.5 (0.9, 2.3)	0.096
Atrial fibrillation				
No	111/401	161/722	1.3 (1.0, 1.6)	0.039
Yes	34/66	40/134	2.4 (1.5, 3.9)	<0.001
Hyperlipidemia				
No	113/341	179/701	1.4 (1.1, 1.7)	0.009
Yes	32/126	22/155	2.1 (1.2, 3.6)	0.009
Hypertension				
No	19/102	54/287	1.0 (0.6, 1.6)	0.924
Yes	126/365	147/569	1.5 (1.2, 1.9)	0.002
Hyperuricaemia				
No	87/353	133/652	1.3 (1.0, 1.7)	0.085
Yes	58/114	68/204	1.8 (1.3, 2.5)	0.001
Anaemia				
No	55/271	102/585	1.2 (0.9, 1.7)	0.218
Yes	90/196	99/271	1.3 (1.0, 1.8)	0.047
Renal dysfunction				
No	79/312	143/708	1.3 (1.0, 1.8)	0.041
Yes	66/155	58/148	1.1 (0.8, 1.5)	0.654
PCI				
No	115/271	158/491	1.4 (1.1, 1.8)	0.004
Yes	30/196	43/365	1.4 (0.9, 2.2)	0.157
Stroke				
No	115/390	159/766	1.5 (1.2, 1.9)	<0.001
Yes	30/77	42/90	0.9 (0.6, 1.4)	0.655
COPD				
No	123/424	151/732	1.5 (1.2, 1.9)	<0.001
Yes	22/43	50/124	1.3 (0.8, 2.1)	0.332
Summary	**145/467**	**201/856**	**1.5 (1.2, 1.9)**	**0.001**

Characteristic Strata	Events/Total with T2DM	Events/Total without T2DM	HR(95%CI)	P−value
Female	135/175	171/273	1.5 (1.2, 1.9)	<0.001
Male	203/292	391/583	1.1 (0.9, 1.3)	0.281
Less than 70 years	163/248	225/373	1.2 (1.0, 1.5)	0.051
Not less than 70 years	175/219	337/483	1.3 (1.1, 1.6)	0.001
NT−proBNP <=441 pg/ml	36/74	85/162	0.9 (0.6, 1.4)	0.717
NT−proBNP >441 pg/ml	270/343	408/602	1.4 (1.2, 1.6)	<0.001
NYHA class II	130/192	250/390	1.1 (0.9, 1.4)	0.335
NYHA class IV/III	208/275	312/466	1.3 (1.1, 1.6)	0.001
Non−Smoker	254/335	352/543	1.4 (1.2, 1.6)	<0.001
Smoker	84/132	210/313	0.9 (0.7, 1.2)	0.444
Obesity				
No	246/352	427/659	1.2 (1.0, 1.4)	0.045
Yes	92/115	135/197	1.4 (1.1, 1.9)	0.007
Atrial fibrillation				
No	280/401	464/722	1.2 (1.0, 1.4)	0.02
Yes	58/66	98/134	1.6 (1.2, 2.3)	0.004
Hyperlipidemia				
No	258/341	464/701	1.3 (1.1, 1.5)	<0.001
Yes	80/126	98/155	1.1 (0.8, 1.5)	0.549
Hypertension				
No	65/102	177/287	1.0 (0.8, 1.4)	0.791
Yes	273/365	385/569	1.3 (1.1, 1.5)	0.004
Hyperuricaemia				
No	239/353	413/652	1.2 (1.0, 1.4)	0.055
Yes	99/114	149/204	1.5 (1.2, 1.9)	0.002
Anaemia				
No	171/271	374/585	1.0 (0.8, 1.2)	0.914
Yes	167/196	188/271	1.6 (1.3, 2.0)	<0.001
Renal dysfunction				
No	209/312	453/708	1.1 (1.0, 1.3)	0.134
Yes	129/155	109/148	1.3 (1.0, 1.6)	0.074
PCI				
No	210/271	338/491	1.3 (1.1, 1.6)	0.002
Yes	128/196	224/365	1.1 (0.9, 1.4)	0.215
Stroke				
No	279/390	492/766	1.3 (1.1, 1.5)	0.002
Yes	59/77	70/90	1.0 (0.7, 1.4)	0.988
COPD				
No	303/424	467/732	1.3 (1.1, 1.5)	0.001
Yes	35/43	95/124	1.2 (0.8, 1.8)	0.378
Summary	**338/467**	**562/856**	**1.3 (1.1, 1.5)**	**0.001**

Fig. 4 Forest plot of stratified analysis for ischemic HFmrEF patients based on the presence/absence of T2DM. (**A**) Outcome event: all-cause mortality. (**B**) Outcome event: cardiovascular event

Table 4 Association between diabetes treatment and clinical outcomes in ischemic HFmrEF patients

Glycemic control regimen	Events/ Total	Events rate(%)	Non-adjusted		Adjust I		Adjust II	
			Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
ALL CAUSE DEATH								
Oral antidiabetic drugs:								
Not on oral medication	88/241	36.51%	Ref.					
One oral medication	45/156	28.85%	0.7 (0.5, 1.0)	0.050	0.7 (0.5, 1.0)	**0.047**	0.7 (0.5, 1.1)	0.097
Two or more oral medications	12/70	17.14%	0.4 (0.2, 0.7)	**0.003**	0.4 (0.2, 0.7)	**0.003**	0.4 (0.2, 0.8)	**0.007**
Insulin/insulin + oral drug:								
Not using insulin	70/206	33.98%	Ref.					
Using insulin	75/261	28.74%	0.8 (0.6, 1.2)	0.316	0.7 (0.5, 0.9)	**0.023**	0.7 (0.5, 0.9)	**0.020**
CARDIOVASCULAR EVENT								
Oral antidiabetic drugs:								
Not on oral medication	187/241	77.59%	Ref.					
One oral medication	107/156	69.87%	0.7 (0.6, 0.9)	**0.006**	0.7 (0.6, 0.9)	**0.005**	0.7 (0.6, 0.9)	**0.016**
Two or more oral medications	44/70	62.86%	0.7 (0.5, 0.9)	**0.022**	0.7 (0.5, 0.9)	**0.020**	0.7 (0.5, 1.0)	**0.039**
Insulin/insulin + oral drug:								
Not using insulin	153/206	74.27%	Ref.					
Using insulin	185/261	70.88%	0.9 (0.7, 1.1)	0.478	0.9 (0.7, 1.1)	0.356	0.9 (0.7, 1.1)	0.354

Statistical significance is indicated by bold values ($p < 0.05$). Hazard ratios and confidence intervals are presented for each outcome. abbreviations can be found in Table 1.

Non-adjusted model adjust for: None

Adjust I model adjust for: Age; Sex

Adjust II model adjust for: Age; Sex; Angiotensin II Receptor Blockers; Angiotensin Receptor-Neprilysin Inhibitor; Beta-blocker; Spironolactone; Sodium-Glucose Co-Transporter 2 inhibitors; Angiotensin-Converting Enzyme inhibitors.

Clinical interpretation:

- Oral antidiabetic medication: Patients using oral medications (especially two or more drugs) show a significant reduction in all-cause death risk and cardiovascular events. This suggests that optimal glycemic control may improve clinical outcomes in ischemic HFmrEF patients.

- Insulin therapy: Insulin use did not significantly reduce the risk of all-cause death, though it was associated with a reduced risk of cardiovascular events in adjusted models (HR 0.7, $p = 0.020$), which warrants further investigation

Discussion

In our retrospective analysis of 1,691 HFmrEF patients from the Central Hospital of Xiangtan, we observed notable differences in patient outcomes based on the coexistence of ischemic heart disease and T2DM. Specifically, the presence of T2DM in patients with ischemic heart disease was associated with a significantly increased risk of all-cause mortality and cardiovascular events compared to their ischemic counterparts without T2DM. Interestingly, among non-ischemic HFmrEF patients, the association between T2DM and these risks remained statistically insignificant.

A key takeaway from our study is the reaffirmation of T2DM as a significant, independent risk factor for both all-cause mortality and cardiovascular complications among those with ischemic HFmrEF. This finding aligns with previous literature, which has consistently identified T2DM as a critical risk enhancer for ischemic heart disease, notably influencing increased mortality rates [24–29]. For instance, studies by Sarwar et al. (2010) and Noguchi et al. (2022) have shown that T2DM significantly worsens outcomes in patients with ischemic heart disease, leading to increased mortality rates [24, 29]. Our results further underscore the critical need for targeted management of T2DM in ischemic HFmrEF patients, given its consistent association with increased mortality and cardiovascular complications.

Diabetes may contribute to the increased risk of ischemic heart disease through changes in the transcriptome of long non-coding RNAs [30]. Moreover, when ischemic heart failure and diabetes coexist, the adverse risk trajectory is further accentuated [10, 11, 31]. Our study further indicates that T2DM does not have a significant impact on non-ischemic HFmrEF. This contrasts with the findings of Charlotte Andersson et al., which demonstrated that diabetes mellitus adversely affects long-term outcomes in both ischemic and non-ischemic heart failure patients [11]. However, the mechanisms underlying the development and progression of different heart failure subtypes are not entirely identical. Ischemic heart failure is primarily driven by direct ischemic damage, while non-ischemic heart failure may involve different pathological processes, such as myocardial fibrosis, genetic factors, and metabolic disturbances unrelated to ischemia [15, 16, 32, 33]. These pathophysiological differences may explain the varying impact of T2DM on these subtypes,

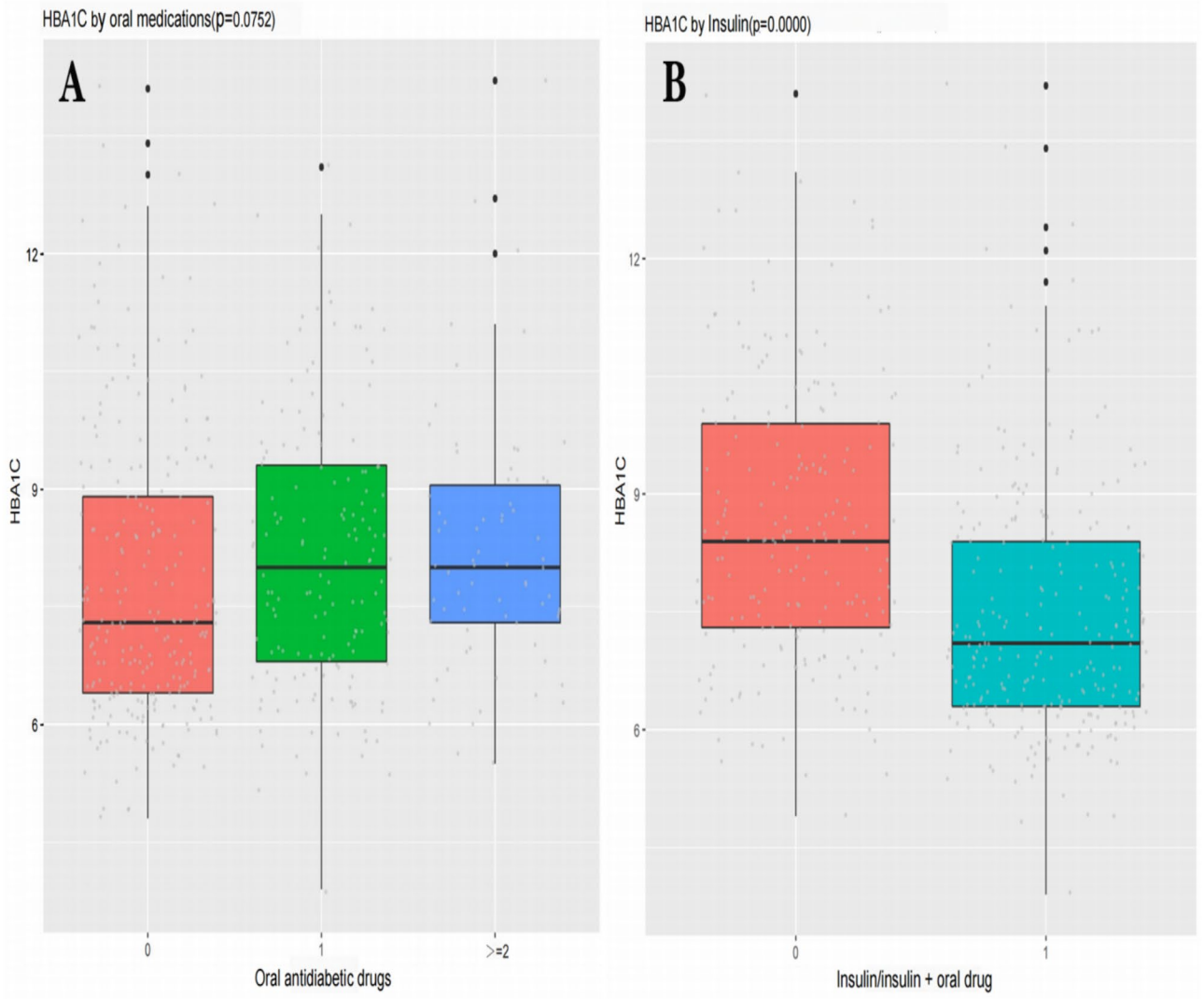


Fig. 5 Effects of glucose-lowering treatment on glycated hemoglobin (HbA1c) in ischemic HFmrEF patients with T2DM. **(A)** Impact of the number of oral hypoglycemic agents on glycated hemoglobin. (**B**) Influence of insulin use on glycated hemoglobin

highlighting the need for further research to elucidate the distinct mechanisms at play.

Historically, diabetes has been established as a formidable risk factor in the context of heart failure [34, 35]. Numerous earlier studies have highlighted a marked prognostic deterioration in heart failure patients with diabetes, particularly in those with reduced ejection fraction characteristics [36–40]. Even amidst other risk factors, T2DM consistently stands out as an independent predictor of adverse clinical outcomes across all heart failure phenotypes [39–42].

One of the novel aspects of our study is its focus on the ischemic HFmrEF population, where the combination of T2DM and ischemic heart disease seems to create a "synergistic" risk for adverse outcomes. Previous research has largely focused on heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), with less emphasis on HFmrEF, which often presents with overlapping characteristics of both HFrEF and HFpEF [43, 44]. Our results suggest that T2DM may act as a critical exacerbator of ischemic damage in HFmrEF patients, further highlighting the need for a targeted therapeutic approach in this population.

Regarding therapeutic strategies, our findings suggest that ischemic HFmrEF patients with coexisting T2DM, when managed with both oral hypoglycemic agents and insulin, exhibit a more favorable mortality profile. However, the current literature is conspicuously lacking robust RCTs that define optimal therapeutic approaches for this specific patient demographic. Nonetheless, the use of hypoglycemic agents has consistently shown efficacy in reducing adverse cardiovascular outcomes [45, 46]. This underscores the need for more rigorous

investigations to establish definitive treatment guidelines for ischemic HFmrEF patients with diabetes.

Furthermore, our dataset highlights a relative paucity in the association between T2DM and the risks of all-cause mortality or cardiovascular complications within the non-ischemic HFmrEF cohort. Given the inherent limitations of our sample size for this subgroup, expanding the research with larger studies is imperative to solidify these preliminary insights.

Limitations and remedial approaches

Our study, due to its retrospective design, may be subject to selection biases inherent in such studies. Prospective cohort studies or randomized controlled trials (RCTs) would provide more robust validation of our findings. The use of a single-center sample limits the external validity of our results, as patient characteristics and outcomes may differ across institutions. Multi-center studies involving diverse patient populations would help enhance the generalizability of our findings. Despite our adjustments for known confounders, there is potential for residual confounding due to unmeasured or unadjusted variables, which may still influence our results. In future research, employing advanced statistical techniques, such as propensity score matching or instrumental variable analysis, may help mitigate the effects of confounding and provide more accurate estimates. Additionally, we acknowledge that the exclusion criteria were stringent and may have led to the selection of a specific patient population, which could limit the applicability of the findings to broader patient groups. Therefore, studies with less restrictive inclusion/exclusion criteria are necessary to assess the findings in a more diverse cohort.

Future research avenues and pertinent queries

While our study highlights the potential importance of T2DM management in ischemic HFmrEF patients, the retrospective nature of our study and the lack of direct intervention data necessitate cautious interpretation of the findings, particularly regarding specific management protocols. To address this gap, future research should focus on well-designed, multicenter randomized controlled trials (RCTs) that evaluate the efficacy of various T2DM management strategies (e.g., pharmacologic treatments, lifestyle interventions) in improving long-term clinical outcomes in ischemic HFmrEF patients. These trials should aim to identify which interventions lead to the most significant reductions in mortality and morbidity in this population.

Additionally, studies comparing the effects of different T2DM therapies (e.g., SGLT2 inhibitors, GLP-1 receptor agonists) in ischemic versus non-ischemic HFmrEF subgroups could provide insights into potential differential treatment effects. Moreover, future research should incorporate long-term follow-up to evaluate the sustained impact of these therapies on cardiovascular events, hospitalization rates, and quality of life in T2DM-associated ischemic heart failure.

We also recommend investigating the role of personalized treatment strategies that tailor T2DM management based on individual patient profiles (e.g., genetic factors, comorbid conditions). For example, precision medicine approaches could help identify which patients are most likely to benefit from specific treatments, optimizing therapeutic outcomes. Additionally, studies focused on optimizing concurrent cardiovascular prevention strategies, such as the use of antiplatelet therapy, statins, and blood pressure control, are needed to further refine management practices.

Conclusion

To sum up, patients with ischemic HFmrEF compounded by T2DM face a significantly increased risk of overall mortality and cardiovascular events compared to those without T2DM. Amidst a myriad of risk factors, T2DM emerges as a significant, independent risk determinant for mortality and cardiovascular episodes in the context of ischemic HFmrEF. These findings offer a foundational framework for further dissecting the interplay between ischemic HFmrEF and T2DM and hold implications for prognostic evaluations and therapeutic interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01627-6.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Zc.L. and Hl.H.: established the hypothesis, performed the statistical analysis, wrote the manuscript. Zc.L.: interpreted statistical analysis and conducted multivariate analysis. Zc.L.: data collection and participated follow-up. My.J. and Jp.Z.: initiated the study hypothesis, edited the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The study protocol was approved by the Ethics Committee of Xiangtan Central Hospital (Xiangtan, China, No.20211036) and conformed to the principles outlined in the Declaration of Helsinki.The need for informed

consent was waived by the ethics committee Review Board of Xiangtan Central Hospital, because of the retrospective nature of the study.

Patient consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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