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Effect of diabetes mellitus on 3-year outcomes in patients with acute myocardial infarction with nonobstructive coronary arteries

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Abstract

Background: *Diabetes mellitus (DM) is a significant factor in increased mortality rates among patients with acute myocardial infarction (AMI), but research on its impact on the long-term outcomes in patients with MI with nonobstructive coronary arteries (MINOCA) is limited. Thus, a comparison of the 3-year clinical outcomes between the DM and non-DM groups among patients with MINOCA was undertaken.*

Methods: *From the Korea AMI Registry-National Institute of Health dataset, 13,104 AMI patients were enrolled. After applying the exclusion criteria, 379 patients with MINOCA were included. The primary clinical outcomes were major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent myocardial infarction (MI), repeat coronary revascularization, and stroke. The secondary outcomes were the individual components of MACCE.*

Results: *The adjusted hazard ratios for 3-year MACCE (2.287, $p = 0.010$), all-cause death (2.845, $p = 0.004$), and non-cardiac death (non-CD, 3.914, $p = 0.008$) were higher in the DM group than in the non-DM group. It is speculated that the higher non-CD rate in the MINOCA group is attributable to a higher proportion of patients with non-ST-segment elevation MI in the total study population. The CD, recurrent MI, revascularization, and stroke rates were similar between the DM and non-DM groups. DM, advanced age, cardiopulmonary resuscitation on admission, and nonuse of statin medications were significant predictors of MACCE.*

Conclusions: *In this study involving patients with MINOCA, the DM group exhibited a higher 3-year mortality rate than the non-DM group. Thus, DM demonstrated a hazardous effect even in patients with MINOCA.* (Cardiol J 2024; 31, 5: 675–689)

Keywords: diabetes, MINOCA, outcomes

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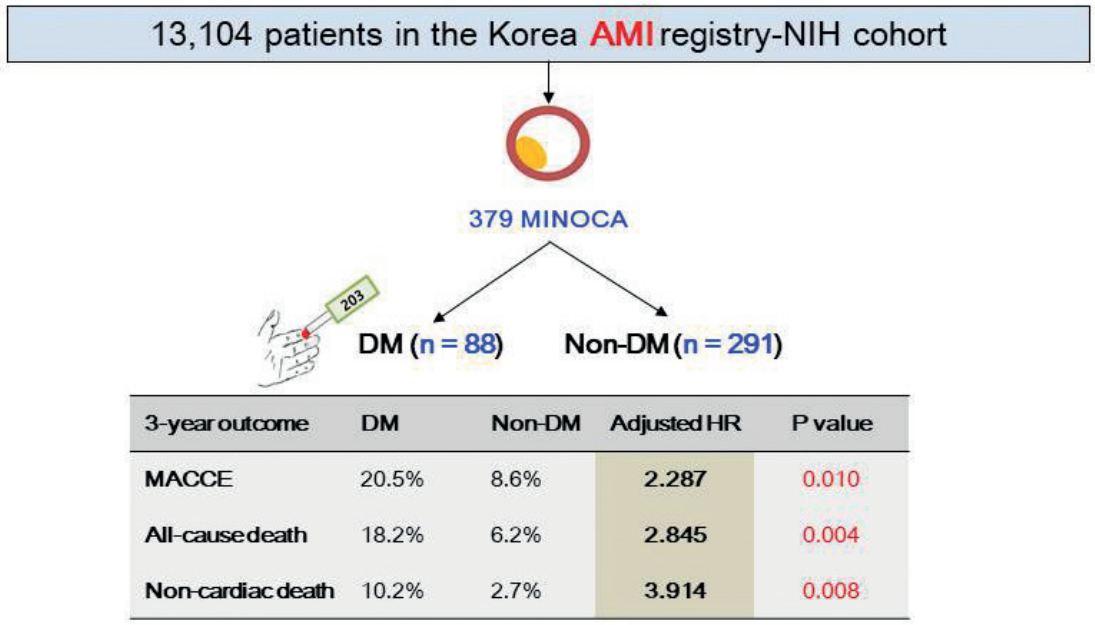
Graphical abstract



3-year outcome	DM	Non-DM	Adjusted HR	P value
MACCE	20.5%	8.6%	2.287	0.010
All-cause death	18.2%	6.2%	2.845	0.004
Non-cardiac death	10.2%	2.7%	3.914	0.008

DM group exhibited higher 3-year mortality rates than the non-DM group

DM demonstrated a hazardous effect even in patients with MINOCA

AMI - acute myocardial infarction; NIH - National Institute of Health; MINOCA - myocardial infarction with nonobstructive coronary arteries; CAD - coronary artery disease; DM - diabetes mellitus; MACCE - major adverse cardiac and cerebrovascular events; HR - hazard ratio.

Introduction

Elevated blood glucose levels are recognized as a risk factor for coronary artery disease (CAD) [1], and the risk of cardiac death (CD) is 2 to 4 times higher in patients with diabetes mellitus (DM) than in their age-matched counterparts without diabetes [2]. Approximately 20% to 30% of patients with acute myocardial infarction (AMI) develop DM [3]. Thrombus formation following the rupture or erosion of vulnerable atherosclerotic plaques is a shared pathophysiological process in both ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) [4]. Patients with STEMI typically present with complete coronary artery occlusion, whereas those with NSTEMI often exhibit partial or intermittent occlusion [5]. Myocardial infarction with nonobstructive coronary arteries (MINOCA) [6] is the term used to describe a condition in which 1% to 13% of AMI cases occur without significant obstructive coronary artery disease (CAD), defined as ≥ 50% diameter stenosis in a major epicardial vessel. However, the exact mechanisms underlying myocardial damage, pathophysiological processes, outcomes of MINOCA, and optimal treatment strategies have not been fully defined [6]. The recent investigation [7] focused on patients with MINOCA has revealed that adverse prognostic factors, akin to those seen in MI with obstructive coronary arteries (MIOCA) patients, include older age, DM (adjusted hazard ratio [aHR], 1.44; 95% confidence interval [CI]:1.21–1.70), and a higher level of creatinine. A comprehensive analysis including 714,780 patients [8] showed that the long-term mortality rate in patients with AMI and DM was approximately 50% higher than those without DM (aHR, 1.48; 95% CI: 1.43–1.53). Hence, DM is an important long-term adverse prognostic fac-

tor in patients with AMI. However, research on the impact of DM on long-term clinical outcomes in patients with MINOCA is very limited [9]. This study compared 3-year clinical outcomes between the DM and non-DM groups of patients with MINOCA.

Methods

Study population

In the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) [10], a multicenter prospective registry, a total of 13,104 patients who were 18 years or older at the time of enrollment and diagnosed with AMI were registered between November 2011 and December 2015. From this cohort, certain individuals were excluded from the analysis for the following reasons: (1) those who did not undergo coronary angiography (CAG), resulting in a total of 209 patients (1.6%); (2) those with a history of previous MI, PCI, or coronary artery bypass graft (CABG), totaling 1608 patients (12.3%); (3) those with incomplete laboratory results, led to the omission of 361 patients from the analysis (2.8%); (4) additionally, 152 patients (1.2%) who could not be followed up were excluded from the study. Thereafter, those with MIOCA (n = 10,395) were excluded. Finally, a total of 379 patients were enrolled and classified into two groups: the DM group, consisting of 88 patients (23.2%), and the non-DM group, comprising 291 patients (76.8%) (Fig. 1). Before enrollment, all 379 patients participating in the study provided written informed consent. A comprehensive 3-year clinical follow-up was conducted for these patients, successfully employing various methods, including in-person visits, telephone tracking, and a thorough review of their medical records. Data collection was carried out by independent clinical research coordinators using a web-based case report form integrated into an Internet-based Clinical Research and Trial management system (iCReaT, No. C110016). This non-randomized study received approval from the Ethics Committee of each participating center, including the Chonnam National University Hospital Institutional Review Board Ethics Committee (CNUH-2011-172), following the ethical guidelines of the 2004 Declaration of Helsinki. The procedures for event adjudication have been detailed and elucidated in a previous publication, and an independent committee assigned to event adjudication within the KAMIR-NIH diligently overseeing and assessing the incidence of all events [10].

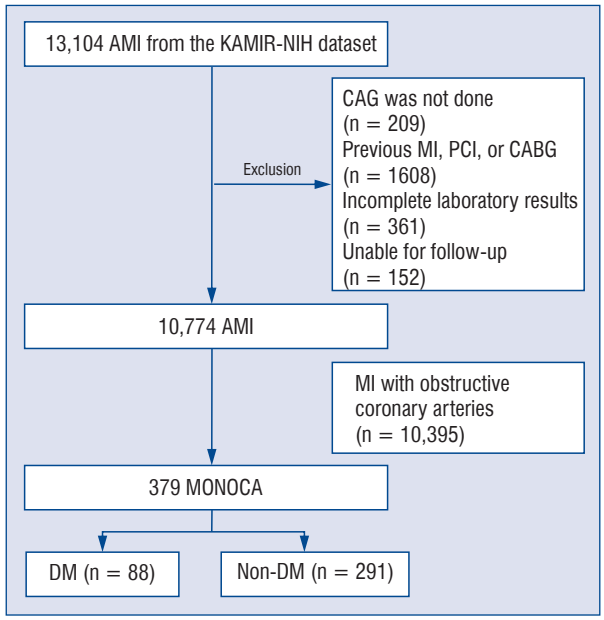


Figure 1. Flowchart; AMI — acute myocardial infarction; CABG — coronary artery bypass graft; CAG — coronary angiography; DM — diabetes mellitus; KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institute of Health; MINOCA — myocardial infarction with nonobstructive coronary; PCI — percutaneous coronary intervention

Percutaneous coronary intervention and medical treatment

According to the established guidelines [11], diagnostic CAG and PCI were performed. When MINOCA is suspected, vasospasm testing is recommended as the standard of care. Vasospasm can be identified by the occurrence of spontaneous coronary spasm with ST-segment elevation (STE ≥ 0.1 mV) on a coronary angiogram and/or documented coronary spasm during an ergonovine provocation test. A positive result for epicardial coronary spasm was determined when there was a focal or diffuse reduction in the epicardial coronary diameter by ≥ 90% compared to the relaxed state, followed by intracoronary nitroglycerin administration [12]. This reduction should be accompanied by reproducing the patient's symptoms and ischemic electrocardiographic shifts [12]. The operators had the discretion to determine the access site, revascularization strategy, and stent options.

Study definitions and clinical endpoints

Diabetes was defined as either known diabetes for which patients received medical treatment (insulin or antidiabetics), or newly diagnosed diabetes defined as a hemoglobin (Hb)A1c level ≥ 6.5%,

fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), and/or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) according to the American Diabetes Association clinical practice recommendations [13]. The guidelines presented in the fourth universal definition of MI [14] served as the basis for its diagnostic criteria. Atypical chest pain is characterized by chest pain that lacks the typical features of angina [14]. The primary clinical outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent MI, any coronary revascularization, and stroke, during a 3-year follow-up period. The secondary clinical outcome was the occurrence of individual components of MACCE. Without a clear non-cardiac explanation, all deaths were considered as CD [15]. In this study, periprocedural MI was not considered a clinical outcome. Clinically indicated revascularization procedures performed after the patient's discharge from index hospitalization were categorized as any revascularization event according to the definitions established by the Academic Research Consortium [16]. According to the American Heart Association/American Stroke Association guidelines [17], stroke is defined as an acute cerebrovascular event that leads to death, neurological deficit lasting for more than 24 hours, or the presence of acute infarction confirmed by imaging studies. In summary, the present study defined MINOCA according to the fourth universal definition of MI [14], which states that the combination of symptoms and a positive cardiac biomarker in the appropriate clinical scenario is diagnostic of AMI while having nonobstructive CAD (< 50% diameter stenosis in a major epicardial vessel), as observed in CAG after applying the exclusion criteria shown in Figure 1.

Statistical analysis

Continuous variables were analyzed using unpaired t-test or the Mann-Whitney rank test. The results for continuous variables are reported as either mean ± standard deviation or median (interquartile range). Categorical variables were assessed using the chi-squared or Fisher's exact test. Categorical variables are presented as counts and percentages. Univariate analyses were conducted for all variables with a significance threshold of $p < 0.05$. To check for the absence of collinearity among the significant variables, multicollinearity tests [18] were conducted (**Suppl. Table S1**). The variance inflation factor values were used to measure the presence of multicollinearity among variables. Values greater than 5 indicated a significant level of multicollinearity [19]. A tolerance value below 0.1 or a condition index above 10 as indicators of multicollinearity among the variables [19] was also considered. The variables included in the multivariate analysis using the Cox regression model were shown in **Suppl. Table S1**. A propensity score (PS)-matched analysis was conducted to account for potential confounding variables, and all variables included in Table 1 were incorporated into the analysis. The concordance statistic (C-statistic) for propensity score-matched analysis was 0.741. Patients with DM were matched to those without DM using a 1:1 nearest available pair-matching method with a caliper width of 0.05. Clinical outcomes were estimated using the Kaplan-Meier curve analysis, and variances between groups were compared using the log-rank test. Statistical significance was defined as a p-value less than 0.05 ($p < 0.05$). Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the study participants. Patients in the DM group had a higher mean age and mean serum creatinine levels than did those in the non-DM group. In addition, there were more patients with atypical chest pain and hypertension in the DM group than in the non-DM group. In contrast, the mean LVEF and HDL cholesterol levels were higher in the non-DM group than in the DM group. More vasospasm-positive patients were in the non-DM group than in the DM group (Table 1).

Clinical outcomes

The major findings over the 3 years are presented in Table 2 and Fig. 2A-N. Before adjustment, the rates of MACCE ($p = 0.002$), all-cause death ($p = 0.001$), and non-CD ($p = 0.004$) were significantly higher in the DM group than in the non-DM group. After multivariable analysis, in the DM group, MACCE (adjusted hazard ratio [aHR], 2.287; 95% CI: 1.214–4.311; $p = 0.010$, Fig. 2A), all-cause death (HR, 2.845; 95% CI: 1.401–5.775; $p = 0.004$, Fig. 2C), and non-CD (HR, 3.914; 95% CI: 1.431–9.897; $p = 0.008$, Fig. 2G) were significantly higher than those in the non-DM group (Table 2). However, the rates of CD ($p = 0.143$; Fig. 2E), recurrent MI ($p = 0.715$; Fig. 2I), revascularization ($p = 0.826$; Fig. 2K), and stroke

Table 1. Baseline characteristics of the DM and Non-DM groups before and after the propensity score-matched analysis

Variables	All patients (n = 379)			Propensity score-matched patients (n = 164)			
	DM (n = 88)	Non-DM (n = 291)	p-value	DM (n = 82)	Non-DM (n = 82)	p-value	SD
Male, n [%]	46 (52.3)	176 (60.5)	0.177	43 (52.4)	47 (57.3)	0.638	–0.98
Age, years	65.9 ± 11.9	60.7 ± 13.0	0.001	63.6 ± 12.2	63.5 ± 12.6	0.864	0.29
LVEF, %	57.5 ± 9.8	61.3 ± 8.8	0.003	58.8 ± 9.7	59.2 ± 8.6	0.817	–0.40
BMI, kg/m^2	24.1 ± 3.1	23.9 ± 3.4	0.557	24.0 ± 3.1	23.8 ± 3.5	0.667	0.61
SBP, mmHg	135.8 ± 27.9	133.5 ± 26.5	0.493	135.4 ± 29.2	136.1 ± 28.1	0.892	–0.24
DBP, mmHg	79.4 ± 16.0	80.8 ± 14.7	0.462	80.3 ± 15.8	80.8 ± 14.4	0.863	–0.30
Cardiogenic shock, n [%]	3 (3.4)	5 (1.7)	0.395	2 (2.4)	2 (2.4)	1.000	0
CPR on admission, n [%]	6 (6.8)	8 (2.7)	0.102	3 (3.7)	2 (2.4)	0.650	0.75
Atypical chest pain, n [%]	28 (31.8)	43 (14.8)	0.001	25 (30.5)	18 (22.0)	0.287	1.94
Dyspnea, n [%]	21 (23.9)	51 (17.5)	0.214	20 (24.4)	16 (19.5)	0.572	1.18
EKG on admission							
ST-segment elevation, n [%]	11 (12.5)	41 (14.1)	0.860	9 (11.0)	8 (9.8)	0.798	0.39
ST-segment depression, n [%]	10 (11.4)	30 (10.3)	0.843	8 (9.8)	7 (8.5)	0.786	0.45
No ST-segment change, n [%]	45 (51.7)	151 (51.9)	0.904	43 (52.4)	46 (56.1)	0.754	–0.74
T-wave inversion, n [%]	18 (20.5)	51 (17.5)	0.531	18 (22.0)	18 (22.0)	1.000	0
Atrial fibrillation, n [%]	7 (8.0)	18 (6.2)	0.624	6 (7.3)	9 (11.0)	0.589	–1.29
Killip class 1I/III, n [%]	14 (15.9)	38 (13.1)	0.484	13 (15.9)	10 (12.2)	0.654	1.07
Hypertension, n [%]	57 (64.8)	126 (43.3)	0.001	52 (63.4)	53 (64.6)	0.871	–0.25
Dyslipidemia, n [%]	9 (10.2)	22 (7.6)	0.505	8 (9.8)	8 (9.8)	1.000	0
Previous HF, n [%]	3 (3.4)	7 (2.4)	0.704	3 (3.7)	2 (2.4)	0.650	0.76
Previous stroke, n [%]	7 (8.0)	10 (3.4)	0.082	7 (8.5)	6 (7.3)	0.773	0.44
Current smokers, n [%]	27 (30.7)	91 (31.3)	0.917	25 (30.5)	29 (35.4)	0.618	–1.04
Peak CK-MB, ng/mL	9.3 (3.2–20.5)	10.3 (4.2–32.7)	0.003	8.7 (3.1–20.2)	7.2 (3.3–16.5)	0.880	0.23
Peak troponin-I, ng/mL	2.6 (0.5–7.7) (n = 82)	1.7 (0.4–6.8) (n = 271)	0.698	2.2 (0.5–7.0) (n = 78)	1.2 (0.4–5.8) (n = 77)	0.791	0.40
Peak troponin-T, ng/mL	0.7 (0.1–1.1) (n = 6)	0.6 (0.1–1.0) (n = 20)	0.277	0.8 (0.2–1.2) (n = 4)	0.5 (0.1–0.8) (n = 5)	0.374	1.68
Blood glucose, mg/dL	214.7 ± 98.8	128.1 ± 42.7	< 0.001	214.0 ± 98.2	124.8 ± 38.0	< 0.001	11.9
Hemoglobin A1c [%]	7.3 ± 1.4	5.8 ± 0.8	< 0.001	7.3 ± 1.3	5.8 ± 0.8	< 0.001	13.8

Table 1. cont. Baseline characteristics of the DM and Non-DM groups before and after the propensity score-matched analysis

Variables	All patients (n = 379)			Propensity score-matched patients (n = 164)			
	DM (n = 88)	Non-DM (n = 291)	p-value	DM (n = 82)	Non-DM (n = 82)	p-value	SD
Serum creatinine, mg/dL	1.23 ± 1.13	0.86 ± 0.88	< 0.001	1.21 ± 1.04	1.06 ± 1.75	0.559	1.39
Total cholesterol, mg/dL	155.3 ± 31.9	175.9 ± 57.3	< 0.001	157.2 ± 30.1	154.4 ± 33.4	0.625	0.88
Triglyceride, mg/dL	132.3 ± 81.0	129.2 ± 99.8	0.884	131.3 ± 90.9	134.1 ± 101.2	0.797	–0.29
HDL cholesterol, mg/dL	44.7 ± 12.8	48.3 ± 13.1	0.023	45.3 ± 12.5	45.7 ± 10.0	0.817	–0.35
LDL cholesterol, mg/dL	92.1 ± 28.6	104.7 ± 33.6	0.001	92.9 ± 29.2	91.1 ± 29.8	0.736	0.61
Discharge medications							
Aspirin, n [%]	68 (77.3)	221 (75.9)	0.887	64 (78.0)	63 (76.8)	0.852	0.29
Clopidogrel, n [%]	41 (46.6)	98 (33.7)	0.032	36 (43.9)	39 (47.6)	0.754	–0.74
Ticagrelor, n [%]	1 (1.1)	8 (2.7)	0.691	1 (1.2)	1 (1.2)	1.000	0
Prasugrel, n [%]	1 (2.1)	5 (1.7)	0.702	1 (1.2)	1 (1.2)	1.000	0
Beta-blockers, n [%]	30 (34.1)	101 (34.7)	0.915	29 (35.4)	31 (37.8)	0.871	–0.49
ACEIs or ARBs, n [%]	46 (52.3)	138 (47.4)	0.466	44 (53.7)	43 (52.4)	0.876	0.26
CCBs, n [%]	39 (44.3)	159 (54.6)	0.113	39 (47.6)	47 (57.3)	0.274	–1.95
Statin, n [%]	67 (76.1)	223 (76.6)	0.923	63 (76.8)	64 (78.0)	0.852	–0.29
Anticoagulant, n [%]	5 (5.7)	10 (3.4)	0.354	4 (4.9)	4 (4.9)	1.000	0
Vasospasm (+), n [%]	14 (15.9)	86 (29.6)	0.013	14 (17.1)	17 (20.7)	0.690	–0.92
DM management							
Diet, n [%]	4 (4.5)			4 (4.9)			
Oral agents, n [%]	72 (81.8)			68 (82.9)			
Insulin, n [%]	7 (8.0)			5 (6.1)			
Untreated, n [%]	5 (5.7)			5 (6.1)			

Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The p-values for continuous data were obtained from the unpaired t-test or a Mann-Whitney rank test. The p-values for categorical data were obtained from the chi-square or Fisher's exact test. ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; BMI — body mass index; CCBs — calcium channel blockers; CK-MB — creatine kinase myocardial band; CPR — cardiopulmonary resuscitation; DBP — diastolic blood pressure; DM — diabetes mellitus; EKG — electrocardiogram; HF — heart failure; HDL — high-density lipoprotein; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; SD — standardized mean difference

Table 2. Three-year clinical outcomes between the DM and non-DM groups

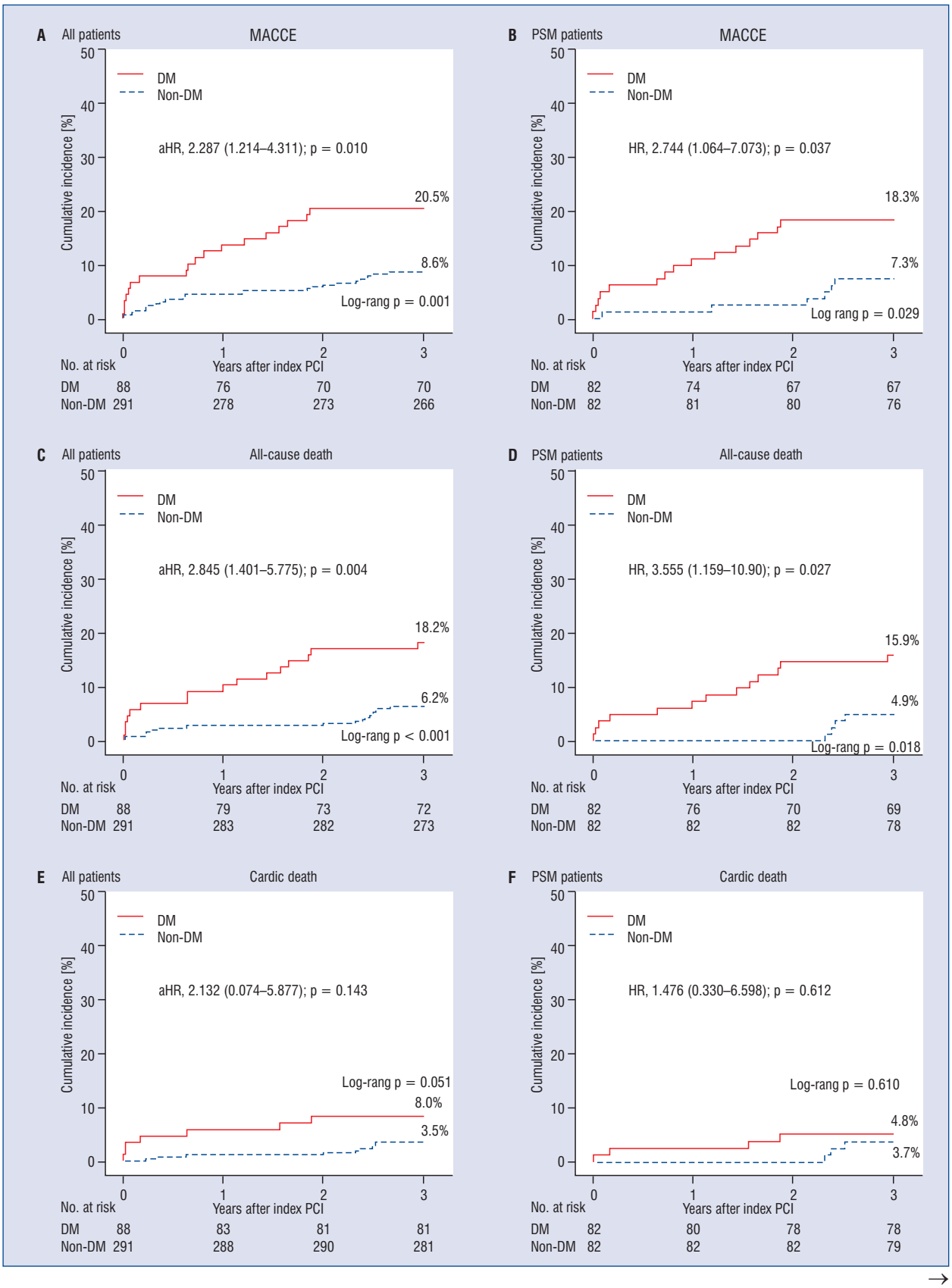
Outcomes	Cumulative events at 3-year [%]				
	DM	Non-DM	Log-rank	Hazard ratio (95% CI)	p-value
Entire Patients					
MACCE	18 (20.5)	25 (8.6)	0.001	2.591 (1.414–4.751)	0.002
All-cause death	16 (18.2)	18 (6.2)	< 0.001	3.198 (1.630–6.272)	0.001
Cardiac death	7 (8.0)	10 (3.5)	0.051	2.532 (0.954–6.655)	0.059
Non-cardiac death	9 (10.2)	8 (2.7)	0.002	4.024 (1.552–10.43)	0.004
Recurrent MI	3 (3.6)	8 (2.7)	0.645	1.364 (0.362–5.143)	0.647
Any revascularization	1 (1.2)	5 (1.6)	0.736	0.693 (0.081–5.932)	0.738
Stroke	3 (3.6)	7 (2.5)	0.535	1.529 (0.395–5.915)	0.538
Multivariate analysis*					
MACCE	18 (20.5)	25 (8.6)	0.001	2.287 (1.214–4.311)	0.010
All-cause death	16 (18.2)	18 (6.2)	< 0.001	2.845 (1.401–5.775)	0.004
Cardiac death	7 (8.0)	10 (3.5)	0.051	2.132 (0.774–5.877)	0.143
Non-cardiac death	9 (10.2)	8 (2.7)	0.002	3.914 (1.431–9.897)	0.008
Recurrent MI	3 (3.6)	8 (2.7)	0.645	1.303 (0.315–5.396)	0.715
Any revascularization	1 (1.2)	5 (1.6)	0.736	1.222 (0.102–13.75)	0.826
Stroke	3 (3.6)	7 (2.5)	0.535	1.005 (0.245–4.118)	0.994
Propensity score--matched patients					
MACCE	15 (18.3)	6 (7.3)	0.029	2.744 (1.064–7.073)	0.037
All-cause death	13 (15.9)	4 (4.9)	0.018	3.555 (1.159–10.90)	0.027
Cardiac death	4 (4.8)	3 (3.7)	0.610	1.476 (0.330–6.598)	0.612
Non-cardiac death	9 (11.1)	1 (1.2)	0.008	9.579 (1.236–71.04)	0.009
Recurrent MI	3 (3.9)	3 (3.7)	0.915	1.091 (0.220–5.409)	0.915
Any revascularization	1 (1.3)	1 (1.2)	0.975	1.045 (0.065–16.71)	0.975
Stroke	3 (3.9)	2 (2.4)	0.606	1.596 (0.267–9.550)	0.609

CK-MB — creatine kinase myocardial band; CPR — cardiopulmonary resuscitation; DM — diabetes mellitus; HDL — high-density lipoprotein; LVEF — left ventricular ejection fraction; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction.
*Adjusted by male sex, age, LVEF, cardiogenic shock, CPR on admission, atypical chest pain, hypertension, peak serum level of CK-MB, serum creatinine, total cholesterol, and HDL cholesterol (**Suppl. Table S1**)

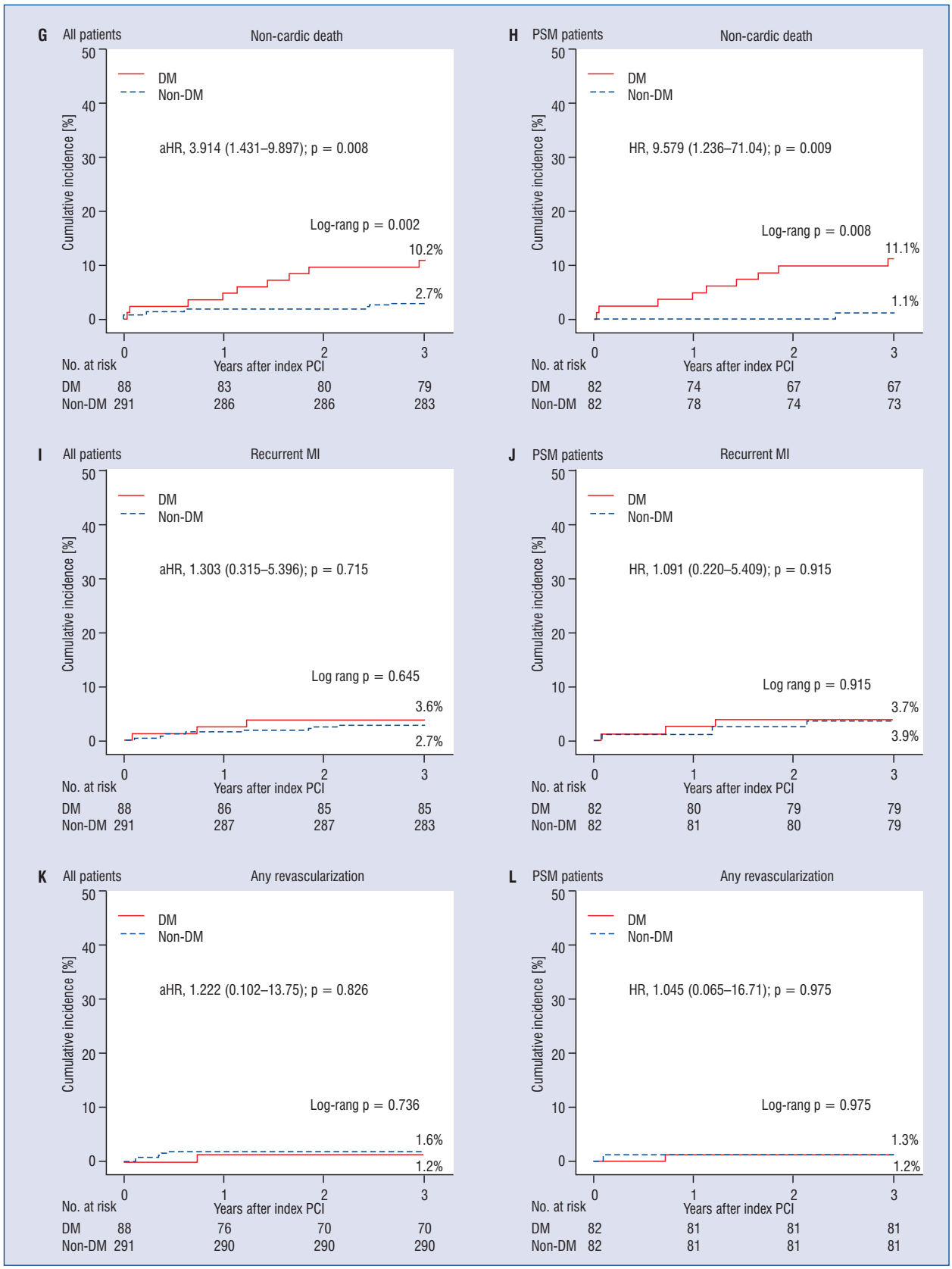
(p = 0.994; Fig. 2M) did not differ significantly between the DM and non-DM groups. These findings were confirmed using PSM analysis. **Suppl. Table S2** shows the causes of non-CD in the total study population. The rate of multiple organ failure was significantly higher in the DM group than in the non-DM group (4.5% vs. 0.3%, p = 0.011). Table 3 shows the independent predictors of MACCE in the total study population. The presence of DM (aHR, 2.244; p = 0.009), old age (≥ 65 years, aHR, 2.436; p = 0.008), cardiopulmonary resuscitation (CPR) on admission (aHR, 6.353; p = 0.001), and nonuse of statin (aHR, 3.115; p = 0.001) were statistically significant independent predictors for MACCE.

Discussion

The key results from this prospective observational study were as follows: over the 3-year follow-up period, the rates of MACCE, all-cause death, and non-CD were significantly elevated in the DM group compared to the non-DM group, and the leading cause of non-CD was multiple organ failure; (2) however, there were no significant differences between the DM and non-DM groups regarding the rates of CD, recurrent MI, any revascularization, and stroke; and (3) the presence of DM, advanced age, CPR on admission, and nonuse of statin medications were identified as significant predictors of MACCE.


A All patients MACCE
DM
Non-DM
aHR, 2.287 (1.214–4.311); p = 0.010
20.5%
8.6%
Log-rang p = 0.001
Cumulative incidence [%]
Years after index PCI
No. at risk
DM 88 76 70 70
Non-DM 291 278 273 266
B PSM patients MACCE
HR, 2.744 (1.064–7.073); p = 0.037
18.3%
7.3%
Log rang p = 0.029
No. at risk
DM 82 74 67 67
Non-DM 82 81 80 76
C All patients All-cause death
aHR, 2.845 (1.401–5.775); p = 0.004
18.2%
6.2%
Log-rang p < 0.001
No. at risk
DM 88 79 73 72
Non-DM 291 283 282 273
D PSM patients All-cause death
HR, 3.555 (1.159–10.90); p = 0.027
15.9%
4.9%
Log-rang p = 0.018
No. at risk
DM 82 76 70 69
Non-DM 82 82 82 78
E All patients Cardic death
aHR, 2.132 (0.074–5.877); p = 0.143
Log-rang p = 0.051
8.0%
3.5%
No. at risk
DM 88 83 81 81
Non-DM 291 288 290 281
F PSM patients Cardic death
HR, 1.476 (0.330–6.598); p = 0.612
Log-rang p = 0.610
4.8%
3.7%
No. at risk
DM 82 80 78 78
Non-DM 82 82 82 79

→


G All patients Non-cardic death
DM
Non-DM
aHR, 3.914 (1.431–9.897); p = 0.008
Log-rang p = 0.002
10.2%
2.7%
Cumulative incidence [%]
Years after index PCI
No. at risk
DM 88 83 80 79
Non-DM 291 286 286 283
H PSM patients Non-cardic death
HR, 9.579 (1.236–71.04); p = 0.009
Log-rang p = 0.008
11.1%
1.1%
No. at risk
DM 82 74 67 67
Non-DM 82 78 74 73
I All patients Recurrent MI
aHR, 1.303 (0.315–5.396); p = 0.715
Log rang p = 0.645
3.6%
2.7%
No. at risk
DM 88 86 85 85
Non-DM 291 287 287 283
J PSM patients Recurrent MI
HR, 1.091 (0.220–5.409); p = 0.915
Log rang p = 0.915
3.7%
3.9%
No. at risk
DM 82 80 79 79
Non-DM 82 81 80 79
K All patients Any revascularization
aHR, 1.222 (0.102–13.75); p = 0.826
Log-rang p = 0.736
1.6%
1.2%
No. at risk
DM 88 76 70 70
Non-DM 291 290 290 290
L PSM patients Any revascularization
HR, 1.045 (0.065–16.71); p = 0.975
Log-rang p = 0.975
1.3%
1.2%
No. at risk
DM 82 81 81 81
Non-DM 82 81 81 81

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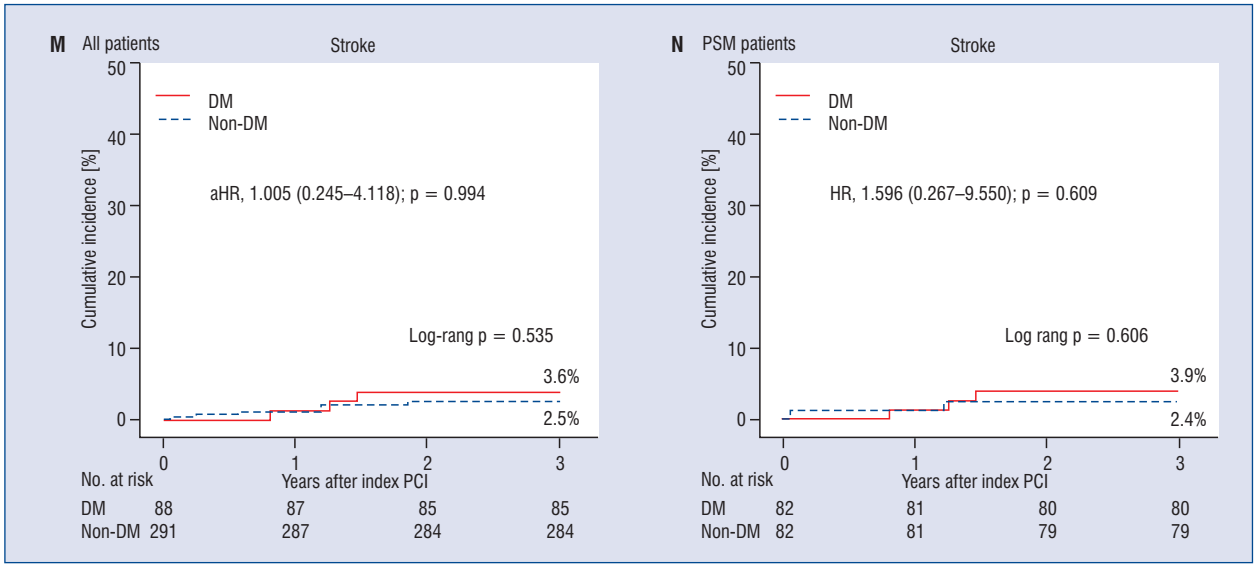

Figure 2. Kaplan-Meier analysis for MACCE (**A** and **B**), all-cause deth (**C** and **D**), cardic death (**G** and **H**), recurrent MI (**I** and **J**), any repeat revascularization (**K** and **L**), and stroke (**M** and **N**) in the total study population (**A**, **C**, **E**, **G**, **I**, **K**, and **M**) and PSM patients (**B**, **D**, **F**, **H**, **J**, **L**, and **N**) during a 3-year follow-up period; DM — diabetes mellitus; MACCE — major adverse cardiac and cerebrovascular events; aHR — adjusted hazard ratio; MI — myocardial infarction; PMS — propensity score matched

Table 3. Independent predictors for MACCE in the total study population

	Unadjusted		Adjusted	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
DM vs. non-DM	2.591 (1.414–4.751)	0.002	2.244 (1.233–4.244)	0.009
Male	1.659 (0.911–3.020)	0.098	1.040 (0.536–2.017)	0.907
Age, ≥ 65 years	3.426 (1.759–6.671)	< 0.001	2.436 (1.315–4.987)	0.008
LVEF, < 50%	3.200 (1.690–6.057)	< 0.001	1.853 (0.908–3.784)	0.090
Cardiogenic shock	1.174 (0.162–8.527)	0.874	4.879 (0.503–47.35)	0.172
CPR on admission	5.989 (2.526–14.20)	< 0.001	6.353 (2.115–19.09)	0.001
Hypertension	1.504 (0.820–2.756)	0.187	1.389 (0.720–2.679)	0.327
CK-MB	1.001 (0.996–1.006)	0.670	1.002 (0.997–1.009)	0.545
Troponin-I	1.003 (0.995–1.012)	0.443	1.000 (0.984–1.017)	0.954
Nonuse of Beta-blocker	1.496 (0.820–2.732)	0.189	1.020 (0.486–2.139)	0.959
Nonuse of ACEI/ARB	1.481 (0.808–2.714)	0.204	1.379 (0.669–2.645)	0.384
Nonuse of CCB	2.670 (1.393–5.120)	0.003	1.804 (0.873–3.728)	0.111
Nonuse of Statin	2.569 (1.402–4.710)	0.002	3.115 (1.614–6.013)	0.001

ACEI/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CK-MB — creatine kinase myocardial band; CCB — calcium channel blocker; CPR — cardiopulmonary resuscitation; DM — diabetes mellitus; HR — hazard ratio; LVEF — left ventricular ejection fraction; MACCE — major adverse cardiac and cerebrovascular events; CI — confidence interval

In 2021, the International Diabetes Federation Diabetes Atlas estimated that the global prevalence of DM in individuals aged 20–79 years was 10.5%, encompassing approximately 536.6 million people [20]. The prevalence is predicted to increase to 12.2% by 2045, affecting approximately 783.2 million people [20]. Patients with DM have a greater atherosclerotic burden and more diffuse and multivessel coronary artery disease [21]. Hence, AMI patients with DM have higher 30-day and 1-year mortality than the non-DM group [22]. Several potential pathological mechanisms have been implicated in the poor clinical outcomes associated with hyperglycemia in patients with AMI.

These mechanisms include elevated levels of free fatty acids that can lead to cardiac arrhythmias, insulin resistance, impaired glucose utilization by the myocardium, microvascular dysfunction, and vascular inflammation [23, 24]. Furthermore, these mechanisms contribute to the enlargement of atheromatous plaques in the coronary arteries and exacerbate the complexity of CAD [25]. The proportion of AMI patients with coexisting DM in this study group was 23.2% (88 of 379) (Table 1), similar to the reported prevalence of 20–30% in AMI patients with DM in previous studies [3]. As previously mentioned, patients with DM have a 2–4 times higher risk of developing CD than those without DM [2]. The present study's aHR for CD was 2.132 for the entire population (Table 2). More than 80% of the patients with MINOCA present with NSTEMI [26]. As indicated in Table 1, patients showing STE were less than 15% of the study population. Conversely, approximately 85% of the study population comprised patients with NSTEMI. In patients with NSTEMI, hyperglycemia causes oxidative stress, inflammation, apoptosis, endothelial dysfunction, hypercoagulation, and platelet aggregation [27]. These factors play significant roles in damaging the ischemic myocardium [28].

According to recent research focusing on MIOCA patients [29], patients with NSTEMI and DM showed significantly higher 2-year rates of major adverse cardiovascular events (MACE) (aHR, 1.326; $p = 0.007$), all-cause death (aHR, 1.701; $p = 0.002$), and non-CD (aHR, 2.549; $p = 0.001$) than did those without diabetes after receiving new-generation drug-eluting stent implantation. Similarly, in that study [29], patients with STEMI and DM had significantly higher rates of MACE ($p < 0.001$), all-cause death ($p < 0.001$), and non-CD ($p = 0.001$) than did those in the non-DM group. The current results, which focused on MINOCA and showed higher rates of 3-year MACCE ($p = 0.010$), all-cause death ($p = 0.004$), and non-CD ($p = 0.008$) in the DM group than in the non-DM group (Table 2), are similar to those of MIOCA [29].

A previous report showed that the all-cause mortality at 12 months was lower in patients with MINOCA (4.7%) than in those with MIOCA (6.7%) [30]. A recent meta-analysis reported that MINOCA was associated with lower 12-month all-cause mortality than MIOCA (3.3% vs. 5.6%; odds ratio, 0.60; $p < 0.001$) [31]. However, another report mentioned that despite MINOCA predominantly occurring at a relatively young age and with fewer comorbidities, the long-term serious cardiovascular events that arise are by no means trivial [32]. In a retrospective analysis of patients from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial [33]. MINOCA patients had a higher risk of mortality at 1 year than did NSTEMI patients with obstructive coronary arteries after PSM (HR, 3.44; $p = 0.04$). An increase in the number of non-CD individuals mainly drove this increased risk. Hence, a paucity of research is dedicated to patients with MINOCA, and long-term clinical outcomes are also subject to debate.

As mentioned, NSTEMI constitutes a larger proportion of MINOCA patients than STEMI patients [26], and NSTEMI is associated with a higher frequency of non-CD than STEMI [29, 34]. Similarly, in the Planer study [33], the NSTEMI MINOCA group exhibited a higher frequency of non-CD than the MIOCA group. As shown in **Suppl. Table S2**, the DM group had a significantly higher incidence of multiple organ failure. In a study by Kim et al. [34], among the total study population, the rate of multiple organ failure ($p = 0.007$) was significantly higher in the NSTEMI group than in the STEMI group. In Table 1, the DM group exhibited significantly higher age than did the non-DM group (65.9 ± 11.9 vs. 65.9 ± 11.9, $p = 0.001$). Furthermore, Table 3 revealed that being ≥ 65 years was a significant independent predictor of MACCE (aHR, 2.436; $p = 0.008$). In the Nordenskjöld et al. study [7], old age was a significant independent predictor for MACE (aHR, 1.05; 95% CI: 1.04–1.06; $p < 0.001$).

The MINOCA should be treated as a "working diagnosis," similar to heart failure, necessitating further assessment to elucidate its underlying mechanism(s) [6], and currently, there is a lack of evidence-based guidelines for the treatment of MINOCA. However, DM is a progressive disease, and patients with DM and AMI are more prone to rapidly accumulating micro- and macrovascular complications, possibly contributing to worse outcomes [35]. In a previous study [36], a comprehensive and intensive intervention addressing various risk factors led to a remarkable 50% decrease in the incidence of cardiovascular events in patients with DM. Given our research findings, which showed higher 3-year mortality in the DM group among MINOCA patients than in the non-DM group, and with the primary objective of achieving better cardiovascular outcomes for individuals with DM, it is essential to implement appropriate and continuous

diabetes prevention interventions [37]. Although this study was conducted in a single country, it was a multicenter prospective study involving 20 tertiary hospitals. Therefore, it was expected that the present results would demonstrate the significance of DM in patients with MINOCA providing valuable information to interventional cardiologists.

Limitations of the study

This study has several limitations. First, although a total of 13,140 KAMIR-NIH datasets from 20 tertiary hospitals in the Republic of Korea were used in this study, the final number of MINOCA patients after applying the exclusion criteria was small and the use of a registry dataset may have resulted in instances of underreporting or missed variables. Second, although a PSM analysis was employed to mitigate the potential impact of residual confounders, these effects could not be completely eliminated. Third, the 3-year follow-up period in this study may be regarded as relatively limited when estimating long-term clinical outcomes. Fourth, MINOCA patients comprise a diverse cohort, and it would have been preferable to exclude those with myocarditis confirmed by Magnetic Resonance Imaging [6]. However, the KAMIR-NIH registry lacks data on whether MRI is performed to detect clinically unrecognized myocarditis, which is a significant limitation. In real-world practice, the utilization of MRI is often limited because of its cost implications. Nevertheless, it was believed that the present study population is appropriate, as it comprises patients commonly encountered by clinicians during routine real-world practice who receive the necessary secondary prevention treatments. Moreover, it is important to recognize that MINOCA is a complex and heterogeneous condition with different underlying causes, such as microvascular dysfunction, plaque disruption without significant blockage, and other non-coronary factors that can trigger myocardial infarction, all of which require thorough investigation [6, 14]. However, it is important to consider the context of the Korean Medical Assurance system, in which intravascular ultrasound, optical coherent tomography, and fractional flow reserve tests for patients with nonobstructive CAD are not covered by insurance, and patients must bear the costs. This was a limitation to the current study. Fifth, despite the limitation of utilizing older data (2011–2015), the authors endeavored to apply the most recent diagnostic criteria (fourth universal definition of MI [14]) available to align with real-world practice as much as possible. However, some diagnostic criteria may not have been verifiable, potentially resulting in imperfect classification. This too constitutes an important limitation of the current study. Finally, diverse antidiabetic modalities, like Sodium-Glucose Cotransporter 2 inhibitors and Glucagon-Like Peptide-1 agonists, can have an effect on the development of cardiovascular events [38]. It is with regret to report that details concerning the diverse, recently introduced antidiabetic treatments from the KAMIR registry were not obtainable. Thus, this presents another limitation to the study.

Conclusions

In this prospective, multicenter, observational study focusing solely on patients with MINOCA, the DM group exhibited a higher 3-year mortality rate than the non-DM group. Thus, DM demonstrated a hazardous effect even in patients with MINOCA. However, more extensive studies are necessary to gather more accurate and reliable information.

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Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Chonnam National University Hospital Institutional Review Board (IRB) Ethics Committee (protocol code CNUH-2011-172 and March 1, 2011).

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