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Diabetes and mortality risk in patients undergoing coronary angiography: The KARDIO study

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Abstract

Background: Diabetes is an established risk factor for adverse cardiovascular outcomes including mortality, but the relationship between diabetes and mortality risk in the presence of the extensive or diffuse form of coronary artery disease (CAD) is controversial.

Aims: We evaluated the association between diabetes and mortality risk in patients who underwent coronary angiography using a real-life clinical database.

Methods: We utilized the KARDIO registry, which comprised data on demographics, prevalent diseases, including diabetes status, cardiovascular risk factors, coronary angiographies, and other interventions in 79,738 patients. Hazard ratios (HRs) (95% confidence intervals [CIs]) for the association between prevalent diabetes and all-cause mortality were estimated.

Results: During a median follow-up of 5.5 years, 11,896 all-cause deaths occurred. In analyses adjusted for age, smoking status, hypertension, family history of CAD, dyslipidaemia, urgency of intervention, body mass index, sex, and sex-age interaction, the HR (95% CI) for mortality comparing diabetes with no diabetes was 1.44 (1.38, 1.50). Following additional adjustment for the degree of CAD (1–3 vessels disease) as confirmed by angiography, the HR (95% CI) for mortality remained similar 1.43 (1.36, 1.49). The association did not vary significantly across several relevant clinical characteristics except for a stronger association in those with a family history of CAD than those without ($p = 0.034$) and former smokers than nonsmokers ($p = 0.046$).

Conclusion: In patients undergoing coronary angiography, diabetes is associated with an increased mortality risk, independent of several risk factors including the degree of CAD. The association may be modified by family history of CAD and smoking status.

KEYWORDS

angiography; diabetes, coronary artery disease; hospital register; mortality

1 | INTRODUCTION

Diabetes mellitus is a global health challenge with substantial epidemiological burden, affecting millions worldwide. Its prevalence is on the rise, partly due to increasing obesity rates, aging populations, and lifestyle factors. Established risk factors for diabetes include obesity, sedentary lifestyle, poor diet patterns, genetic predisposition, and certain ethnic backgrounds.[1] Diabetes significantly increases the risk of various cardiovascular outcomes, notably coronary artery disease (CAD), heart failure (HF), sudden cardiac death, and stroke.[2–8] Studies have consistently demonstrated that individuals with diabetes have a two to four times higher mortality rate from heart diseases and stroke compared to those without diabetes, which can be explained by the accumulation of many coronary heart disease risk factors.[4,5,9]

Despite the acknowledged connection between diabetes and cardiovascular morbidity and mortality, evidence on the specific association between diabetes and mortality among cardiac patients, especially in the context of angiographically assessed CAD, remains sparse. Previous research indicates that diabetes is often associated with a more severe form of CAD characterized by a greater number of significant stenoses, more diffuse disease, and multivessel involvement.[10,11] However, the precise impact of diabetes on the patterns of CAD and how these patterns contribute to the prognosis of patients with diabetes are not well understood. Specific lesions severity and anatomical locations in coronary arteries that might be typically affected in patients with diabetes have not been clarified in earlier studies.[12] The research gap in knowledge underscores the need for further investigation into how diabetes influences mortality risk among patients who have undergone coronary angiography. This study aims to fill this gap by employing a real-life clinical database to examine the independent association between diabetes and all-cause mortality in patients after coronary angiography and whether this association is modified by relevant clinical factors.

2 | METHODS

2.1 | Patient population

This research utilizes data sourced from the Finnish KARDIO registry, which records cardiac patients undergoing invasive diagnostic and therapeutic procedures.[13] Established in 2010, the registry's goal is to provide evidence-based data on cardiac care, thus facilitating advancements in treatment modalities for heart diseases. It combines information on demographic profiles, existing chronic conditions, cardiovascular risk elements, along with details of coronary angiographies and surgical interventions such as percutaneous coronary interventions (PCIs) and coronary artery bypass graftings (CABGs). The KARDIO registry is continuously updated by the attending physicians, offering access to dynamic online reports. These reports track the care process and outcomes, enabling benchmarking across different time periods and hospitals.[13] Data were collected from seven cardiology centers located in Western, Central, and Northern Finland. From January 1, 2012 to December 30, 2018, a cohort of 82,911 individuals aged over 17 years underwent cardiac catheterization procedures. Within this period, the KARDIO database documented a total of 149,028 procedures performed on these patients. This registry encompasses individuals who received diagnostic coronary angiography either for the initial diagnosis or to assess the severity of existing CAD. A significant number of these patients presented with acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction (STEMI), non-ST elevation ACS (NSTEMI), or unstable angina pectoris. The study included those who received revascularization treatments, whether catheter-based or surgical, as well as patients managed with conservative treatment strategies. However, individuals referred for cardiac catheterization primarily due to valvular heart disease were not considered, resulting in 79,738 patients being analyzed in the study. The first hospital visit with angiography of the patients was included in the baseline data.

In this study, missing data for one or more key variables were noted in 48,727 patients, and diabetes status was available for 71,459 patients. The considerable workload faced by cardiologists is identified as a potential factor contributing to the incomplete entry of data. Table S1 displays the percentages and counts of missing data for key variables. Data are assumed to be missing at random. Under Finnish national and ethical guidelines governing the utilization of hospital quality registry data for research and development, obtaining written informed consent from patients for data registration is not required. The standard practices for coronary intervention procedures and their management were determined based on the treating physicians' judgment. The National Board of Health and Welfare in Finland approved both the registry itself and the process of linking it with the national death registry. This linkage was facilitated through the use of the Personal Identification Code (PIN), assigned to every Finnish citizen and permanent resident.

2.2 | Clinical data collection

Diabetes was characterized as a clinical diagnosis managed through diet, oral medication, or insulin therapy.[10] Body mass index (BMI) was calculated as the individual's weight in kilograms divided by their height in meters squared. Resting hypertension was identified based on the ongoing use of antihypertensive drugs, a systolic blood pressure of 140 mmHg or higher, or a diastolic blood pressure of 90 mmHg or above. Dyslipidemia refers to the usage of lipid-lowering drugs or a plasma low-density lipoprotein cholesterol level exceeding 3.0 mmol/L. Smoking status was categorized as a nonsmoker, a current or previous smoker, with current smokers identified as those who had smoked regularly and continued smoking cigarettes, cigars, or pipes within the month preceding hospital admission. A positive family history of CAD was established when a first-degree relative had been diagnosed with MI or CAD that necessitated revascularization, before turning 65 years for women and 55 for men. Variables related to hospitalization, such as the final diagnosis, complications related to therapy, and outcomes of other interventions, were documented. The care standards for coronary interventions and related management were determined by the discretion of the attending physicians.[13] The data collection was performed using an online data collection system by a responsible cardiologist right before or after the angiography. Before coronary angiography, the collected data included patient age, gender, smoking habits, presence of hypertension, diabetes, dyslipidemia, the New York Heart Association functional class, symptoms of angina pectoris, renal function, current medications, initial symptoms, and electrocardiogram alterations, including specific intervals (notably for STEMI patients), history of MI, any coronary revascularization procedures, occurrences of HF, and any incidents of stroke.[10]

2.3 | All-cause mortality events

In addition to the phenotypic data gathered, the KARDIO registry is directly linked with the National Death Registry, ensuring ongoing updates on the mortality rates of all patients treated.[13] The primary endpoint in this study was all-cause mortality when the follow-up started from the first hospital visit with angiography. The study design ensured that a first clinical evaluation was made at hospital discharge (a baseline visit) and follow-up was carried out by linkage to the National Death Registry using a PIN, continuing the follow-up until the end of 2018. Follow-up data were available by merging data from the mandatory Finnish Cause of Death Register with the KARDIO register data: merging was performed at the National Board of Health and Welfare in Finland based on the PIN. There was no loss to follow-up.

2.4 | Statistical analysis

Continuous variables were presented either as mean (with standard deviation, SD) or median (including the interquartile range, IQR), while categorical data were shown as frequencies (percentages). Descriptive statistics were used to summarize the baseline characteristics overall and according to diabetes status (Yes vs. No). Missing data were multiply imputed using the aregImpute function from the Hmisc R package.[14,15] The imputation process included 20 rounds and followed the procedures utilized in our earlier study.[13] The only exception was the addition of HF, kidney failure, and arteriosclerosis obliterans (ASO) into the model. The analysis utilized the Cox proportional hazards model to explore the relationship between diabetes and all-cause mortality, adjusting for several factors across three models: (Model 1) age; (Model 2) Model 1 plus smoking status, hypertension, family history of CAD, dyslipidemia, urgency, BMI, sex, and sex–age interaction; and (Model 3) Model 2 plus angiographic findings and number of PCI operations. Dyslipidemia, urgency, and angiographic findings were stratified for to maintain the proportional hazards assumptions, as verified by analyzing scaled Schoenfeld residuals.[16] The variables of BMI and the number of PCI operations underwent P-spline transformation to appropriately model nonlinear relationships.[17] Rubin's rules were applied to estimate the pooled hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Subgroup interaction analyses were performed using the following clinical characteristics: hypertension, smoking status, family history of CAD, gender, HF, chronic kidney disease, ASO, and BMI. The subgroups for BMI were <25 kg/m^2 (normal weight), 25–30 kg/m^2 (overweight), and >30 kg/m^2 (obese).

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics overall and according to the diabetes status are shown in Table 1. The majority of patients were male (61.6%) and overall mean ± SD age was 66 ± 11 years. Patients with diabetes were more likely to be slightly older (66 ± 11 vs. 65 ± 11 years), have higher BMI levels and higher prevalence of comorbidities such as hypertension, kidney disease, MI, and 1–3 vessel CAD compared to patients without diabetes. Regarding treatments, CABG was more prevalently conducted among patients with diabetes (Table 1).

3.2 | Follow-up

During a median (IQR) follow-up of 5.5 (2.5–8.6) years (445,641 person-years at risk), a total of 11,896 all-cause- deaths were recorded. The age-adjusted all-cause mortality risk (HR 1.43, 95% CI 1.37, 1.50) was increased among patients with diabetes (Model 1). In analyses adjusted for age, smoking status, hypertension, family history of CAD, dyslipidaemia, urgency of intervention, BMI, sex and sex-age interaction, the HR (95% CI) for mortality comparing diabetes with no diabetes was 1.44 (1.38, 1.50) (Model 2). Following additional adjustment for the degree of CAD (1–3 vessel disease) as confirmed by angiography and number of PCI interventions, the HR (95% CI) for mortality remained similar 1.43 (1.36, 1.49) (Model 3). For the complete case analysis, the HRs (95% CIs) for the adjusted Models 2 and 3 were 1.33 (1.22, 1.46) and 1.31 (1.19, 1.43), respectively.

3.3 | Subgroup analyses

In subgroup analyses, the associations did not vary importantly by hypertension, gender, HF, chronic kidney disease, ASO, or BMI (p-values for interaction for all >0.05). However, the association between diabetes and mortality was more extreme in those with a family history of CAD than those without (p = 0.034) and former smokers than nonsmokers (p = 0.046) (Figure 1).

4 | DISCUSSION

In this real-life clinical database comprising patients who had undergone coronary angiography, a diagnosis of diabetes was associated with established cardiovascular risk factors such as high BMI,

TABLE 1 Baseline clinical characteristics according to diabetes status.

Variable	No	Yes	Total	Missing (*n* (%))
Patient, *N*	47,696	23,763	71,459	-
Age, years	65.3 (11.18)	66.5 (10.66)	65.7 (11.03)	0 (0.0)
Body mass index, kg/m^2	27.5 (4.53)	29.6 (5.40)	28.1 (4.90)	30,299 (42.4)
Ejection fraction, %[a]	60 (50–65)	58 (48–65)	60 (50–65)	58,344 (81.6)
Sex, female	18,896 (39.6)	9256 (39.0)	28,152 (39.4)	0 (0.0)
Hypertension, yes	21,763 (46.4)	14,306 (61.0)	36,069 (51.2)	1063 (1.5)
Heart failure, yes	2009 (4.3)	1214 (5.3)	3223 (4.6)	1752 (2.5)
Kidney failure, yes	1711 (3.7)	1618 (7.0)	3329 (4.8)	1750 (2.4)
Anticoagulation, yes	3900 (10.3)	2185 (10.7)	6085 (10.5)	13,336 (18.7)
ASO, yes	738 (3.4)	548 (7.8)	1286 (4.5)	42,997 (60.2)
NYHA class				36,663 (51.3)
I	2519 (8.1)	731 (4.1)	3250 (6.7)	
II	6120 (19.8)	2366 (13.3)	8486 (17.4)	
III	7756 (25.1)	5035 (28.4)	12,791 (26.3)	
IV	6170 (19.9)	4099 (23.1)	10,269 (21.1)	
Coronary artery dominant				10,321 (14.4)
Balanced	9777 (23.8)	4652 (23.2)	14,429 (23.6)	
Right	21,645 (52.7)	10,201 (50.8)	31,846 (52.1)	
Left	9654 (23.5)	5209 (26.0)	14,863 (24.3)	
Family history of CAD	19,283 (44.4)	8155 (37.8)	27,438 (42.2)	6504 (9.1)
Smoking status				9068 (12.7)
Never	32,990 (80.3)	17,667 (83.0)	50,657 (81.2)	
Former	2841 (6.9)	1211 (5.7)	4052 (6.5)	
Current	5275 (12.8)	2407 (11.3)	7682 (12.3)	
Dyslipidemia, yes	31,324 (69.1)	15,466 (67.2)	46,790 (68.5)	3109 (4.4)
Prior stroke, yes	1054 (4.4)	554 (6.6)	1608 (5.0)	39,305 (55.0)
Prior MI, yes	26,689 (57.0)	16,904 (73.1)	43,593 (62.3)	1489 (2.1)
Prior PCI, yes	3815 (8.1)	2735 (11.7)	6550 (9.3)	1072 (1.5)
Urgency, elective	18,702 (50.0)	9846 (50.8)	28,548 (50.3)	14,675 (20.5)
Angiographic findings				4038 (5.7)
<50%	16,637 (37.1)	6902 (30.5)	23,539 (34.9)	
1–3-VD	26,193 (58.4)	14,475 (64.0)	40,668 (60.3)	
Left main stenosis	1639 (3.7)	1058 (4.7)	2697 (4.0)	
Other	345 (0.8)	172 (0.8)	517 (0.8)	
Treatment decision				1728 (2.4)
No treatment for CAD	3784 (8.1)	887 (3.8)	4671 (6.7)	
Medical treatment	18,828 (40.5)	9771 (42.0)	28,599 (41.0)	
PCI	19,653 (42.3)	9760 (41.9)	29,413 (42.2)	
CABG	3621 (7.8)	2447 (10.5)	6068 (8.7)	

TABLE 1 (Continued)

Variable	No	Yes	Total	Missing (*n* (%))
Aortic valve surgery	16 (0.0)	4 (0.0)	20 (0.0)	
Mitral valve surgery	455 (1.0)	376 (1.6)	831 (1.2)	
CAD (PCI/CABG) + valve surgery	13 (0.0)	7 (0.0)	20 (0.0)	
Other surgery	82 (0.2)	17 (0.1)	99 (0.1)	
Hybrid operation	8 (0.0)	2 (0.0)	10 (0.0)	
All-cause death, yes	5962 (12.5)	4542 (19.1)	10,504 (14.7)	0 (0.0)

Note: Patients with missing data on diabetes status data have not been included.

Abbreviations: ASO, arteriosclerosis obliterans; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; VD, vessel disease.

[a]Reported as median and interquartile range.

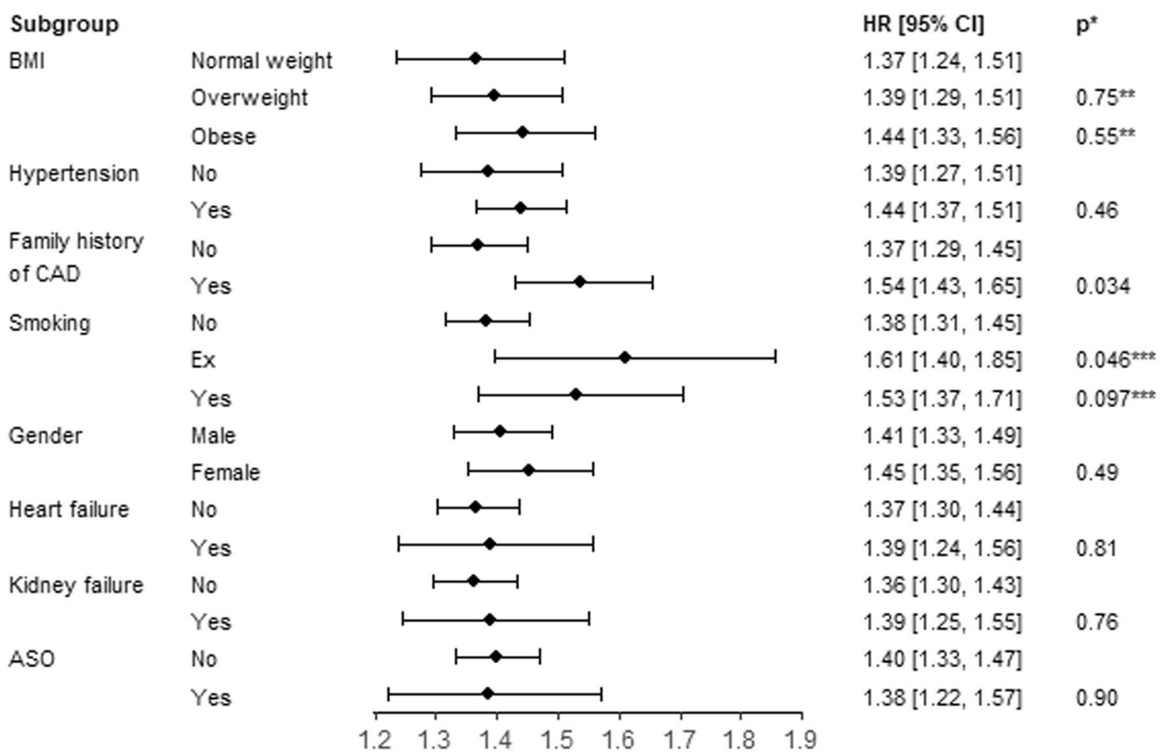

FIGURE 1 Association between diabetes and all-cause mortality in subgroups. BMI categories <25 kg/m^2 (normal weight), 25–30 kg/m^2 (overweight), >30 kg/m^2 (obese); **p* value for interaction terms; and *p* value for interaction term when contrasted with normal weight** or nonsmokers*** participants. ASO, arteriosclerosis obliterans; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval.

hypertension, and kidney disease. Having a history of diabetes was associated with an increased risk of mortality, which was independent of several established risk factors and potential confounders including the degree of CAD. The associations were not significantly modified by several clinical characteristics, except for a stronger association in those with a family history of CAD than those without and former smokers than nonsmokers. Given the multiple tests for interaction and wide CIs, the subgroup results need to be interpreted with caution.

The findings from this study align with previous studies which have consistently shown that individuals with diabetes exhibit an increased risk of cardiovascular morbidity and mortality, disproportionately affecting them compared to those without diabetes.[18,19] There is, however, limited research on the relationship between diabetes and adverse cardiovascular outcomes in patients undergoing coronary angiography using real-world data. In a retrospective analysis of 1353 consecutive patients 80 years and above who were admitted to the cardiac unit and further underwent coronary angiography, diabetes was shown to be associated with late or repeated revascularization and mortality independently of age, gender, BMI, hypertension, hyperlipidemia, active smoking, renal failure, presentation with ACS and index revascularization.[20] In 3156 patients undergoing PCI for in-stent restenosis, patients with diabetes had a higher rate of all-cause mortality and MI at 1-year follow-up, however, the associations were no longer significant on multivariable-adjusted analysis, with a relatively short follow-up time.[21] In a retrospective analysis of 8868 patients (men aged <45 years, women aged <55 years) who underwent coronary angiography, prediabetes, and diabetes versus normoglycemia were shown to be associated with an increased risk of all-cause mortality independently of several risk factors.[22] Notable aspects of our study include the very large sample based on real-world data, adjustment for potential confounders including the degree of CAD, and assessment for effect modification by relevant clinical characteristics. Our study's observation that smoking further exacerbates the risk of mortality in diabetic patients undergoing coronary angiography is supported by recent findings that smoking is independently associated with CAD in patients with diabetes.[23] Given that BMI is a major risk factor for adverse cardiometabolic outcomes such as diabetes, CAD and mortality and the possibility of an "obesity paradox,"[24] we adjusted for BMI and also examined for potential effect modification by BMI subgroups. Our findings indicated no evidence that the association between diabetes and mortality was influenced or modified by BMI. This observation aligns with several other studies in the field, which question the existence of an "obesity paradox" in populations with diabetes.[25,26]

The observed association between diabetes and increased mortality risk in patients undergoing coronary angiography may be attributed to several underlying mechanisms. First, diabetes is known to exacerbate the progression of CAD through the promotion of atherosclerosis.[27] This process is often accelerated in the presence of diabetes due to hyperglycemia, hyperlipidemia, oxidative stress, and endothelial cell dysfunction.[11] Diabetes is closely linked with a cluster of cardiovascular risk factors, including hypertension, insulin resistance, and dyslipidemia.[9,10] These conditions, when combined with hyperglycemia, create a pro-inflammatory and pro-thrombotic state that significantly increases the risk of cardiovascular events and mortality. The compounded effects of these risk factors can lead to poorer cardiovascular outcomes in patients with diabetes compared to those without diabetes. Patients with diabetes have a more severe, extensive-diffuse, and rapidly progressive form of coronary atherosclerosis with an unfavorable angiographic anatomy limiting the possibility to perform a successful and complete revascularization.[28] Additionally, the study findings regarding the stronger association of mortality risk in patients with a family history of CAD and former smokers underscore the role of genetic predisposition and lifestyle factors in the prognosis of CAD. Genetic factors may predispose individuals to both diabetes and CAD,[29] thereby amplifying the risk of adverse outcomes. Smoking, on the other hand, further compounds the risk by damaging the vascular endothelium and promoting atherogenesis,[30] which can be more detrimental in the presence of diabetes. In summary, the complex interplay between diabetes, associated cardiovascular risk factors, genetic predisposition, and lifestyle choices like smoking contributes to the increased mortality risk observed in patients with diabetes undergoing coronary angiography.

The main results from this registry-based study underscore the critical importance of diabetes management in patients undergoing coronary angiography. The established association between diabetes and an increased mortality risk, regardless of other cardiovascular risk factors and the severity of CAD, highlights the need for rigorous cardiovascular risk assessment and management strategies in patients with diabetes.[2,3] The stronger mortality association in diabetic patients with a family history of CAD and in former smokers suggests that these subgroups require particularly attentive care. For clinicians, this implies the necessity of a comprehensive approach that not only focuses on glycemic control but also on aggressive management of coexisting cardiovascular risk factors. Moreover, the independence of the diabetes-mortality association from the degree of CAD suggests that the impact of diabetes on mortality may not be solely through its effect on coronary atherosclerosis. This indicates the potential role of diabetes-related factors, such as hyperglycemia-induced vascular damage, in contributing to the increased risk.[3] Therefore, interventions aimed at reducing cardiovascular risk in patients with diabetes should encompass a broad spectrum of measures, including lifestyle modifications, pharmacological interventions to control blood pressure, lipid levels, and glucose levels, as well as smoking cessation support.

4.1 | Strength and limitations

A major strength of the KARDIO register study is its ongoing prospective data collection protocol which provides real-world contemporary data on invasive cardiology interventions and outcomes in Finland.[13] The study benefits from comprehensive data contributions from all participating hospitals, which are central to providing invasive cardiology services within the country's unified public healthcare system. Key advantages of this study include its substantial sample size, encompassing a wide range of patients with prevalent risk factors and conditions such as diabetes, and its representation of the broader invasive cardiology patient population. This is further enriched by a detailed collection of clinical, comorbidity, and lifestyle data, allowing for comprehensive adjustment for confounders. However, several limitations warrant attention. As our results are based on observational data, the direct magnitude of the possible causal effect of diabetes on mortality cannot be inferred even though we can provide accurate data on the association; further research is needed to confirm these findings. A limitation is that the register-collected diabetes status could not be classified into various subtypes such as type 1 or type 2 diabetes. However, considering the demographics and prevalence, it is reasonable to infer that the majority of the cohort would consist of patients with type 2 diabetes. The study focuses on all-cause mortality, not specifically cardiovascular mortality, due to the unavailability of cause-specific death data. The potential for residual confounding remains, as data on long-term secondary prevention practices and other diabetes-related factors such as physical activity, socioeconomic status, or cardiorespiratory fitness were not collected.[31–33] We did not have data on diabetes treatments, including newer diabetes medications (including sodium–glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists) used during the follow-up. These unmeasured variables could potentially skew the observed associations. Additionally, the absence of data on contrast agent use, laboratory values postangiography, or PCI, and the significant missing data on ejection fraction in the multivariable models, limits the depth of analysis. Despite these constraints, the consistency of the findings with previous research suggests they accurately represent the clinical scenario.

5 | CONCLUSIONS

According to data from an invasive cardiology registry study comprising patients undergoing coronary angiography, diabetes is associated with increased mortality risk, independent of several risk factors including the degree of CAD. Furthermore, the observed association between diabetes and all-cause mortality may be modified by family history of CAD and smoking status.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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