Research Square

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Prognostic Utility of Coronary CT Angiography-derived Plaque Information on Long-Term Outcome in Patients With and Without Diabetes mellitus

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Abstract

Purpose

To investigate the long-term prognostic value of coronary CT angiography (cCTA)-derived plaque information on major adverse cardiac events (MACE) in patients with and without diabetes mellitus.

Methods

64 patients with diabetes (63.3±10.1 years, 66% male) and suspected coronary artery disease (CAD) who underwent cCTA were matched with 297 patients without diabetes according to age, sex, cardiovascular risk factors, statin and antithrombotic therapy. Major adverse cardiac events (MACE) were recorded. cCTA-derived risk scores and plaque measures were assessed. The discriminatory power to identify MACE was evaluated using multivariable regression analysis and concordance indices (CIs).

Results

After a median follow-up of 5.4 years, MACE occurred in 31 patients (8.6%). In patients with diabetes, cCTA risk scores and plaque measures were significantly higher compared to non-diabetic patients (all $p<0.05$). The following plaque measures were predictors of MACE using multivariable Cox regression analysis (hazard ratio [HR]) in patients with diabetes: segment stenosis score (HR 1.20, $p<0.001$), low-attenuation plaque (HR 3.47, $p=0.05$), and in non-diabetic patients: segment stenosis score (HR 1.92, $p<0.001$), Agatston score (HR 1.0009, $p=0.04$), and low-attenuation plaque (HR 4.15, $p=0.04$). A multivariable model showed significantly improved C-index of 0.96 (95% CI 0.94-0.0.97) for MACE prediction, when compared to single measures alone.

Conclusion

Diabetes is associated with a significantly higher extent of CAD and plaque features, which have independent predictive values for MACE. cCTA-derived plaque information portends improved risk stratification of patients with diabetes beyond assessment of obstructive stenosis on cCTA alone.

1. Introduction

Coronary CT angiography (cCTA) is a well-established modality for the assessment of coronary artery disease (CAD) and non-invasive plaque quantification [1–3]. Recent studies have demonstrated the predictive value of coronary plaque measures (i.e. extent, composition, location) for improved risk stratification [4, 5].

Diabetes mellitus (DM) is a well-known cardiovascular risk factor for CAD with increased rates in morbidity and mortality [6]. Patients with diabetes present overall higher coronary plaque burden and are at higher risk for adverse cardiovascular events when compared to non-diabetic patients [7]. However, conventional risk scores recommended by societal guidelines are often challenging to apply effectively in

patients with diabetes and do not necessarily meet the required prevention care of cardiovascular disease in this specific patient population [8]. Recent investigations have demonstrated improved risk stratification in diabetic patients provided by cCTA-derived risk scores and plaque quantification [9, 10]. However, the impact of CT scores, especially high-risk plaque features, on major adverse cardiovascular events (MACE) in patients with diabetes has yet to be investigated.

Thus, we sought to evaluate the long-term prognostic value of cCTA-derived coronary plaque information on MACE in patients with and without diabetes mellitus.

2. Material And Methods

2.1 Study population

This retrospective single-center study was approved by the institutional review board, and the need for written informed consent was waived due to the retrospective nature of this investigation.
The study was performed in compliance with HIPAA. All consecutive patients with suspected or known CAD who underwent 64-slice cCTA as part of their clinical workup between April 2009 and October 2013 were included.
64 patients with diabetes mellitus were matched with 297 patients without diabetes according to the following parameters: age, sex, cardiovascular risk factors, statin and antithrombotic therapy.
Portions of this patient population have been reported in a prior study [11]. However, the prior study focused on outcome prediction in a general patient population using machine learning principles, whereas the present study aims to investigate cCTA-derived plaque measures for risk stratification in patients with and without diabetes.

MACE were recorded on follow-up. MACE were defined as cardiac death (fatal myocardial infarction [MI]), non-fatal MI (ST-segment elevation [STEMI] and non-ST-segment elevation MI [NSTEMI]), and unstable angina leading to coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), with more than 6 weeks between cCTA and invasive coronary angiography (ICA) with the revascularization procedure [12]. The patients' Framingham risk score was calculated to reflect clinical risk for cardiovascular events [13]. Diabetes was defined as fasting glucose ≥ 126 mg/dl and/or treatment with insulin or oral hypoglycemic medication [8]. cCTA data with non-diagnostic image quality was excluded from further analysis. Likewise, patients were excluded if they underwent coronary revascularization within six weeks of the CT scan, or had a history of previous MI, PCI or CABG. Demographic and clinical data were collected from medical records.

2.2 Coronary CTA acquisition

A sixty-four-slice CT (Philips Brilliance 64, Philips Medical, Eindhoven, Netherlands) was used for image acquisition. Patients initially underwent a non-contrast enhanced calcium scoring scan (collimation, 32 x 1.2 mm; 120 kV tube voltage; tube current, 75 mA; 3 mm slice thickness with 1.5 mm increment). A retrospectively ECG-gated protocol in spiral technique was used for the subsequent contrast-enhanced

cCTA with the following scan parameters: 120 kV, 600 mAs, temporal resolution of 165 ms, collimation 64 x 0.6 mm. Contrast enhancement was achieved by injecting 50–80 ml contrast agent at 4–6 ml/sec followed by a 30 ml saline bolus chaser. Weighted filtered back projection image reconstruction was performed in the cardiac phase with the least motion: section thickness of 0.75 mm, reconstruction increment of 0.5 mm, and a smooth convolution kernel.

2.3 Analysis of cCTA data, cCTA scores and plaque measures

cCTA datasets were analyzed on a commercially available post-processing software (Philips Medical, Eindhoven, The Netherlands). Two observers, who were blinded to the patients' history, independently analyzed the lesion characteristics. All discordant cases were resolved by consensus. Transverse sections and automatically generated curved multiplanar reformations were used as the reference for diameter and area stenosis quantification. Average dimensions of non-affected vessel segments immediately proximal and distal to the lesion of interest were measured at points free of atherosclerotic plaque. The CAD-RADS™ (coronary artery disease reporting and data system) was used to determine the degree of stenosis: 1. none (0%) or minimal (1–24%), 2. mild (25–49% stenosis), 3. moderate (50–69% stenosis), 4. severe (70–99% stenosis), 5. total occlusion (100%). Obstructive CAD was defined as ≥ 50% luminal stenosis[14]. A coronary plaque was defined as a structure > 1 mm^2 located within or adjacent to the coronary artery lumen. Plaques with a CT attenuation of ≤30 Hounsfield units (HU) were defined as low-attenuation plaques[15]. On vessel cross-sections, the presence of positive vessel remodeling was measured as the ratio of the vessel area of the lesion over the proximal luminal reference area. A remodeling index ≥1.1 was defined as positive vessel remodeling [15, 16]. The presence of a positive napkin-ring sign, described as a low attenuating plaque core circumscribed by an area of higher attenuation, was evaluated [17]. Spotty calcifications were visually assessed as calcifications covering < 90° of the vessel circumference while being > 3 mm of length [18]. Segment involvement score and segment stenosis score were calculated as previously reported[19]. Presence of low-attenuation plaque, napkin-ring sign, positive remodeling, and spotty calcifications deemed "high-risk" plaque features were evaluated [20, 21].

2.4 Statistical Analysis

MedCalc (MedCalc Software, version 15, Ostend, Belgium) and the python module scikit-survival [22] were used for statistical analysis. Continuous variables are displayed as mean ± standard deviation or median with interquartile range when not normally distributed. Normal distribution was assessed using Kolmogorov-Smirnov testing. Student t-test and Mann-Whitney *U*-test were used for parametric and non-parametric data, respectively. First, predictors of MACE were assessed for patients with and without diabetes using univariable and multivariable Cox proportional hazards analysis with backward elimination based on *p*-values as selection criterion. The resulting hazard ratios (HR) and 95% confidence intervals were reported. Second, the prognostic discriminatory capacity for predicting events in the overall dataset was evaluated by Cox proportional hazards analysis corrected for Diabetes mellitus, and concordance (C)-indices were determined as proposed by Harrell et al. [23]. To avoid overfitting, a

multivariable model was built utilizing recursive feature elimination with 5-fold cross-validation and C-indices as performance criterion. Improvement in the prediction performance of MACE was calculated using continuous net reclassification improvement (NRI) according to Pencina et al. [24]. Event rates were estimated by Kaplan-Meier curves and compared by log-rank test in patients with and without diabetes according to segment stenosis score (≥10 vs. <10), presence of low-attenuation plaque (yes/no), and high-risk plaque features (≥2 vs. <2). Statistical significance was assumed with a *p*-value ≤0.05.

3. Results

3.1 Patient characteristics

A total of 361 patients were included: 64 diabetic patients (63.3 ± 10.1 years, 66% male) and 297 non-diabetics (61.6 ± 10.4 years, 64% male). MACE occurred after a median follow-up of 5.4 years (IQR 4.9–5.7 years) in 31 patients (8.6%), 21 with diabetes and 10 without diabetes. Baseline characteristics were well balanced in both groups (**Table 1**). However, Framingham risk score, which includes diabetes as a determining factor, was significantly higher in diabetic patients (13.2 [IQR 10.1–14.7] in comparison to non-diabetic patients (9.7 [IQR 7.8–13.0, $p < 0.001$].

Table 1 Patient demographics. Total patient cohort (*n*=361).

Parameter	All patients (*n*=361)	Patients with diabetes (*n*=64)	Patients without diabetes (*n*=297)	*p* value
Age *(years)*	61.9±10.3	63.3±10.1	61.6±10.4	0.28
Male sex *n (%)*	233 (65%)	42 (66%)	191 (64%)	0.84
Body-mass-index *(kg/m^2)*	28.3±5.4	28.7±6.0	28.2±5.3	0.80
Framingham risk score	Median 10.2 (IQR 8.0,13.2)	Median 13.2 (IQR 10.1, 14.7)	Median 9.7 (IQR 7.8, 13.0)	<0.001
Cardiovascular risk factors				
*Hypertension n (%)**	205 (56%)	41 (64%)	164 (55%)	0.17
Dyslipidemia *n (%)*†	161 (45%)	26 (40%)	135 (45%)	0.48
Tobacco abuse *n (%)*	94 (26%)	22 (34%)	97 (32%)	0.19
CAD family history *n (%)*	91 (25%)	16 (25%)	75 (25%)	0.97
Medication at admission				
Aspirin	126 (35%)	24 (38%)	102 (34%)	0.29
Statins	169 (47%)	31 (48%)	138 (46%)	0.62
Betablocker	86 (24%)	18 (28%)	68 (22%)	0.58
ACE inhibitor	76 (21%)	15 (23%)	61 (21%)	0.46
Diuretics	65 (18%)	13 (20%)	52 (18%)	0.22
Clinical presentation at admission				
No chest pain	130 (36%)	33 (52%)	97 (35%)	<0.01
Non-cardiac chest pain	58 (16%)	8 (13%)	50 (18%)	
Typical chest pain	45 (12%)	9 (14%)	36 (13%)	
Atypical chest pain	111 (31%)	17 (278%)	94 (34%)	

Data presented as medians with 25th and 75th percentile, mean ± standard deviation or percentages in parentheses (%). CAD = coronary artery disease. *****Defined as blood pressure >140 mmHg systolic, >90 mmHg diastolic, or use of antihypertensive medication**;** †Defined as a total cholesterol of >200mg/dl or use of anti-lipidemic medication.

Diabetes was treated with oral antidiabetic medication in 47 patients (73%) and with insulin in 17 patients (27%).
The remaining patients were treated by dietary restrictions only.

3.2 Analysis of cCTA scores and plaque measures in patients with and without diabetes

cCTA analysis revealed obstructive CAD in 34 diabetic patients (53%) and 66 non-diabetic patients (22%, $p < 0.001$). Median CT scores were significantly different between patients with and without diabetes (segment involvement score: 5 [IQR 2.0, 7.0] vs. 2.0 [IQR 0.0–4.0, $p < 0.001$], and segment stenosis score: 7.5 [IQR 2.0, 13.0] vs. 3.0 [IQR 0.0–6.0, $p < 0.001$]). Furthermore, prevalence of all plaque measures were significantly higher in the diabetes group when compared to non-diabetics (Table 2).

Table 2

Parameter	All patients (*n* = 361)	Patients with diabetes (*n* = 64)	Patients without diabetes (*n* = 297)	*p* value
Age *(years)*	61.9 ± 10.3	63.3 ± 10.1	61.6 ± 10.4	0.28
Male sex *n (%)*	233 (65%)	42 (66%)	191 (64%)	0.84
Body-mass-index *(kg/m^2)*	28.3 ± 5.4	28.7 ± 6.0	28.2 ± 5.3	0.80
Framingham risk score	Median 10.2 (IQR 8.0,13.2)	Median 13.2 (IQR 10.1, 14.7)	Median 9.7 (IQR 7.8, 13.0)	< 0.001
Cardiovascular risk factors				
*Hypertension n (%)**	205 (56%)	41 (64%)	164 (55%)	0.17
Dyslipidemia *n (%)*†	161 (45%)	26 (40%)	135 (45%)	0.48
Tobacco abuse *n (%)*	94 (26%)	22 (34%)	97 (32%)	0.19
CAD family history *n (%)*	91 (25%)	16 (25%)	75 (25%)	0.97
Medication at admission				
Aspirin	126 (35%)	24 (38%)	102 (34%)	0.29
Statins	169 (47%)	31 (48%)	138 (46%)	0.62
Betablocker	86 (24%)	18 (28%)	68 (22%)	0.58
ACE inhibitor	76 (21%)	15 (23%)	61 (21%)	0.46
Diuretics	65 (18%)	13 (20%)	52 (18%)	0.22
Clinical presentation at admission				
No chest pain	130 (36%)	33 (52%)	97 (35%)	< 0.01
Non-cardiac chest pain	58 (16%)	8 (13%)	50 (18%)	
Typical chest pain	45 (12%)	9 (14%)	36 (13%)	
Atypical chest pain	111 (31%)	17 (278%)	94 (34%)	

Quantitative analysis of coronary CT-derived markers in patients with diabetes and without diabetes.

Parameter	All patients (*n* = 361)	Patients with diabetes (*n* = 64)	Patients without diabetes (*n* = 297)	*p* value

Data presented as medians with 25th and 75th percentile, mean ± standard deviation or percentages in parentheses (%). CAD = coronary artery disease. *Defined as blood pressure > 140 mmHg systolic, > 90 mmHg diastolic, or use of antihypertensive medication; †Defined as a total cholesterol of > 200mg/dl or use of anti-lipidemic medication.

Quantitative analysis of coronary CT-derived markers in patients with diabetes and without diabetes.

3.3 Association of cCTA scores and plaque measures with MACE

Patients with diabetes who suffered MACE yielded higher cCTA scores and prevalence of plaque measures (Table 3). Similar results were demonstrated for patients without diabetes. Results of the univariable and multivariable Cox regression analysis are displayed in Table 4 and Table 5. In multivariable analysis, only segment stenosis score (HR 1.20, [95% CI 1.07–1.33], $p < 0.001$), and low-attenuation plaque (HR 3.47 [95% CI 1.02–11.80], $p = 0.05$) remained independent predictors for MACE in patients with diabetes. The following markers showed predictive value of MACE in the non-diabetic group: segment stenosis score (HR 1.92 [1.46–2.54], $p < 0.001$), Agatston score (HR 1.0009 [95% CI 1.00006–1.0017, $p = 0.04$], and low-attenuation plaque (HR 4.15 [95% CI 1.04–16.64], $p = 0.04$).

Table 3

Parameter	All patients (*n* = 361)	Patients with diabetes (*n* = 64)	Patients without diabetes (*n* = 297)	*p* value
Segment stenosis score	Median 3 (IQR 1.0, 7.0)	Median 7.5 (IQR 2.0, 13.0)	Median 3.0 (IQR 0.0, 6.0)	< 0.001
Segment involvement score	Median 3.0 (IQR 1.0, 5.0)	Median 5.0 (IQR 2.0, 7.0)	Median 2.0 (IQR 0.0, 4.0)	< 0.001
Agatston score	Median 9.7 (IQR 0.0, 103.8)	Median 64.1 (IQR 6.2, 482.7)	Median 4.9 (IQR 0.0, 75.6)	< 0.001
Obstructive CAD	100 (28%)	34 (53%)	66 (22%)	< 0.001
Low-attenuation plaque	74 (21%)	22 (34%)	52 (18%)	< 0.001
Spotty calcification	76 (21%)	23 (36%)	53 (18%)	< 0.001
Positive remodeling	94 (26%)	20 (31%)	74 (25%)	0.022
Napkin-ring sign	67 (18%)	19 (29%)	48 (17%)	< 0.001
≥2 high-risk features	92 (25%)	30 (46%)	62 (21%)	< 0.001
1 vessel CAD	52 (14%)	13 (20%)	39 (13%)	0.02
2 vessel CAD	32 (9%)	12 (19%)	20 (7%)	
3 vessel CAD	13 (4%)	10 (15%)	3 (1%)	

Data presented as medians with 25th and 75th percentile or numbers with percentages (%). CAD = coronary artery disease.

Quantitative analysis of coronary CT-derived markers in patients with diabetes and without diabetes according to MACE.

Table 4

Patients with Diabetes				
Parameter	**All patients (n = 64)**	**MACE (n = 21)**	**No MACE (n = 43)**	p**value**
Segment stenosis score	Median 3 (IQR 0.0, 9.0)	Median 12 (IQR 10.0, 16.3)	Median 3 (IQR 1.0, 8.5)	< 0.001
Segment involvement score	Median 5.0 (IQR 0.0, 9.0)	Median 7.0 (IQR 5.7, 8.3)	Median 4.0 (IQR 1.0, 6.0)	0.001
Agatston score	Median 65.1 (IQR 6.2, 487.2)	Median 482.7 (IQR 178.4, 1545.5)	Median 4.9 (IQR 0.0, 75.6)	0.001
Obstructive CAD	34 (53%)	17 (81%)	17 (40%)	0.002
Low-attenuation plaque	25 (39%)	17 (81%)	8 (19%)	< 0.001
Spotty calcification	27 (42%)	14 (%)	13 (30%)	0.007
Positive remodeling	24 (38%)	14 (67%)	10 (23%)	0.001
Napkin-ring sign	21 (32%)	14 (67%)	7 (16%)	0.001
≥ 2 high-risk features	30 (47%)	19 (90%)	11 (26%)	< 0.001
Patients without Diabetes				
Parameter	**All patients (n = 297)**	**MACE (n = 10)**	**No MACE (n = 287)**	p**value**
Segment stenosis score	Median 5 (IQR 1.0, 7.0)	Median 13.5 (IQR 12.0, 17.0)	Median 2.0 (IQR 0.0, 5.0)	< 0.001
Segment involvement score	Median 2.0 (IQR 0.0, 4.0)	Median 7.5 (IQR 6.0, 9.0)	Median 2.0 (IQR 0.0, 4.0)	< 0.001
Agatston score	Median 4.9 (IQR 0.0, 75.7)	Median 283.7 (IQR 67.5, 854.4)	Median 4.2 (IQR 0.0, 64.6)	0.005
Obstructive CAD	66 (22%)	8 (80%)	58 (20%)	< 0.001
Low-attenuation plaque	49 (16%)	5 (50%)	44 (15%)	0.0041

Univariate Cox proportional hazards regression analysis of coronary CT-derived markers in patients with diabetes and without diabetes for the prediction of MACE.

Patients with Diabetes				
Spotty calcification	49 (16%)	7 (70%)	42 (14%)	< 0.001
Positive remodeling	70 (24%)	5 (50%)	65 (23%)	0.046
Napkin-ring sign	46 (15%)	4 (40%)	42 (15%)	0.031
≥ 2 high-risk features	62 (21%)	7 (70%)	55 (19%)	0.001

Data presented as medians with 25th and 75th percentile or numbers with percentages (%); TPV = total plaque volume, CPV = calcified plaque volume, NCPV = non-calcified plaque volume, SSS = segment stenosis score, SIS = segment involvement score.

Univariate Cox proportional hazards regression analysis of coronary CT-derived markers in patients with diabetes and without diabetes for the prediction of MACE.

Table 5

Parameter	Hazard ratio	95% CI of Hazard ratio	*p* value
Patients with Diabetes			
Segment stenosis score	1.26	1.15–1.39	< 0.001
Segment involvement score	1.44	1.21–1.72	< 0.001
Framingham risk score	1.09	0.98–1.21	0.11
Agatston score	1.0003	1.00006-1.00058	0.01
Obstructive CAD	4.83	1.62–14.39	0.005
Low-attenuation plaque	10.01	3.35–29.96	< 0.001
Spotty calcification	3.42	1.38–8.50	0.01
Positive remodeling	4.33	1.74–10.78	0.002
Napkin-ring sign	5.55	2.23–13.85	< 0.001
≥2 high-risk features	15.14	3.51–65.33	< 0.001
Parameter	**Hazard ratio**	**95% CI of Hazard ratio**	p**value**
Patients without Diabetes			
Segment stenosis score	1.55	1.35–1.79	< 0.001
Segment involvement score	1.54	1.54–2.47	< 0.001
Framingham risk score	1.02	0.97–1.07	0.38
Agatston score	0.998	0.994–1.003	0.58
Obstructive CAD	14.64	3.11–68.96	< 0.001
Low-attenuation plaque	5.24	1.52–18.10	0.01
Spotty calcification	12.42	3.21–48.04	< 0.001
Positive remodeling	3.35	0.97–11.58	0.06
Napkin-ring sign	3.72	1.05–13.17	0.04
≥2 high-risk features	9.24	2.39–35.72	0.001

Multivariable Cox proportional hazards regression analysis of coronary CT-derived markers in patients with diabetes and without diabetes for the prediction of MACE.

ROC analysis demonstrated that the multivariable model including diabetes mellitus, segment stenosis score, segment involvement score, low-attenuation plaque, and positive remodeling resulted in a significantly improved C-index of 0.96 (95% CI 0.94–0.97) for MACE prediction, when compared to these parameters alone: low-attenuation plaque: C-index 0.82 (95% CI 0.75–0.90, $p < 0.001$), and ≥2 high-risk features: C-index 0.86 (95% CI 0.80–0.93, $p = 0.003$). Segment stenosis score yielded a C-index of 0.94 (95% CI 0.92–0.96, $p = 0.049$), comparable to that of the multivariable model (Fig. 1).

To assess the ability of appropriate reclassification of patient risk for MACE, the NRI was calculated. The NRI of the multivariable model compared to segment stenosis score was 0.45 (95% CI 0.08–0.81), 0.28 (95% CI 0.004–0.51) when compared to low-attenuation plaque, and 0.29 (95% CI 0.004–0.54) when compared to ≥2 high-risk features.

The Kaplan–Meier survival curves showed that patients with diabetes and addition of one of the following characteristics (≥ 2 high-risk plaque features, presence of low-attenuation plaque, or segment stenosis score > 10) had substantially higher event rates than patients without these findings ($p < 0.001$) (Fig. 2). A case example of coronary stenosis on cCTA with corresponding high-risk plaque feature is shown in Fig. 3.

4. Discussion

The present study assessed the long-term prognostic value of cCTA-derived plaque information on MACE in patients with and without diabetes mellitus. Our results demonstrate the predictive value of cCTA measures for MACE in patients with diabetes, with segment stenosis score (HR 1.20, $p < 0.001$) and low-attenuation plaque (HR 3.47, $p = 0.05$), showing predictive power beyond cCTA stenosis grading and the Framingham risk score. These markers portend improved risk stratification in both patients with and without diabetes. Additionally, a multivariable model showed a significantly improved C-index of 0.96 (95% CI 0.94–0.97) for MACE prediction, when compared to single measures alone (all $p < 0.05$).

Several prior studies have evaluated the prognostic value of cCTA-derived plaque information using semiautomatic plaque quantifications and CT scores in patients with diabetes compared to patients without diabetes [7, 9, 10]. A recent study by van Hoogen et al. [9] and Hadamitzky et al. [25] showed that plaque related scores (i.e. segment stenosis score/segment involvement score) were significantly different in patients with and without diabetes and demonstrated predictive value. We also demonstrated a significant difference in CT scores between diabetic and non-diabetic patients (median segment stenosis score: 7.5 vs. 3.0, $p < 0.001$, median segment involvement score: 5.0 vs. 2.0, $p < 0.001$) with segment stenosis score serving as an independent predictor of MACE in both patients with diabetes (HR 1.20, $p < 0.001$) and without diabetes (HR 1.92, $p < 0.001$). A recent study by Deseive et al. [26] investigated the impact of different plaque features on adverse outcome in diabetic patients. They demonstrated that total plaque volume and non-calcified plaque volume were significantly different between both groups, with total plaque volume providing independent predictive value for the identification of MACE in diabetic patients. However, they did not assess the impact of high-risk plaque

features which are established markers for MACE prediction. Our results are in line with the aforementioned results and go beyond their findings as we demonstrated that all high-risk features were significantly different in diabetic patients vs. non-diabetic patients. Multivariable Cox regression analysis revealed that the presence of low-attenuation plaque demonstrated incremental predictive value in patients with diabetes (HR 3.47, $p = 0.05$) and without diabetes (HR 4.15, $p = 0.04$). We proved that the above-mentioned CT measures demonstrated superior discriminatory power in the prediction of MACE (CIs 0.82–0.95) beyond Framingham risk score (CI 0.80, $p < .001$). Whereas most recent studies focused on CT risk scores that reflect the cardiovascular disease burden (i.e. Leiden cCTA risk score, CT Leaman score) [9, 27], we additionally investigated high-risk plaque features that have been demonstrated as independent predictors of adverse cardiovascular outcome and have yet to be investigated in patients with diabetes. We demonstrated that patients with diabetes exhibited higher overall plaque burden and higher prevalence of high-risk plaque features. The presence of plaque features was associated with significantly decreased event-free survival at Kaplan-Meier analysis (Fig. 2), which is in line with findings by Blanke et al. [27].

A major drawback is the necessity for manually performed time-consuming plaque analysis that hampers its applicability in a real-world clinical setting. Although semiautomatic plaque software has been used in prior investigations [1, 26, 28], manual adjustment is still required. Technical advances such as machine-learning applications may reduce this limitation and allow for improved risk stratification in a timely and cost-effective manner [29, 30].

This study has several limitations that deserve mentioning.

A relatively small number of patients with different types of diabetes as well as various medical therapies were included, which may incur selection bias.
Furthermore, the number of MACE in non-diabetic patients is very small compared to diabetics, which may be explained be the retrospective study design resulting in selection bias. Therefore, prospective studies on larger study cohorts are necessary to validate our findings. Our results on multivariable analysis may be underpowered by the limited number of observations per variable included [31]. Therefore, the data generated in this study should only be considered hypothesis generating. Patient follow-up was performed using electronic medical records of the hospitals; potentially resulting in missed events that may have occurred outside the hospital system.

In conclusion, this study demonstrates that the presence of diabetes is associated with a significantly higher extent of CAD and plaque features, which have independent predictive values for MACE. cCTA-derived plaque information portends improved risk stratification of patients with diabetes beyond assessment of obstructive stenosis on cCTA alone.

Abbreviations

AUC Area under the curve

CAD Coronary artery disease

cCTA Coronary CT angiography

CV Cross-validation

ICA Invasive coronary angiography

MACE Major adverse cardiac events

ML Machine learning

NPV Negative predictive value

NSTEMI Non-ST-segment elevation myocardial infarction

PPV Positive predictive value

RI Remodeling Index

ROC Receiver-operating characteristics

STEMI ST-segment elevation myocardial infarction

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Figures

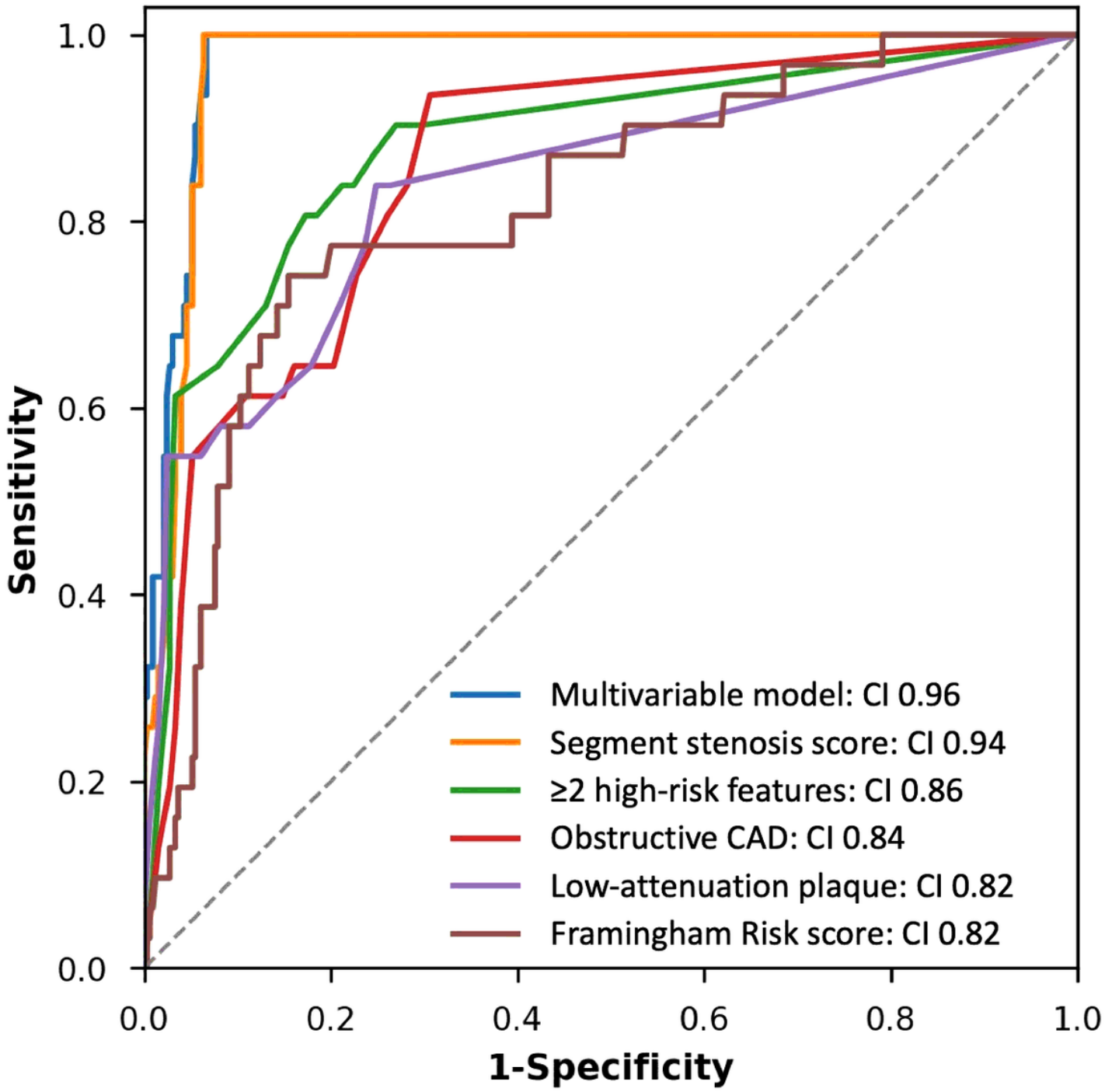

Figure 1

Diagnostic performance for the prediction of MACE. C-indices of the in the overall study population are shown with the receiver operating characteristics curves for the multivariable model (0.96 [95%CI 0.94-0.97]) in comparison to low-attenuation plaque (0.82 [95%CI 0.75-0.90]), ≥2 high-risk plaque features (0.86 [95%CI 0.80-0.93]), segment stenosis score (0.94 [95%CI 0.92-0.96]), Framingham risk score (0.80 [95%CI 0.73-0.88]), and obstructive CAD (0.84 [95%CI 0.78-0.91]) (each model corrected for diabetes mellitus).

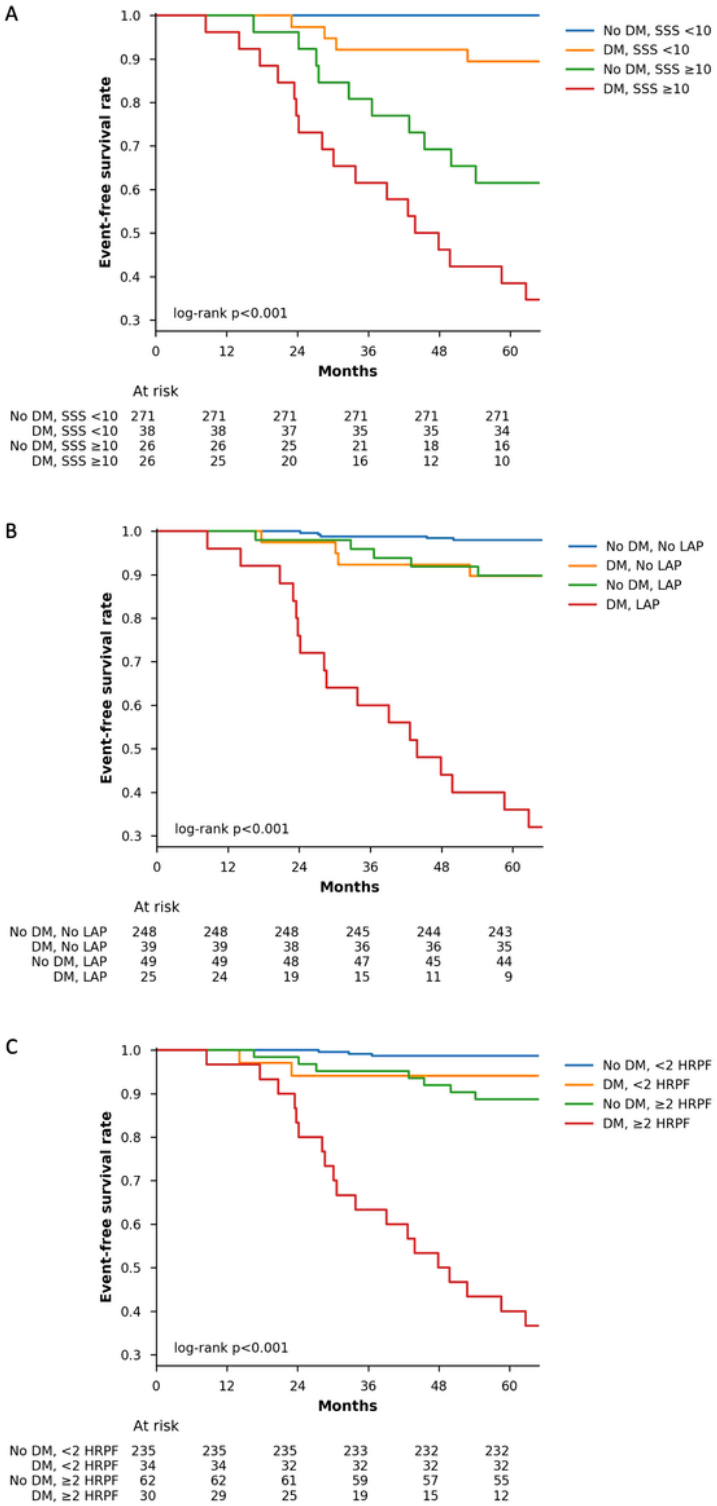

Figure 2

Kaplan-Meier curves stratified by a combination of diabetes and segment stenosis score, presence of low-attenuation plaque, and ≥2 high-risk plaque features. Kaplan-Meier curves stratified by (a) a combination of diabetes and segment stenosis score and (b) a combination of diabetes and presence of low-attenuation plaque, and (c) a combination of diabetes and ≥2 high-risk plaque features. DM = diabetes mellitus, SSS = segment stenosis score, LAP = low-attenuation plaque, HRPF = high-risk plaque features.

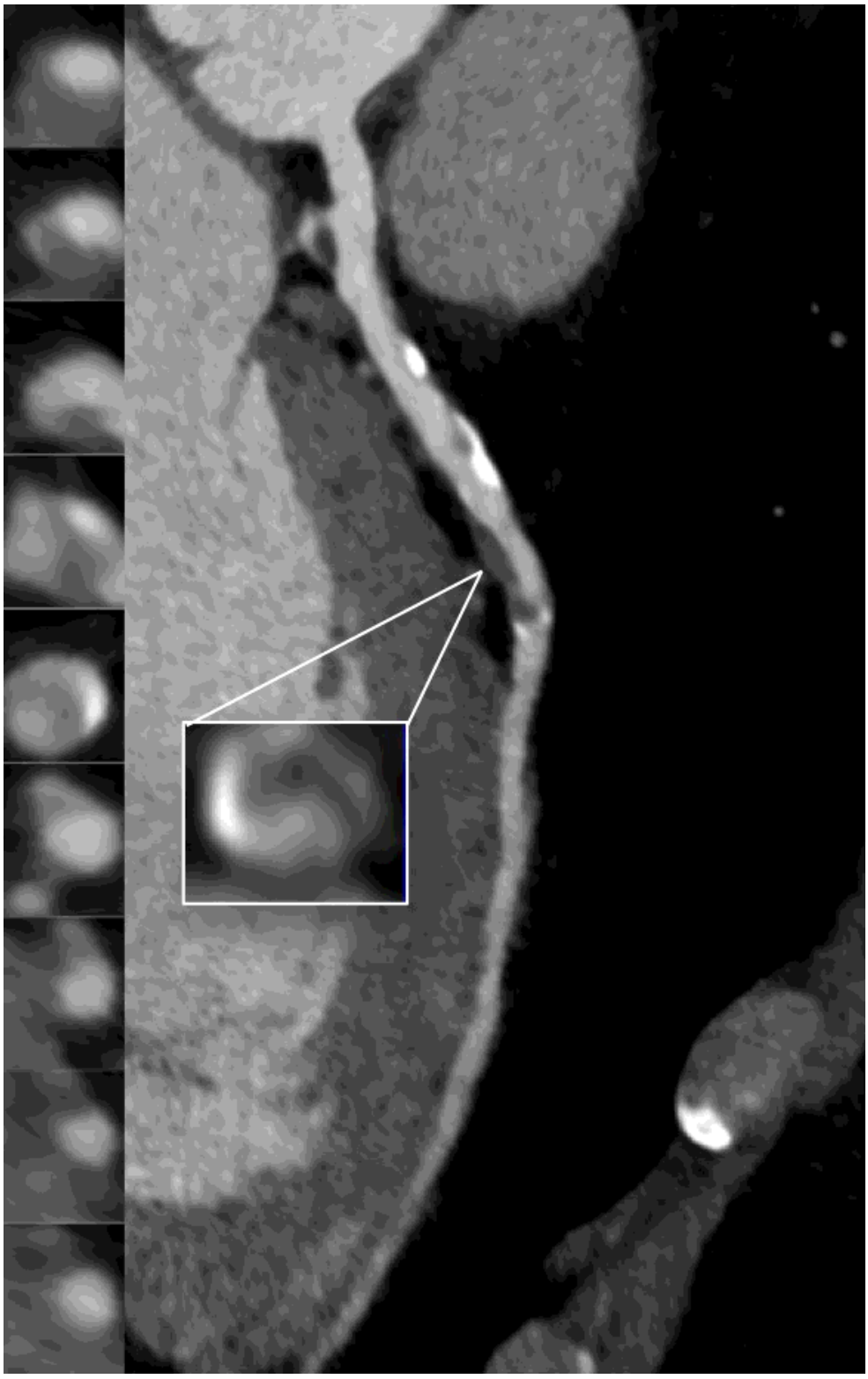

Figure 3

Case example of coronary stenosis on cCTA with corresponding high-risk plaque feature. 72-year-old man with diabetes mellitus and chest pain who underwent cCTA for suspected CAD. (A) cCTA shows mixed high-risk plaque of the medial LAD with napkin-ring sign. Cross-sectional images of the lesion demonstrate outer hyperdense fibrous rim and hypodense lipid-rich necrotic core (<30 HU).