Cardiovascular Diabetology

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The association between the triglyceride–glucose index and vulnerable plaques in patients with type 2 diabetes mellitus: insights from coronary computed tomography angiography

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Abstract

Background The triglyceride–glucose index (TyG index) has been verified to be a useful predictor of insulin resistance (IR), and is associated with the occurrence of acute coronary syndrome (ACS). However, the effect of the TyG index on vulnerable plaques (VP), which were identified when at least two high-risk features are present within the same lesion, in type 2 diabetes mellitus (T2DM) patients is not fully understood. This study aimed to explore the association between the TyG index and the presence of VP.

Methods We retrospectively enrolled 2056 T2DM patients who underwent coronary computed tomography angiography (CCTA) examinations at West China Hospital from February 2017 to February 2022. These patients were divided into four groups on the basis of the quartiles of the TyG index. The high-risk coronary plaque features, vulnerable plaques, plaque type, coronary artery stenosis, segment involvement score (SIS), segment stenosis score (SSS) and multivessel disease (MVD) based on CCTA data were evaluated and compared among the four groups.

Results Patients with a higher TyG index had more noncalcified and mixed plaques, high-risk plaque features, vulnerable plaques and fewer calcified plaques ($P < 0.05$ for all). The proportion of patients with high-risk plaque features, including low-attenuation noncalcified plaques, positive remodeling and "napkin ring" sign was associated with the TyG index (P for trend < 0.05 for all). Multivariate analysis revealed that the TyG index was significantly associated with vulnerable plaques in T2DM patients [OR = 1.23 (95% CI 1.00–1.51), P = 0.046]. Subgroup analysis

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revealed that the association between the TyG index and vulnerable plaques varied with age and the prevalence of cardiovascular (CVD) symptoms, even after controlling for confounding factors (P for interaction < 0.05 for both).

Conclusion The TyG index was independently associated with vulnerable plaques of the coronary artery among patients with T2DM. The TyG index could be regarded as a marker to reduce the incidence of cardiovascular events in the targeted population of T2DM patients.

Research insights

What is currently known about this topic? The TyG index has been verified to be a useful IR and the occurrence of ACS. Vulnerable plaques are associated with ACS.

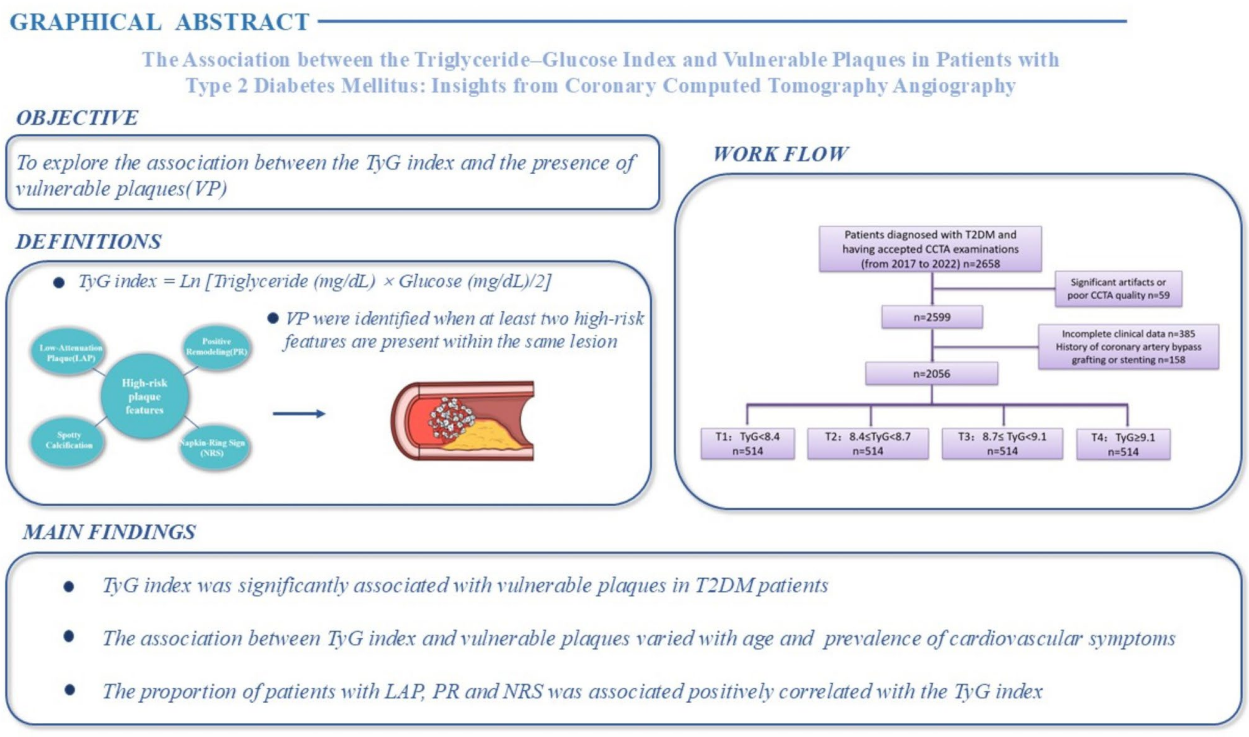
What is the key research question? What is the relationship betwwen the TyG index and vulnerable plaques in T2DM patients?.

What is new? TyG index was significantly associated with vulnerable plaques in T2DM patients. The association between TyG index and vulnerable plaques varied with age and prevalence of CVD symptoms. The proportion of patients with LAP, PR and NRS was associated positively correlated with the TyG index.

How might this study influence clinical practice? TyG index might be regarded as a marker to reduce the incidence of cardiovascular events in T2DM patients.

Keywords TyG index, Type 2 diabetes mellitus, Coronary computed tomography angiography, Atherosclerosis, Coronary artery plaque

Graphical Abstract



Introduction

Diabetes mellitus (DM) is a prevalent chronic disease that poses a substantial threat to global health and a significant social and economic burden. By 2040, the global prevalence of diabetes is projected to reach 642 million adults, with the majority having type 2 diabetes (T2DM) [1]. Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with T2DM, highlighting the critical need for effective risk stratification to improve the management and prognosis of this population [2].

Insulin resistance (IR), characterized by reduced sensitivity and responsiveness to insulin, plays a pivotal role in the pathophysiology of T2DM [3]. Studies have consistently shown that IR predisposes patients to various metabolic disorders, including hyperglycemia, hypoglycemia,

and hypertension, all of which are strongly associated with adverse cardiovascular outcomes [4]. The triglyceride-glucose (TyG) index has emerged as a simple and reliable marker for assessing IR [5, 6]. Recent evidence indicates that the TyG index is significantly associated with the incidence of CVD, regardless of the presence of diabetes, and is correlated with coronary artery stenosis, coronary artery calcification, and the prevalence of multivessel disease (MVD) [7, 8]. The TyG index and its derived metrics have demonstrated potential utility in risk stratification and prognosis prediction in patients with acute coronary syndrome (ACS), irrespective of diabetic status [5, 6, 9].

Coronary computed tomography angiography (CCTA) is a noninvasive imaging method that can accurately assess the size of the lumen and the outer vessel wall, high-risk plaque burden and morphology, and remodelling patterns [10, 11]. High-risk plaque features and vulnerable plaques identified by CCTA have shown strong predictive value for ACS occurrence [6, 12, 13]. However, few studies have investigated the association between the TyG index and vulnerable coronary plaques. This study aimed to investigate the association between the TyG index and the presence of high-risk plaque features and vulnerable plaques in patients with T2DM, which could provide emphasis for the association between the TyG index and CVD from an imaging perspective.

Methods

Study population

This retrospective study was approved by our Institutional Ethics Committee, obviating the need for informed consent. From February 2017 to February 2022, we retrospectively included 2658 inpatients with T2DM who underwent CCTA examination at our hospital. The inclusion criteria included patients who were clinically diagnosed with T2DM and underwent CCTA for reasons such as screening due to CAD risk factors (e.g., hypertension, hyperlipidemia, family history), evaluation of CAD-related symptoms, routine health check-ups, or preoperative cardiovascular risk assessment. Exclusion criteria included: absence of imaging files, significant artifacts, or insufficient image quality for assessment; coronary artery bypass grafting or stent implantation prior to CCTA examinations; absence of key clinical data such as triglycerides (TGs) and glycemia; incomplete or missing clinical medical records. According to the above inclusion and exclusion criteria, 2056 patients were enrolled and divided into four groups based on TyG index quartiles: quartile1 (T1, n = 514, TyG < 8.4), quartile 2 (T2, n = 514, 8.4 ≤ TyG < 8.7), quartile 3 (T3, n = 514, 8.7 ≤ TyG < 9.1) and quartile 4 (T4, n = 514, TyG index ≥ 9.1), and the characteristics were depicted (Fig. 1).

Clinical data collection and definitions

Demographic data such as age, gender, and height were obtained upon admission. Disease histories were retrieved from medical records, including symptoms of cardiovascular diseases, hypertension, smoking, alcohol consumption, etc. Regarding the collection of therapeutic agents (including hypoglycemic and lipid-lowering agents), we simultaneously took into account the patients' medical history records as well as the inpatient medical orders during their hospital stay. Routine laboratory tests were carried out using fasting blood samples. The laboratory data were aquired from the

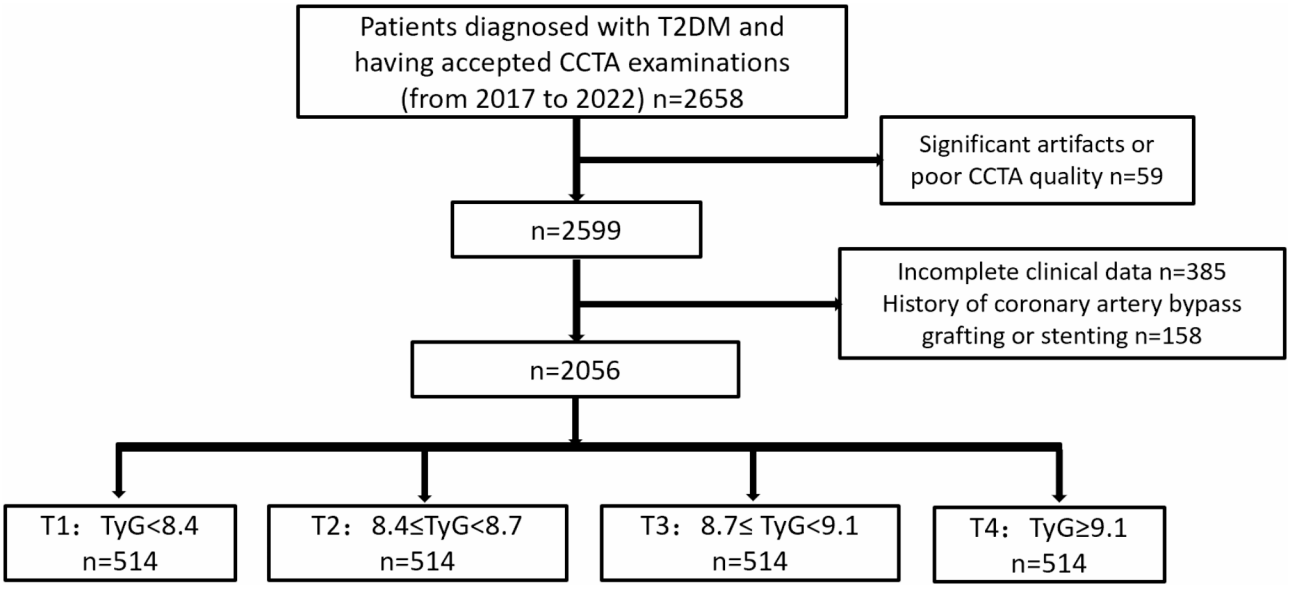


Fig. 1 Flowchart of participant selection

first blood test at admission.T2DM was defined according to American Diabetes Association guidelines or treated with oral glucose-lowering agents or insulin [14]. The TyG index was calculated via the formula TyG index = Ln [Triglyceride (mg/dL) × Glucose (mg/dL)/2] [15]. Patients with symptomatic CVD were identified as those with a history of angina: the clinical diagnosis included a diagnosis without complementary tests. Hypertension was defined as having two consecutive systolic/diastolic blood pressure readings exceeding 140/90 mm Hg or the current use of antihypertensive medication. Dyslipidemia was diagnosed on the basis of the presence of one or more of the following conditions: (1) hypercholesterolemia (TC ≥ 6.2 mmol/L), (2) hyper-LDL-C (LDL-C ≥ 4.1 mmol/L), (3) hypertriglyceridaemia (TG ≥ 2.3 mmol/L), and (4) hypo-HDL-C (HDL-C < 1.0 mmol/L in men and < 1.3 mmol/L in women) [16]. A history of smoking was recorded regardless of smoking cessation status, as was a history of alcohol consumption.

CCTA scanning protocols

All of the patients underwent CCTA scanning via Revolution CT (GE Healthcare, Waukesha, WI, USA) or multidetector CT systems (SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany; SOMATOM Definition FLASH, Siemens Medical Solutions, Forchheim, Germany). Heart rate was controlled without the use of beta-blockers. All patients were placed in the supine position. They received an intravenous infusion of 70 to 90 ml (adjusted for body weight) of iodine contrast agent, followed by an injection of 30 ml of normal saline at the same flow rate. The CT scan covered the region from the bifurcation of the trachea to 20 mm below the apex of the heart. The Revolution CT system uses kV assist and Smart-mA to automatically adjust the tube voltage and tube current on the basis of the patient's scout image, with a collimation of 256 × 0.625 mm and a rotation time of 0.28 s. The SOMATOM Definition system operates at a tube voltage of 100–120 kV, a tube current of 220 mAs, collimation of 64/128 × 0.6 mm, and a rotation time of 0.33 s. The retrospective electrocardiographic gating technique was employed to eliminate cardiac motion artifacts. The initial dataset was reconstructed postscanning, and images were transferred to either an AW volumeshare5 (GE Healthcare, Waukesha, WI, USA) or Syngo-Imaging (Siemens Medical Solution Systems, Forchheim, Germany) image processing workstation for analysis. When the plaque is highly calcified, the iterative reconstruction algorithm (SAFIRE) is employed to mitigate image noise and optimize image quality. Coronary plaque assessment includes maximum density projection, multiplane reconstruction, curvature plane reconstruction, and volume reconstruction.

Image analysis

The images of all patients were independently analysed by two experienced radiologists, who were blinded to the clinical information of the patients. In cases of disagreement, the two observers discussed and reached a consensus. The coronary arteries in this study were categorized into four branches: the left main artery (LM), left anterior descending branch (LAD), left circumflex branch (LCX), and right coronary artery (RCA). These branches were further divided into 16 segments according to the revised standards of the American Heart Association (Fig. 2) [17]. Each plaque was categorized on the basis of its composition as (a) calcified plaque (plaques with higher density than contrast-enhanced lumen); (b) noncalcified plaque (plaques with lower CT attenuation than contrast-enhanced lumen, no calcification); and (c) mixed plaques (calcified with noncalcified components in a single plaque) [18]. The coronary lumen cross-sectional diameter was measured at the largest stenosis and compared with the means of the proximal and distal reference sites to evaluate the degree of coronary artery stenosis. Coronary artery stenosis was evaluated according to the following five categories: Grade 0, no visible luminal stenosis; Grade 1, lumen stenosis < 25%; Grade 2, lumen stenosis 25–49%; Grade 3, lumen stenosis 50–69%; Grade 4, lumen stenosis 70–99%; and Grade 5, completely occluded [19]. Obstructive stenosis was defined as lumen stenosis ≥ 50%. The SIS was defined as the number of coronary artery segments exhibiting plaques for each patient (0–16), which indicates the extent of coronary plaque involvement. The SSS was defined as the sum of the stenosis scores of the relevant stenosis grades of all segments for each patient (0–80), which indicates the degree of stenosis of the coronary artery (Fig. 2) [17]. According to the American College of Cardiology/American Heart Association guidelines, multivessel obstructive disease (MVD) was defined as the presence of more than one vessel with stenosis ≥ 70% or LM stenosis ≥ 50% [20]. The high-risk plaque features included low-attenuation noncalcified plaque, positive remodelling, spotty calcification and "napkin ring" signs. Low-attenuation noncalcified plaques, generally defined as areas within plaques > 1 mm^2 with CT values < 30 HU. The remodeling index was defined as the ratio between the maximum vascular diameter of the diseased segment (including the plaque and the lumen) and the diameter of the normal proximal lumen (arterial remodeling index = lesion plaque area/reference area). A remodeling index of ≥ 1.1 indicates positive remodeling. Spotty calcification was characterized as small focal calcifications of < 3 mm in any direction [21]. The "napkin ring" sign describes an annular slightly higher density sign at the edge of the low-density patch. More specifically, the "napkin ring" was defined as a coronary plaque exhibiting a ring of high attenuation around

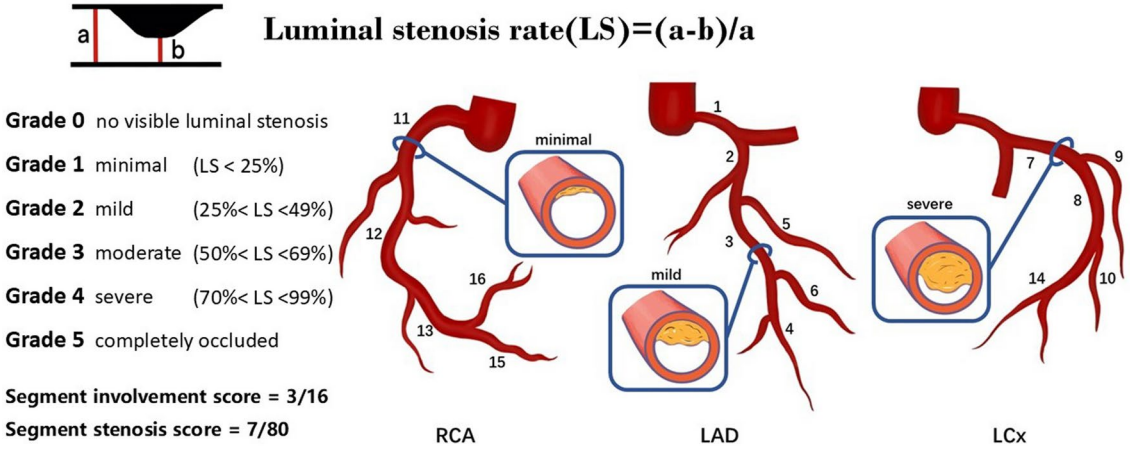


Fig. 2 Schematic diagram of the degree of coronary artery stenosis and coronary artery segmentation. In this example, plaques distribute on proximal RCA, mid-LAD and proximal LCx. SIS was calculated by the number of coronary artery segments observed with plaques, which was 3 out of a possible 16 in this example. SSS was calculated by the minimal plaque in the proximal RCA (scored 1), mild plaque in the mid-LAD (scored 2) and severe plaque in the proximal LCx (scored 4). Thus, the SSS was 7 out of a possible 80. *LAD* Left anterior descending artery, *LCx* Left circumflex, *RCA* Right coronary artery, *SIS* Segment involvement score, *SSS* Segement stenosis score.

it, and the attenuation of the ring presented higher than those of the adjacent plaque and not > 130 HU [22]. Vulnerable plaques are identified when at least two high-risk features are present within the same lesion [23].

Statistical analysis

SPSS software (version 26.0) was utilized for conducting the statistical analysis. Categorical variables are presented as numbers (%) and were compared via the chi-square test. Continuous variables with a normal distribution were expressed as the mean ± standard deviation and were analysed via one-way ANOVA. Non-normally distributed continuous variables were presented as medians (interquartile ranges) and analysed via the Kruskal–Wallis test. Bonferroni correction for multiple comparisons was applied. The statistical significance level was considered $\alpha = 0.05/n$ for Bonferroni-corrected comparisons, where n is the number of performed comparisons. Regarding the characteristics of coronary artery plaques, we conducted both "per—patient" and "per—segment" analyses. For the former, the proportion of patients with at least one plaque among the total patients was calculated and Chi—square test was applied to compare differences between groups. For the latter, the number of segment-based plaques among different groups were compared using a generalised estimating equations (GEE) approach. $\chi 2$ tests with linear-by-linear associations were applied to examine the significance of any linear trend in the presence of any high-risk plaque feature according to quartiles of the TyG index. We standardized (Z score) the TyG index and then included it in univariate and multivariate logistic analyses to explore the impact of an increase in the TyG index per standard deviation (SD) on the presence of any vulnerable plaque. Before constructing the multivariate model, we examined the collinearity between the TyG index and other variables by calculating the variance inflation factor (VIF) and tolerance. When the VIF was greater than 5 and tolerance was lower than 0.2, we considered collinearity to exist. Variables with P values ≤ 0.1 in the univariate analysis and recognized cardiovascular risk factors were entered en bloc into the multivariable model. We excluded TC, TG, and LDL-C from the analyses because of high collinearity with the TyG index. Based on the principles above, we finally adjusted for age, male sex, BMI, hypertension, smoking history, drinking history, use of statin, HDL and CysC level in the multivariable model. Additionally, subgroup analyses were performed to explore whether the association was modified by sex, age, hypertension, and the presence of CVD symptoms. Interactions between the TyG index and the variables above were examined separately. A two-tailed P value less than 0.05 was considered statistically significant.

Results

Study population

A total of 2056 T2DM patients were included in this study after the exclusion criteria were applied. The patients were divided into quartiles on the basis of their TyG index (Table 1). The mean age of the participants

Table 1 Baseline characteristics of study population by TyG index quartile

	T1(n = 514)	T2(n = 514)	T3(n = 514)	T4(n = 514)	p
Variables clinical parameters					
Age, years	70.44 ± 9.71	69.25 ± 9.33	68.43 ± 10.44[a]	65.54 ± 11.29 [abc]	**< 0.001**
Male, n (%)	329(64%)	310(60%)	315(61%)	320(62%)	0.673
Height, cm	162.7 ± 8.30	162.54 ± 8.59	162.35 ± 9.53	162.63 ± 10.93	0.938
Weight, kg	62.84 ± 10.90	64.45 ± 12.19 [a]	65.91 ± 12.43[a]	69.52 ± 14.39 [abc]	**< 0.001**
BMI, kg/m^2	23.66 ± 3.22	24.31 ± 3.65	25.49 ± 16.09[a]	27.52 ± 23.05 [abc]	**< 0.001**
SBP, mmHg	136.21 ± 19.74	136.05 ± 19.66	137.25 ± 19.84	138.04 ± 19.9	0.330
DBP, mmHg	77.19 ± 11.46	78.21 ± 11.85	79.77 ± 12.21[ab]	82.12 ± 12.14 [abc]	**< 0.001**
Hypertension, n (%)	242(47%)	236(46%)	250(49%)	263(51%)	0.324
Dyslipidemia, n (%)	173(34%)	240(47%) [a]	306(60%) [ab]	430(84%) [abc]	**< 0.001**
Symptomatic CVD	95(18%)	91(18%)	94(18%)	96(19%)	0.980
Smoking history	188(37%)	172(33%)	209(41%)	189(37%)	0.124
Drinking history	129(25%)	130(25%)	146(28%)	140(27%)	0.572
Use of statin, n (%)	237(46%)	200(39%)[a]	193(38%) [a]	218(42%)	0.025
Use of antidiabetic agents (n%)	356(68%)	344(67%)	372(72%)	366(71%)	0.460
Biguanides, n (%)	141(27%)	140(26%)	157(31%)	161(31%)	0.456
Insuin, n (%)	141(27%)	136(26%)	158(31%)	149(29%)	0.395
α-Glucosidase inhibitor, n (%)	117(23%)	101(20%)	102(20%)	76(15%) [a]	**0.013**
Other oral, n (%)	142(28%)	110(23%)	118(23%)	85(17%) [a]	**0.005**
Biochemical parameters					
TyG index	8.19 ± 0.28	8.74 ± 0.12[a]	9.16 ± 0.13[ab]	9.91 ± 0.44 [abc]	**< 0.001**
Glycemia, mg/dl	102.04 ± 23.96	117.88 ± 24.10[a]	128.62 ± 28.10[ab]	142.35 ± 28.15 [abc]	**< 0.001**
TG, mg/dl	73.39 ± 20.43	103.52 ± 22.31[a]	137.46 ± 32.74[ab]	244.03 ± 109.41 [abc]	**< 0.001**
TC, mmol/L	3.63 ± 0.97	3.96 ± 1.00[a]	4.18 ± 1.18[ab]	4.56 ± 1.15 [abc]	**< 0.001**
HDL, mg/dl	1.29 ± 0.36	1.20 ± 0.33[a]	1.11 ± 0.33[ab]	0.98 ± 0.28 [abc]	**< 0.001**
LDL, mg/dl	2.02 ± 0.79	2.31 ± 0.87[a]	2.50 ± 1.01[ab]	2.57 ± 0.95[ab]	**< 0.001**
UREA, mg/dl	6.12 ± 3.15	6.00 ± 2.64	6.42 ± 4.10	6.43 ± 4.68	0.166
Cr, mg/dl	83.79 ± 72.15	82.08 ± 60.48	88.29 ± 71.72	89.55 ± 77.15	0.276
CysC, mg/dl	1.14 ± 0.68	1.17 ± 0.76	1.21 ± 0.83	1.22 ± 0.90	0.375
CK, IU/L	100.85 ± 106.13	111.06 ± 196.74	116.31 ± 243.85	96.34 ± 110.29	0.242
LDH, IU/L	175.77 ± 50.30	179.36 ± 61.20	180.88 ± 63.42	173.55 ± 53.02	0.141

Data are presented as mean ± SD or number (percentage)

BMI Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *TG* Triglycerides, *TC* Total cholesterol, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *CysC* Cystatin C, *CK* Creatine kinase, *LDH* Lactate dehydrogenase

P values in bold are < 0.05

a adjuted P < 0.05 vs. T1

b adjuted P < 0.05 vs. T2

c adjuted P < 0.05 vs. T3

was 68.4 ± 10.4 years, and 62% were male. The subjects were divided into quartiles on the basis of their TyG index. The highest TyG index quartile had a greater proportion of patients with dyslipidemia (P < 0.05); highest weight, body mass index (BMI), distolic blood pressure (DBP), glycemia, triglycerides (TGs), total cholesterol (TC) and low-density protein cholesterol (LDL-C) levels (P < 0.05); and lowest high-density lipoprotein cholesterol (HDL-C levels) (P < 0.05). The use of statin in T1 group was higher than that in T2 and T3 group (P < 0.05). The four groups of patients did not differ significantly in terms of sex, height, systolic blood presure (SBP), smoking history, drinking history, levels of cystatin C (CysC), Creatine kinase (CK), Lactate dehydrogenase (LDH) or the use of antidiabetic agents (p > 0.05 for all).

Results of CCTA among T2DM patients grouped by quartiles of the TyG index

On a per-segment basis, patients in the T3 and T4 groups had fewer calcified plaques (1.96 ± 2.30 vs. 1.70 ± 2.13 vs. ± 1.51 vs.1.90 vs.1.44 ± 1.81, P = 0.002), more noncalcified (0.73 ± 1.04 vs. 0.87 ± 1.29 vs. 0.88 ± 1.24 vs. 0.94 ± 1.27, P = 0.032) and more mixed plaques (1.55 ± 2.15 vs. 1.86 ± 2.38 vs. 1.97 ± 2.64 vs. 2.02 ± 2.75, P = 0.008) than T1 group (Table 2). For high-risk plaque features and vulnerable plaques, patients in the T3 and T4 groups had more low-attenuation noncalcified plaques (0.18 ± 0.56

Table 2 Characteristics of coronary artery plaques detected by CCTA by TyG index quartile

	T1(n = 514)	T2(n = 514)	T3(n = 514)	T4(n = 514)	p
Per patient					
Plaque type, n (%)					
Calcified plaque	320(62%)	318(62%)	308(60%)	295(57%)	0.322
Mixed plaque	266(52%)	298(58%)	295(57%)	288(56%)	0.219
Noncalcified plaque	227(44%)	236(46%)	240(47%)	253(49%)	0.368
High-risk Plaque Feature, n (%)					
Low-Attenuation Noncalcified Plaque	62(12.1%)	89(17.3%)[a]	94(18.3%)[a]	96(18.7%) [a]	**0.015**
Positive remodeling	75(14.6%)	117(22.8%)[a]	116(22.6%)[a]	120(23.3%)[a]	**0.001**
Spotty Calcification	64(12.5%)	69(13.4%)	86(16.7%)	74(14.4%)	0.236
Napkin-Ring sign	8(1.6%)	7(1.4%)	16(3.1%)	16(3.1%)	0.096
Vulnerable Plaque, n (%)	64(12.5%)	105(20.4%)[a]	114(22.2%)[a]	127(24.7%)[a]	**0.007**
MVD, n (%)	43(6.0%)	48(6.7%)	49(6.8%)	57(8.0%)	0.524
Per segment					
Plaque type,					
Calcified plaque	1.96 ± 2.30	1.70 ± 2.13[a]	1.51 ± 1.90[a]	1.44 ± 1.81[a]	**0.002**
Mixed plaque	1.55 ± 2.15	1.86 ± 2.38	1.97 ± 2.64[a]	2.02 ± 2.75[a]	**0.008**
Noncalcified plaque	0.73 ± 1.04	0.87 ± 1.29	0.88 ± 1.24[a]	0.94 ± 1.27[a]	**0.032**
Stenosis caused by plaques					
Obstructive Stenosis	1.33 ± 2.23	1.46 ± 2.21	1.50 ± 2.44	1.55 ± 2.50	0.598
Nonobstructive Stenosis	2.90 ± 2.31	2.97 ± 2.28	2.88 ± 2.29	2.84 ± 2.24	0.631
High-risk plaque feature					
Low-attenuation noncalcified plaque	0.18 ± 0.56	0.28 ± 0.74[a]	0.32 ± 0.85[a]	0.33 ± 0.85[a]	**< 0.001**
Positive remodeling	0.22 ± 0.71	0.34 ± 0.76	0.35 ± 0.82[a]	0.35 ± 0.78[a]	**< 0.001**
Spotty calcification	0.20 ± 0.61	0.19 ± 0.55	0.28 ± 0.81	0.22 ± 0.67	0.840
Napkin-ring sign	0.02 ± 0.16	0.01 ± 0.12	0.04 ± 0.25[b]	0.04 ± 0.26[b]	**0.038**
Vulnerable plaque	0.12 ± 0.44	0.22 ± 0.65[a]	0.25 ± 0.71[a]	0.23 ± 0.65[a]	**0.002**
Extent of the coronary plaque					
SIS	8.83 ± 8.85	9.51 ± 8.78	9.43 ± 9.67	9.51 ± 9.72	0.791
SSS	4.23 ± 3.38	4.43 ± 3.32	4.36 ± 3.47	4.39 ± 3.46	0.540

Data are presented as the mean ± SD or number (percentage)

T1 the first TyG index quartile, T4 the fourth TyG index quartile

P values in bold are < 0.05

a adjuted P < 0.05 vs. T1

b adjuted P < 0.05 vs. T2

c adjuted P < 0.05 vs. T3

vs. 0.28 ± 0.74 vs. 0.32 ± 0.85 vs. 0.33 ± 0.85, P = < 0.001), positive remodelling plaques (0.22 ± 0.71 vs. 0.34 ± 0.76vs. 0.35 ± 0.82 vs. 0.35 ± 0.78, P = < 0.001, "napkin ring" sign (0.02 ± 0.16 vs. 0.01 ± 0.12 vs. 0.04 ± 0.25 vs. 0.04 ± 0.26, P = 0.038), and more vulnerable plaques (0.12 ± 0.44 vs. 0.22 ± 0.65 vs. 0.25 ± 0.71 vs. 0.23 ± 0.65, P = 0.002) than the T1 or T2 group (Table 2). There was no significant difference in the number of obstructive stenoses and nonobstructive stenoses or the SIS and SSS scores among the TyG index quartiles (p > 0.05 for all).

On a per-patient basis, the T2, T3 and T4 groups had a greater proportion of patients with low-attenuation noncalcified plaques and positive remodelling (low-attenuation noncalcified plaques: 12.1% vs. 17.3% vs. 18.3% vs. 18.7%, P = 0.015; positive remodelling: 14.6% vs. 22.8% vs. 22.6% vs. 23.3%, P = 0.001) than did the T1 group (, Table 2). No significant differences were detected in the prevalence of calcified plaques, non-calcified plaques, mixed plaques, obstructive stenoses, nonobstructive stenoses, or SIS and SSS scores among TyG index quartiles (p > 0.05 for all).

Associations between the TyG index and high-risk plaque features

We evaluated any association between the quartiles of TyG index and presence of any high-risk plaque feature. As the TyG index increased, so did the of proportion of patients with low-attenuation noncalcified plaque, positive remodelling and "napkin ring" sign. The proportion of subjects with low-attenuation noncalcified plaques increased gradually from 12.1% in T1 group to 18.7% in those in T4 group (*P* for trend = 0.005; Fig. 4a). A similar trend was observed when we evaluated relationship between the TyG index and positive remodelling

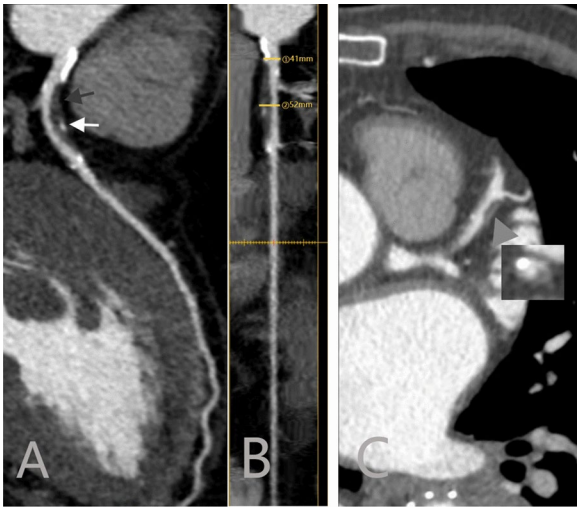


Fig. 3 **A** Curvature plane reconstruction image of the coronary artery in a 69-year-old male with high TyG index (in T4 group): low-attenuation noncalcified plaque (grey arrow), spotty calcification (white arrow) and positive remodeling can be seen in the left anterior descending artery (LAD); **B** Measurement of the positive remodelling index of the plaque in panel **A** remodelling index = 1.27 {lesion plaque area (0.52 cm)/ reference area (0.41 cm)}; **C** Napkin ring sign in a 68-year-old male with high TyG index (in T4 group)

(*P* for trend = 0.001; Fig. 4b) or "napkin-ring sign" (*P* for trend = 0.029; Fig. 4d). No significant difference was detected in the presence of any spotty calcification across TyG quartiles (P for trend > 0.05) (Fig. 4c).

Univariate and multivariate analysis for predictors of vulnerable plaques

The results of the univariate and multivariate regression analyses are shown in Table3 . In the univariate analysis, the TyG index, male sex, smoking history, drinking history, HDL and CysC levels were significantly associated with the prevalence of any vulnerable plaque ($p < 0.05$ for all). In the multivariate regression analysis, the TyG index was independently associated with vulnerable plaques after adjustment for age, male sex, BMI, hypertension, smoking history, drinking history, and use of statins and HDL and CysC levels. (TyG index: OR = 1.23, p = 0.046) (Table 3).

Subgroup analysis of the associations between the TyG index and vulnerable plaques

Subgroup analyses revealed that the TyG index was independently associated with the presence of any vulnerable

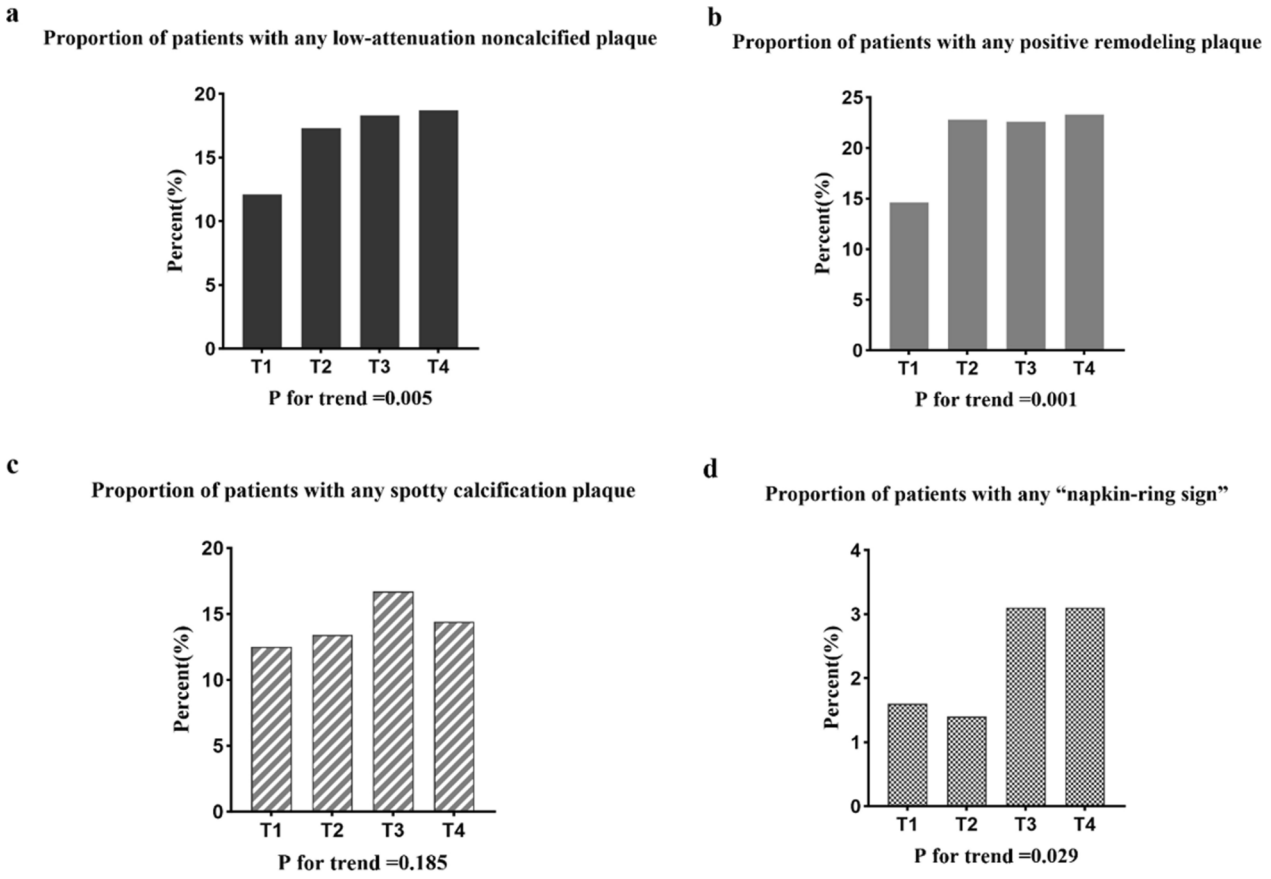


Fig. 4 Association between the TyG index and high-risk plaque feature: **a** low-attenuation noncalcified plaque; **b** positive remodeling; **c** spotty Calcification; **d** napkin-ring sign

Table 3 Univariate and multivariate analysis for predictors of any vulnerable plaque in T2DM population

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Any Vulnerable plaque				
TyG	1.25(1.04–1.50)	**0.018**	1.23(1.00–1.51)	**0.046**
Sex	1.52(1.16–2.00)	**0.003**	1.15(0.81–1.64)	0.432
Age	1.00(0.90–1.01)	0.859	1.01(0.99–1.02)	0.309
BMI	1.00(0.99–1.01)	0.594	1.00(0.99–1.01)	0.962
HDL	0.64(0.43–0.94)	**0.022**	0.84(0.60–1.12)	0.503
CysC	1.15(1.02–1.31)	**0.029**	1.12(0.98–1.28)	0.087
Smoking	1.65(1.27–2.13)	**< 0.001**	1.33(0.95–1.88)	0.100
Drinking	1.65(1.26–2.16)	**< 0.001**	1.34(0.96–1.87)	0.087
Hypertension	1.24(0.96–1.59)	0.104	1.23(0.95–1.60)	0.113
Use of statin	1.12(0.87–1.45)	0.387	1.10(0.85–1.44)	0.452

P values in bold are < 0.05

OR Odds ratio, *CI* Confidence interval, *SD* Standard deviation

Multivariate analysis: adjusted for age, male sex, use of statin, hypertension, smoking history, drinking history, BMI, HDL and CysC level

Table 4 Subgroup analysis for association between TyG index (per 1 SD) and Vulnerable plaque

Subgroup	Unadjusted	Unadjusted	Adjusted	Adjusted	P for interaction
	OR (95% CI)	p value	OR (95% CI)	p value	
Gender					0.117
Male	1.12(0.88–1.43)	0.347	1.10(0.84–1.43)	0.502	
Female	1.52(1.14–2.03)	**0.005**	1.48(1.07–2.06)	**0.020**	
Age, years					**0.006**
Age < 60	1.01(0.69–1.47)	0.977	1.04(0.69–1.57)	0.849	
Age ≥ 60	1.34(1.08–1.66)	**0.009**	1.32(1.04–1.68)	**0.021**	
Hypertension					0.098
Yes	1.25(0.99–1.59)	0.063	1.16(0.84–1.62)	0.371	
No	1.21(0.90–1.63)	0.199	1.25(0.96–1.63)	0.094	
Symptom					**0.012**
Yes	1.74(1.15–2.62)	**0.008**	1.60(1.01–2.55)	**0.046**	
No	1.15(0.93–1.43)	0.190	1.19(0.94–1.51)	0.147	

Adjusted model: Adjusted for age, use of statin, hypertension, BMI, level of HDL and CysC, smoking and drinking history

OR Odds ratio, *CI* Confidence interval

Factors with a P value of less than 0.1 and recognized cardiovascular risk factors remained in the models. P values in bold are < 0.05

plaque in elderly patients (≥ 60 years old) and symptomatic CVD patients after adjusting for confounding factors (elderly patients: OR = 1.32, p = 0.021; and symptomatic CVD patients: OR = 1.60, p = 0.046) (Table 4).

Discussion

This study explored the associations between the TyG index and high-risk plaque features and vulnerable plaques in T2DM patients undergoing CCTA. The main findings are as follows: (1) T2DM patients with a higher TyG index had more noncalcified and mixed plaques, more high-risk plaque features, more vulnerable plaques and fewer calcified plaques. (2) The proportion of patients with any high-risk plaque feature increased as the TyG index rose. (3) The TyG index was significantly associated with vulnerable plaques in T2DM patients. (4) Subgroup analysis revealed that the TyG index was significantly associated with vulnerable plaques in elderly (age ≥ 60), and symptomatic CVD patients with T2DM.

The association among TyG index, IR and coronary atherosclerosis

The exact mechanism of the relationship between the TyG index and CVD is unknown. It is clear that TyG is an indicator of two CVD risk factors, lipid-related factors and glucose-related factors, which reflect IR in the human body [24]. Recent studies have identified the TyG index as a reliable marker of IR, which may be one of the explanations for this association. IR is a risk factor for CVD, which not only causes CVD in the general population and patients with diabetes but can also be used to predict the cardiovascular prognosis of patients with CVD [24]. IR may contribute to the development of CVD through several mechanisms. First, IR can induce glucose and lipid metabolism disorders, which in turn trigger inflammation and oxidative stress [25]. Second, in the formed ischemic myocardium, decreased insulin activity limits glucose bioavailability and leads to a shift in fatty acid metabolism, ultimately leading to increased myocardial oxygen consumption and a decrease in non-infarcted myocardial compensatory capacity [26]. In

addition, studies have shown that IR can increase the production of glycosylation products and free radicals, leading to nitric oxide (NO) inactivation. Abnormal IR-related NO secretion destroys the vascular endothelium, causing endothelium-dependent vasodilation [27]. Moreover, in the state of insulin resistance, the inhibitory function of insulin on hormone-sensitive lipase (HSL) in adipocytes is impaired, leading to an increase in the flux of free fatty acids (FFAs) from the visceral fat depot. The increased FFAs flow from adipose tissue to non—adipose tissues, promoting the liver to synthesize moreTGs and VLDLs. Meanwhile, this flow of FFAs causes tissue damage through lipotoxicity, which is characteristic of insulin resistance syndrome and type 2 diabetes, and may play a crucial role in the progression from normal glucose tolerance to fasting hyperglycemia [28]. In our study, we observed that the TyG index remains significantly associated with vulnerable plaques, even in patients receiving lipid-lowering or diabetes treatments. While this finding suggests a potential link between the TyG index and residual cardiovascular risk, it is important to consider that our results are preliminary and should be interpreted with caution. The association between the TyG index and vulnerable plaques may indicate that standard treatments have not fully addressed all cardiovascular risk factors, such as IR and lipid-related abnormalities. Additionally, long-term metabolic disturbances may continue to impact cardiovascular health over time, even though treatments may have alleviated the current metabolic burden. Further research is needed to validate these findings and determine the clinical significance of the TyG index in this context.

The effect of the TyG index on the characteristics of coronary plaques

This study comprehensively evaluated the impact of the TyG index on the characteristics of coronary artery plaques, especially high-risk plaques and vulnerable plaques. First, patients with a higher TyG index have fewer calcified plaques and more mixed plaques and noncalcified plaques. Compared with calcified plaques, mixed plaques and noncalcified plaques are more unstable and are closely associated with an increased risk of adverse cardiovascular events [29].

Second, after adjusting for confounding factors, the TyG index was an independent predictor for the prevalence of vulnerable plaques, which have diverse imaging features. And our results showed that the TyG index affects mainly low-density plaques,positive remodelling and the “napkin ring” sign. A randomized controlled trial revealed that high-risk plaque features were significantly associated with the occurrence of ACS. The presence of high-risk plaque characteristics is significantly associated with an increased risk of ACS [30]. The SCOT-HEART trial, with a 5-year follow-up of 1769 patients, revealed that low-attenuation plaque burden serves as the strongest independent predictor of myocardial infarction. This association remained significant even after adjusting for cardiovascular risk scores, coronary artery calcium scores, or the degree of coronary stenosis [31]. Previously, it was generally believed that ACS is caused by the rupture of small-volume plaques, but recent data suggest that plaques expand relatively rapidly before the occurrence of ACS and plaque progression is a necessary step between early atherosclerosis and the cardiovascular event [32]. Patients with large plaque burdens or high-risk features (such as low attenuation and positive vessel remodelling) are more likely to progress [33, 34]. In patients with progressing plaques, the incidence of further coronary artery events is much higher, at approximately 15–20% at 12 months, than the < 1% reported in patients without progression [12, 35]. These data suggest that identifying and preventing plaque progression and the formation of vulnerable plaques in the early stages of the disease can significantly reduce the risk of CAD events. The association between the TyG index and vulnerable plaques in our study suggests that for T2DM patients with a high TyG index, early intervention may reduce the incidence of cardiovascular events.

Most acute coronary events are caused by sudden luminal thrombosis due to plaque rupture, which is characterized by a necrotic core covered with a thin fibrous cap [36]. However, a significant proportion of ACS events also occur on the basis of plaque erosion rather than plaque rupture [37]. The treatment strategies and prognoses for ACS differ because of different pathological mechanisms. Plaque rupture is often associated with ST-elevation MI (STEMI) manifestations in ACS patients, whereas plaque erosion is more common in patients with non-ST-elevation MI (NSTEMI) [38]. In addition, patients whose culprit is plaque rupture have a worse prognosis than those whose culprit is plaque erosion [38]. The high-risk plaque features and vulnerable plaques discussed in this study are indicative of large necrotic cores and thin fibrous caps, which are more likely to cause plaque rupture, suggesting a poor prognosis.

The TyG index was associated with vulnerable plaques in old and symptomatic CVD patients with T2DM

Our study suggested that the TyG index was associated with vulnerable plaques in the elderly population but was not significantly associated with vulnerable plaques in young individuals. Yang et al. reported that the TyG index was associated with major adverse cardiac and cerebrovascular events (MACCEs) in the elderly population, which is consistent with our study findings. One possible explanation is that physiological functions decline with age, increasing the susceptibility of older individuals to

multiple metabolic disorders [39]. This process is often accompanied by IR, which in turn exacerbates metabolic disorders, ultimately leading to pathological and physiological changes such as endothelial dysfunction, inflammation, and platelet hyperactivity, thereby increasing the risk of cardiovascular disease [39]. Moreover, several recent studies have confirmed that with advancing age, blood vessels become more prone to endothelial dysfunction, characterized by reduced vasodilation and antithrombotic properties, along with increased oxidative stress and inflammatory cytokines. These alterations collectively promote atherosclerosis and thrombus formation, thereby elevating the risk of developing CVD [40].Our research also indicated that the TyG index was independently associated with vulnerable plaques in patients with symptomatic CVD, but not in asymptomatic individuals. This association may be explained by the fact that T2DM patients with symptomatic cardiovascular disease often exhibit more severe metabolic disturbances, which predispose them to the development of vulnerable plaques and increase their risk of ACS. While our study focused on Chinese T2DM population, the TyG index's applicability to non-Asian populations and non-diabetic individuals warrants consideration. Ethnic variations in insulin resistance and plaque characteristics may influence its predictive value. However, the TyG index has been validated in diverse populations, including non-Asian cohorts and non-diabetic patients with metabolic syndrome, as a marker of cardiovascular risk [41, 42]. Moreover, a recent meta-analysis of 50 cohorts has shown that the association between the TyG index and MACEs as well as cardiovascular mortality does not vary based on the presence or absence of diabetes [43]. For non-diabetic individuals, particularly those with metabolic abnormalities, the TyG index may remain relevant due to its reflection of insulin resistance and dyslipidemia. Further studies are needed to confirm its utility across broader ethnic and clinical populations, including non-diabetic patients with varying metabolic and cardiovascular profiles.

Limitations

This study has several limitations that warrant consideration. First, as a retrospective, single-center study, it is susceptible to potential confounding factors that might not be adequately addressed, alongside a degree of selection bias. As such, the findings of this study should be interpreted with caution and need validation through prospective, multicenter trials. Second, the cross-sectional nature of this study limits our ability to establish causality between the observed variables. Future longitudinal studies are necessary to further elucidate the long-term impact of the TyG index on plaque vulnerability and to confirm the causal relationships suggested by our findings.

Conclusion

The TyG index is independently associated with vulnerable plaques of the coronary artery among patients with T2DM. Subgroup analysis revealed that the ability of the TyG index to predict vulnerable plaques varies with age and the prevalence of CVD symptoms. The TyG index might be regarded as a marker to reduce the incidence of cardiovascular events in the targeted population of T2DM patients.

Abbreviations

TyG index	Triglyceride glucose index
T2DM	Type 2 diabetes mellitus
ACS	Acute coronary syndrome
MVD	Multivessel disease
CVD	Cardiovascular disease
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
SIS	Segment involvement score
SSS	Segment stenosis score
LM	Left main
RCA	Right coronary artery
LAD	Left anterior descending
LCX	Left circumflex
CVD	Cardiovascular disease
ACS	Acute coronary syndrome
SBP	Systolic blood presure
DBP	Distolic blood pressure
BMI	Body mass index
LDL-C	Low-density protein cholesterol
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
CysC	Cystatin C
MACCEs	Major adverse cardiac and cerebrovascular events
GEE	Generalised estimating equations
NO	Nitric oxide
HSL	Hormone-sensitive lipase
FFAs	Fatty acids
STEMI	ST-elevation MI
NSTEMI	Non-ST-elevation MI

Author contributions

YSZ designed the study. YSZ and RS interpreted the data and wrote the manuscript. YSZ analysed the data, and RS provided advice on data presentation. YNJ, WFY and YG were responsible for collecting and sorting the statistical data. ZGY researched the data and reviewed the manuscript. YL supervised the overall study and reviewed the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Biomedical Research Ethics Committee of our hospital. Informed consent was waived because of the retrospective nature of the research. The patient-sensitive data were protected with full confidentiality.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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