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Association of non-insulin-dependent insulin resistance indices with lower limb artery restenosis after drug-coated balloon angioplasty

Zhentao Qiao[1*†], Yuansong Zhuang[2†] and Zhiwei Wang[1]

Abstract

Background This study aimed to investigate the associations between noninsulin-dependent insulin resistance indices (NI-IRIs), including the triglyceride-glucose (TyG) index, TyG-BMI, triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), and metabolic score for insulin resistance (METS-IR), as well as the occurrence of restenosis in patients with lower extremity atherosclerotic occlusive disease after drug-coated balloon (DCB) treatment.

Methods The primary endpoint was restenosis within one year after the procedure, which was defined as ≥ 50% stenosis of the treated artery segment. The association between NI-IRIs and restenosis was assessed via multivariable logistic regression analysis. Restricted cubic spline (RCS) analysis was performed to quantify nonlinearity. The consistency of these associations was confirmed through subgroup and interaction analyses. Additionally, the additional predictive value of NI-IRIs beyond established risk factors for restenosis was evaluated via receiver operating characteristic (ROC) curves, the net reclassification improvement (NRI), and integrated discrimination improvement (IDI) indices.

Results Except for the TyG index, the other three NI-IRIs demonstrated nonlinear relationships with the probability of postoperative restenosis. Specifically, TG/HDL-C (inflection point: 1.48, P for nonlinearity: 0.003) exhibited a saturating effect, whereas METS-IR (inflection point: 49.30, P for nonlinearity: 0.017) and TyG-BMI (inflection point: 221.53, P for nonlinearity: 0.039) showed threshold effects. Subgroup analysis revealed that the interactions among the subgroups were not statistically significant. Furthermore, among the four NI-IRIs, the addition of the TG/HDL-C index significantly enhanced the predictive power of the base model for restenosis in ASO patients following DCB angioplasty (AUC values: 0.726 vs. 0.760, $P = 0.042$). The P values for the NRI and IDI were 0.001 and 0.002, respectively.

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Conclusion TG/HDL-C showed a saturating effect on restenosis within one year after DCB treatment in ASO patients, and METS-IR and TyG-BMI showed threshold effects. The addition of the TG/HDL-C index significantly improved the predictive ability of the base model for restenosis in ASO patients who underwent DCB angioplasty.

Keywords Insulin resistance, Atherosclerotic occlusive disease, Drug-coated balloon, Restenosis, Retrospective study

Background

Atherosclerosis encompasses a wide range of cardiovascular diseases and is the leading cause of death and disability worldwide [1, 2]. Arterial sclerosis obliterans (ASO), a common form of atherosclerotic vascular disease, is characterized by thickening of the intima-media in the arteries that supply blood to the lower limbs, leading to lumen narrowing or even occlusion. This results in inadequate blood supply, causing symptoms such as intermittent claudication, numbness, reduced skin temperature, and pain. In severe cases, ulceration or necrosis may develop, significantly impairing patients' quality of life and prognosis [3–5]. Current treatment strategies for ASO include medication, interventional therapies, and surgery. Interventional therapy, which involves procedures such as stent implantation and balloon dilation, alleviates ischaemic symptoms by restoring blood flow. However, prior studies have reported restenosis rates as high as 33% within six months of treating femoropopliteal artery disease via standard balloon dilation [6]. Drug-coated balloons (DCBs) were developed to reduce restenosis by delivering antiproliferative agents directly to the vessel wall. Despite this advancement, some patients still experience restenosis after DCB treatment [7], highlighting the need for further research into the long-term effects of DCB therapy and the underlying mechanisms of postoperative restenosis.

Insulin resistance (IR), characterized by reduced sensitivity to insulin and diminished glucose uptake and utilization, plays a central role in various metabolic disorders, including diabetes, obesity, and metabolic syndrome [8]. IR is strongly linked to the onset and progression of peripheral artery disease (PAD), likely through mechanisms such as increased inflammation, oxidative stress, and impaired endothelial function, all of which exacerbate atherosclerosis and increase the risk of PAD [9, 10]. Although the hyperinsulinaemic-normoglycaemic clamp and intravenous glucose tolerance test are considered the gold standards for assessing IR, these methods are limited by their complexity and cost [11]. In contrast, noninsulin-based insulin resistance indices (NI-IRIs), including the triglyceride-glucose index (TyG), TyG-BMI, triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), and metabolic score for insulin resistance (METS-IR), provide simpler, more cost-effective alternatives that have shown accuracy and feasibility in assessing IR [12].

Although a relationship between IR and PAD has been established, few studies have explored the association between IR and restenosis in ASO patients treated with DCBs. This study aimed to investigate the association between NI-IRIs and restenosis in lower limb arteries after DCB treatment. These findings could help identify high-risk individuals for restenosis after DCB treatment, guiding the development of personalized treatment strategies to minimize restenosis risk and improve patient outcomes.

Methods

Study population

This study is an observational, single-centre, retrospective cohort study. The inclusion criteria were as follows: (1) patients aged 18 years or older; (2) patients with first-time diagnosis of lower limb atherosclerotic occlusive disease treated with DCBs between January 2018 and June 2023 at the First Affiliated Hospital of Zhengzhou University; and (3) patients with lesions located in the femoral or popliteal arteries. The exclusion criteria were as follows: (1) patients with lower extremity arterial stenosis resulting from nonatherosclerotic causes, such as immune or inflammatory conditions; (2) patients with incomplete or missing medical records or follow-up data; (3) patients requiring remedial stent implantation during the procedure; (4) patients with haemorrhagic or coagulation disorders; (5) patients with severe parenchymal organ dysfunction; (6) patients with no infrapopliteal outflow tracts; (7) patients who underwent endoluminal volume reduction techniques during the procedure; and (8) a history of malignancy. A total of 533 eligible ASO patients were enrolled in this study. The restenosis group included patients who developed restenosis or occlusion within one year after DCB treatment ($N=121$), whereas the patency group consisted of 242 patients without restenosis or occlusion, selected at a 1:2 ratio on the basis of sex, age group (<60 years or ≥60 years), and smoking and alcohol consumption history. The patient selection process is shown in Fig. 1. More information about patient selection can be found in the supplementary materials.

Data collection

Data for all patients were retrospectively collected from electronic medical records, including (1) demographic information such as age, sex, height, weight, body mass index (BMI), and smoking and alcohol consumption

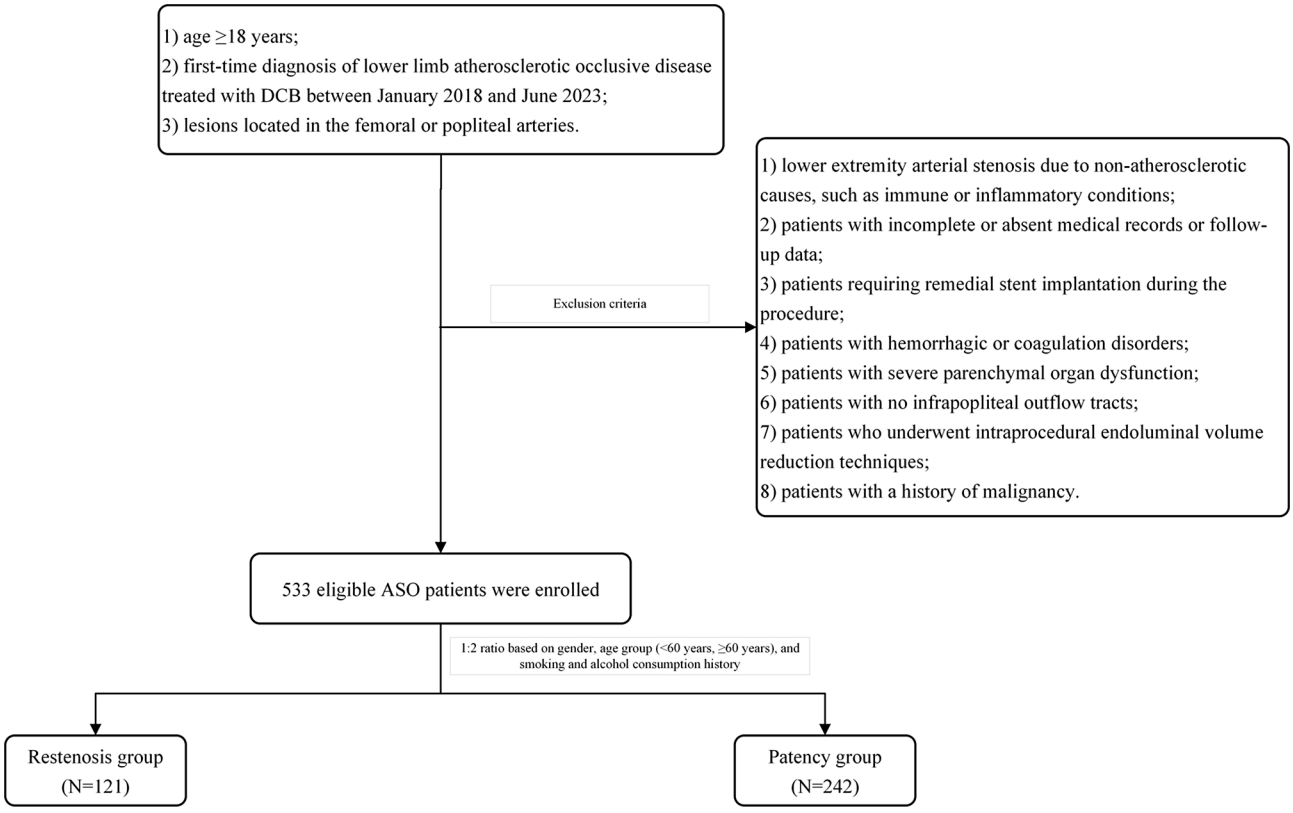

Fig. 1 Flowchart for the selection of patients

history; (2) medical history, including hypertension, diabetes, coronary heart disease, and stroke; (3) lesion characteristics, including transatlantic intersociety consensus (TASC) II classification and distal outflow assessment; (4) imaging data, specifically pre- and post-balloon dilatation computed tomography angiography (CTA) or digital subtraction angiography (DSA) of the lower limb arteries; (5) postoperative medication regimens; and (6) laboratory test results, including complete blood count, fasting blood glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), creatinine, uric acid, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). All biochemical parameters were measured via standardized methods at the Central Laboratory of the First Affiliated Hospital of Zhengzhou University based on fasting blood samples collected before the DCB procedure.

Study endpoints

The primary endpoint of this study was restenosis within one year after the procedure, defined as ≥50% stenosis of the treated vessel segment as detected by computed tomography angiography (CTA) or digital subtraction angiography (DSA) during the one-year follow-up period.

Table 1 The definition of the four NI-IRIs

NI-IRI	Definition
TyG index	TyG = Ln (TG × FBG/2)
METS-IR index	METS-IR = Ln (2 × FPG + TG) × BMI / Ln (HDL-C)
TG/HDL-C ratio	TG/HDL-C = TG / HDL-C
TyG-BMI index	TyG-BMI = Ln (TG × FBG/2) × BMI

(BMI (kg/m^2): Body Mass Index; FBG (mg/dl): Fasting Blood Glucose; HDL-C (mg/dl): High-Density Lipoprotein Cholesterol; TG (mg/dl): Triglycerides; TyG index: Triglycerides and Glucose Index; TyG-BMI index: Triglycerides and Glucose Body Mass Index; TG/HDL-C ratio: Ratio of Triglycerides to High-Density Lipoprotein Cholesterol; METS-IR index: Metabolic Insulin Resistance Score)

Related definitions

1. The definitions for the NI-IRIs are shown in Table 1.
2. Details of procedure of percutaneous drug-coated balloons angioplasty can be found in the supplementary materials.
3. Chronic lower extremity ischemia-femoral popliteal arteriopathy TASC II subtypes are defined in Table S1.

Statistical analysis

All the statistical analyses were performed via R software (version 4.3.1). Continuous variables following a normal distribution are expressed as the means and standard deviations, and independent samples t tests were used

for group comparisons. Nonnormally distributed data are presented as medians and interquartile ranges, with group comparisons made via the Mann–Whitney U test. Categorical variables are reported as frequencies (%) and were compared via chi-square tests. Box plots were generated via the ggplot2 package (version 3.5.1) to visualize the distributions of different NI-IRIs between the two groups. To enhance comparability, the four NI-IRIs were standardized via Z scores. Variables with P values less than 0.1 from univariable logistic regression models were considered to correspond to covariable groups, and variance inflation factor (VIF) values were calculated to assess for multicollinearity among independent variables. Different covariables were adjusted sequentially to explore the associations between NI-IRIs and restenosis within one year after DCB treatment.

Furthermore, restricted cubic spline (RCS) plots were generated via the rms package (version 6.8-2) to explore potential linear or nonlinear associations between the four NI-IRIs and the probability of restenosis. Segmented logistic regression models were employed to evaluate the threshold effect between NI-IRIs and restenosis after DCB treatment. Subgroup analyses were conducted on the basis of sex, age, BMI, hypertension, diabetes, coronary artery disease, and stroke status, with interaction P values calculated. Receiver operating characteristic (ROC) curves were plotted via the pROC package (version 1.18.4), and the area under the curve (AUC) was calculated to assess the model's predictive accuracy. Additionally, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated via the PredictABEL package (version 1.2-4) to evaluate the incremental predictive value beyond established risk factors. All the statistical tests were two-tailed, with a P value < 0.05 considered statistically significant.

Research ethics

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. As the study was retrospective, the Ethics Committee waived the requirement for written informed consent (Ethics Approval Number: 2024-KY-1169-001). All procedures involving human participants adhered to the ethical standards of the Declaration of Helsinki.

Results

Demographic and laboratory data of the enrolled patients

Table 2 presents a detailed comparison of the demographic and laboratory characteristics between the restenosis and patency groups. The results revealed that compared with those in the patency group, patients who developed restenosis had significantly greater BMIs, blood glucose levels, and LDL-C ($P<0.05$). Conversely, ALT and AST levels were significantly lower in the restenosis group ($P<0.05$). In addition, the restenosis group presented a greater prevalence of coronary heart disease, diabetes, and stroke ($P<0.05$). Among the four NI-IRIs, METS-IR, TG/HDL-C, and TyG-BMI were significantly elevated in the restenosis group ($P<0.05$), whereas no significant difference in TyG index distribution was observed between the two groups ($P>0.05$). Regarding the distribution of NI-IRIs in the two groups, please refer to Fig. S1 in the supplementary materials. Other variables, including leukocytes, erythrocytes, platelets, albumin, total bilirubin, direct bilirubin, TC, TG, uric acid, HDL-C, eGFR, use of antihypertensive medications, use of diabetes medication, and TASC II classification of lesions, did not significantly differ between the groups ($P>0.05$).

Associations between NI-IRIs and restenosis after DCB angioplasty

Univariable logistic regression analysis was performed to assess the associations between each variable and restenosis following DCB angioplasty, and the results are presented in Table S2. Variables with a P value < 0.1 and those identified as potential clinical confounders were included in the adjusted models. These covariables were scrutinized for multicollinearity. All the VIF values were less than 2, indicating that there was no multicollinearity. These findings are presented in Table S3.

RCS analysis was used to further explore the relationship between NI-IRIs and restenosis risk. As presented in Fig. 2, the results demonstrated that, with the exception of the TyG index, the other NI-IRIs exhibited a nonlinear association with the likelihood of postoperative restenosis (P for nonlinearity < 0.05).

Multivariable logistic regression models were employed to investigate the association between TyG index and restenosis after DCB treatment, as detailed in Table 3. After adjusting for all covariables (Model 3), we found that TyG index (OR: 1.17, 95% CI: 0.93–1.49, $P=0.186$) were no significantly associated with restenosis after DCB angioplasty.

Segmented logistic regression models were used to assess the differential effects before and after the inflection points of the RCS curves, as shown in Table 4. A significant threshold effect was observed for the METS-IR and TyG-BMI, indicating that when the METS-IR was below 49.30 or the TyG-BMI was below 221.53, no significant association with restenosis was found. However, when the METS-IR reached 49.30 or higher or the TyG-BMI reached 221.53 or higher, the risk of postoperative restenosis increased by 74% (OR: 1.74, 95% CI: 1.18–2.91, $P=0.012$) and 68% (OR: 1.68, 95% CI: 1.22–1.94, $P=0.024$), respectively, per increase in the standard deviation. In contrast, TG/HDL-C showed a saturation effect. When the TG/HDL-C ratio was less than 1.48, the

Table 2 Demographic and laboratory test data results of enrolled patients

Characteristic	Overall ($n=363$)	Patency group ($n=242$)	Restenosis group ($n=121$)	*P* value
Sex (%)				1.000
Male	219 (60.3)	146 (60.3)	73 (60.3)	
Female	144 (39.7)	96 (39.7)	48 (39.7)	
Age (year)	62.6 ± 10.5	62.3 ± 10.6	63.3 ± 10.2	0.373
BMI (Kg/m^2)	23.6 ± 4.2	23.3 ± 3.8	24.2 ± 4.9	0.028
Smoking (%)				1.000
No	210 (57.9)	140 (57.9)	70 (57.9)	
Yes	153 (42.1)	102 (42.1)	51 (42.1)	
Alcohol (%)				1.000
No	219 (60.3)	146 (60.3)	73 (60.3)	
Yes	144 (39.7)	96 (39.7)	48 (39.7)	
Leukocyte (10^9/L)	6.4 (5.4, 7.7)	6.3 (5.4, 7.7)	6.4 (5.6, 7.7)	0.509
Erythrocyte (10^9/L)	4.3 (4.0, 4.6)	4.3 (4.0, 4.6)	4.3 (4.0, 4.7)	0.310
Platelet (10^9/L)	212.5 (173.0, 258.2)	213.0 (171.8, 259.0)	212.0 (174.5, 245.8)	0.743
ALT (U/L)	18.0 (12.0, 41.0)	21.0 (12.0, 41.0)	17.0 (12.0, 30.0)	0.032
AST (U/L)	20.0 (16.0, 31.0)	20.0 (16.0, 31.0)	19.0 (13.5, 31.0)	0.037
ALB (g/L)	42.1 (39.5, 44.2)	42.0 (39.0, 44.2)	42.1 (40.0, 44.2)	0.703
Total bilirubin (μmol/L)	8.8 ± 4.1	8.9 ± 3.6	8.6 ± 4.9	0.487
Direct bilirubin (μmol/L)	4.1 ± 2.1	4.2 ± 1.9	4.0 ± 2.4	0.336
TC (mmol/L)	3.6 (2.9, 4.4)	3.6 (2.9, 4.4)	3.6 (2.8, 4.3)	0.397
TG (mmol/L)	1.5 (1.0, 2.1)	1.5 (1.0, 2.1)	1.5 (1.0, 2.0)	0.654
Glucose(mmol/L)	7.1 (5.7, 9.1)	7.0 (5.7, 8.8)	7.6 (6.0, 10.2)	0.013
UA (mmol/L)	285.0 (237.0, 346.0)	279.0 (227.8, 343.0)	292.0 (253.0, 351.0)	0.062
HDL-C (mmol/L)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.1)	0.210
LDL-C (mmol/L)	2.6 (1.7, 3.0)	2.3 (1.6, 3.0)	2.9 (1.9, 3.1)	0.003
eGFR (ml/min/1.73m^2)	96.0 (85.9, 103.7)	97.1 (86.2, 104.4)	95.0 (84.4, 103.0)	0.151
TyG	9.1 (8.7, 9.5)	9.0 (8.6, 9.5)	9.1 (8.7, 9.5)	0.143
METS-IR	47.2 (41.7, 55.1)	46.8 (41.5, 53.7)	49.3 (42.2, 59.3)	0.008
TG/HDL	1.6 (1.0, 2.5)	1.4 (0.9, 2.4)	1.8 (1.3, 2.7)	< 0.001
TyG-BMI	210.9 (193.1, 246.5)	204.4 (185.5, 232.4)	215.5 (202.0, 268.6)	0.004
Hypertension (%)				0.546
No	149 (41.0)	102 (42.1)	47 (38.8)	
Yes	214 (59.0)	140 (57.9)	74 (61.2)	
Diabetes (%)				0.001
No	170 (46.8)	128 (52.9)	42 (34.7)	
Yes	193 (53.2)	114 (47.1)	79 (65.3)	
Coronary heart disease (%)				< 0.001
No	287 (79.1)	208 (86)	79 (65.3)	
Yes	76 (20.9)	34 (14)	42 (34.7)	
Stroke (%)				< 0.001
No	256 (70.5)	187 (77.3)	69 (57)	
Yes	107 (29.5)	55 (22.7)	52 (43)	
Antihypertensive medications (%)				0.546
No	149 (41.0)	102 (42.1)	47 (38.8)	
Yes	214 (59.0)	140 (57.9)	74 (61.2)	
Diabetes medication (%)				0.603
No	181 (49.9)	123 (50.8)	58 (47.9)	
Yes	182 (50.1)	119 (49.2)	63 (52.1)	
TASCII classification				0.444
A	90 (24.8)	58 (24)	32 (26.4)	
B	141 (38.8)	93 (38.4)	48 (39.7)	

Table 2 (continued)

Characteristic	Overall (*n* = 363)	Patency group (*n* = 242)	Restenosis group (*n* = 121)	*P* value
C	102 (28.1)	67 (27.7)	35 (28.9)	
D	30 (8.3)	24 (9.9)	6 (5)	

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALB: albumin, TC: total cholesterol, TG: triglycerides, UA: uric acid, eGFR: estimated glomerular filtration rate, TASC II: the TransAtlantic Inter-Society Consensus II

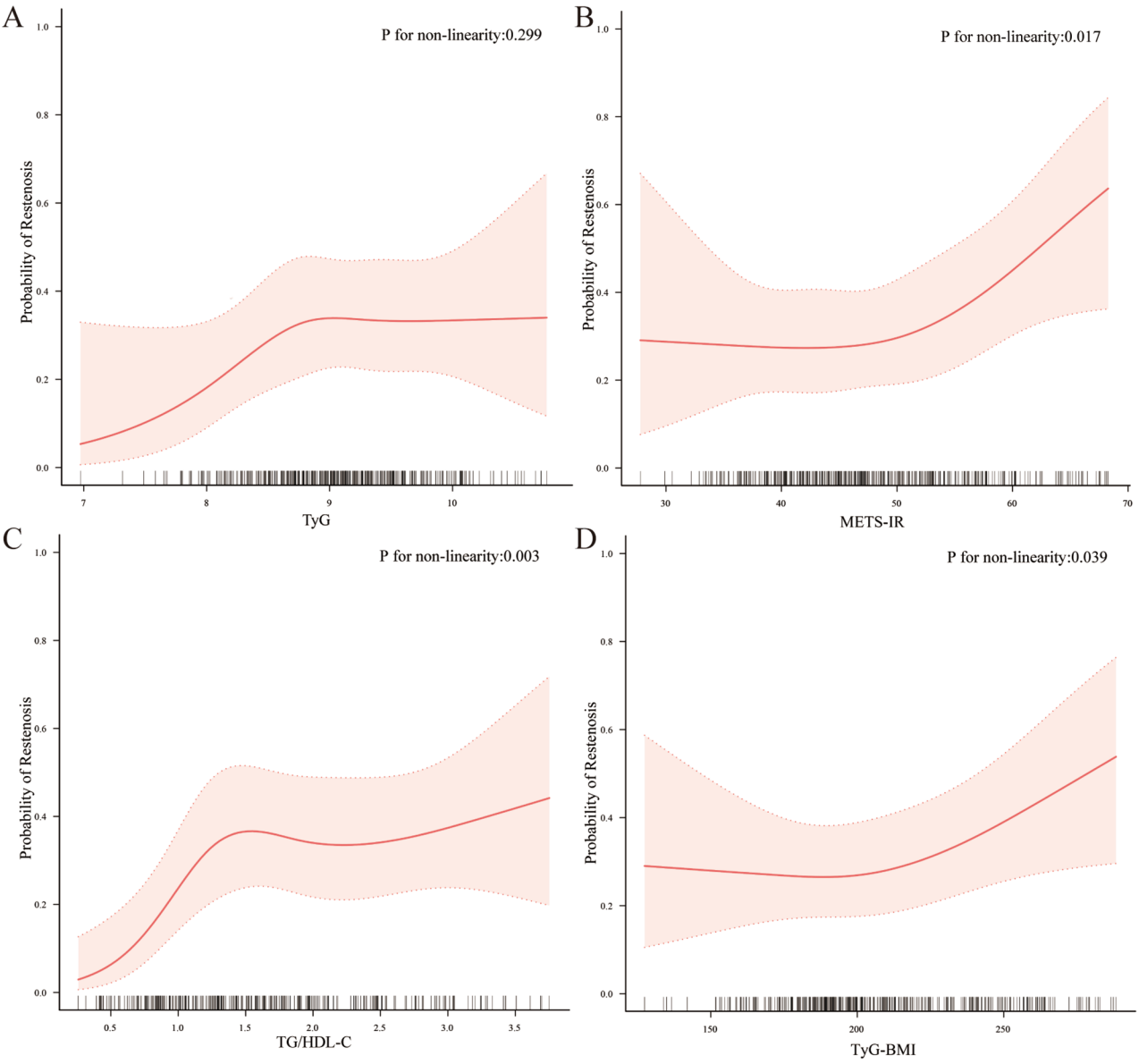

Fig. 2 Restricted cubic spline curves for the four IR Indices. (The curves have been adjusted for age, hypertension, diabetes, coronary artery disease, stroke, leukocyte, erythrocyte, platelet, uric acid, AST, albumin, total bilirubin, eGFR, and TASC II classification. The solid red line represents the probability of restenosis occurrence, while the red shaded area indicates the 95% confidence interval for restenosis probability)

risk of postoperative restenosis increased by 113% per 1 standard deviation increase (OR: 2.13, 95% CI: 1.24–3.02; P=0.014). However, at TG/HDL-C levels of 1.48 or above, its association with restenosis after DCB angioplasty in ASO patients was no longer significant.

Subgroup analyses

Subgroup analyses of the four NI-IRIs were stratified by sex, age, BMI, hypertension, diabetes, coronary artery disease, and stroke (Figs. 3, 4, 5 and 6). No significant association between the TyG index and restenosis was

Table 3 Results of multivariable logistic regression

Characteristic	Model 1		Model 2		Model 3	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
TyG	1.14 (0.94–1.39)	0.185	1.16 (0.94–1.43)	0.169	1.17 (0.93–1.49)	0.186

Model 1: no adjustment; Model 2: adjusted for age, hypertension, diabetes, coronary artery disease, and stroke; Model 3: further adjusted for leukocytes, erythrocyte, platelet, uric acid, aspartate aminotransferase, albumin, total bilirubin, estimated glomerular filtration rate, and TASC II fractionation, on the basis of Model 2

Table 4 Threshold analysis results

Characteristic	OR (95%CI)	*P* Value	*P* for LRT
METS-IR			0.015
METS-IR < 49.30	0.91 (0.27–3.08)	0.789	
METS-IR ≥ 49.30	1.74 (1.18–2.91)	0.012	
TG/HDL-C			0.039
TG/HDL-C < 1.48	2.13 (1.24–3.02)	0.014	
TG/HDL-C ≥ 1.48	1.04 (0.67–1.61)	0.858	
TyG-BMI			0.044
TyG-BMI < 221.53	1.18 (0.78–1.76)	0.871	
TyG-BMI ≥ 221.53	1.68 (1.22–1.94)	0.024	

The segmented regression model was also adjusted for age, hypertension, diabetes, coronary artery disease, stroke, leukocyte, erythrocyte, platelet, uric acid, AST, albumin, total bilirubin, eGFR, and TASC II classification. P for LRT refers to the likelihood ratio test

observed in any subgroup. In contrast, METS-IR was significantly associated with restenosis in patients with hypertension, coronary artery disease, no diabetes, and no history of stroke. TG/HDL-C was significantly associated with restenosis across all subgroups except those aged < 60 years and patients with coronary artery disease. The TyG-BMI was significantly associated with restenosis in patients aged ≥ 60 years, those with hypertension, nondiabetic patients, and those without stroke. Importantly, no significant interaction was found between any of the insulin resistance indices and restenosis across subgroups.

Incremental effect of NI-IRIs on the predictive value of base risk factors

To evaluate the incremental impact of the four IR-related indices on the predictive performance of classical restenosis risk models, we constructed a base model incorporating variables such as sex, smoking, hypertension, diabetes mellitus, coronary artery disease, stroke, age, and lesion site, based on previous literature [6, 7, 13, 14]. The results of the ROC analysis revealed that the AUC of the base model was 0.726 (95% CI: 0.673–0.775).

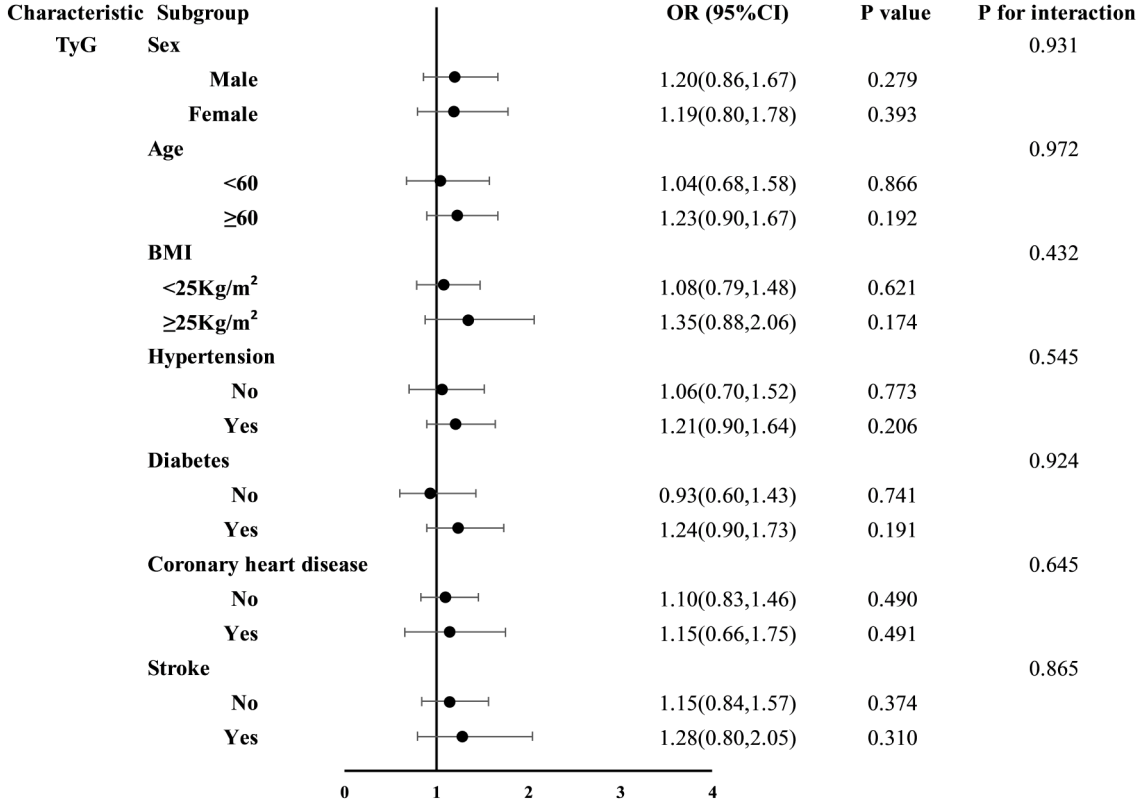

Fig. 3 Subgroup analysis results of the TyG index

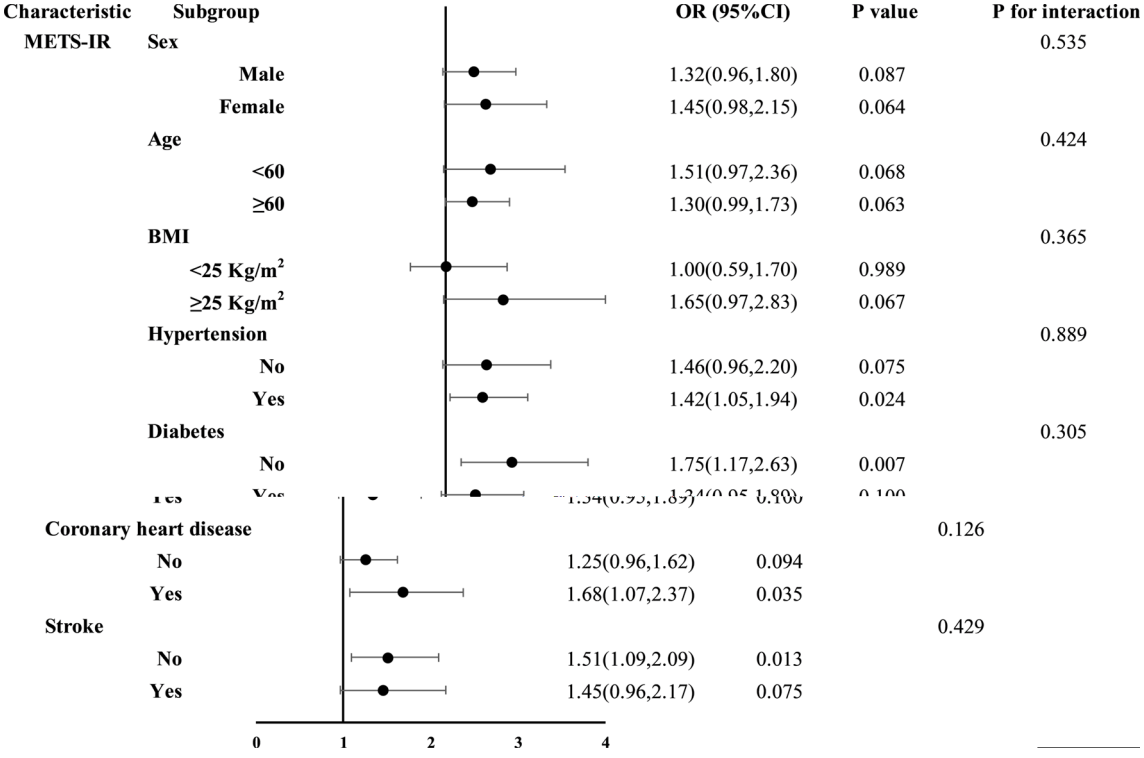

Fig. 4 Subgroup analysis results of the METS-IR

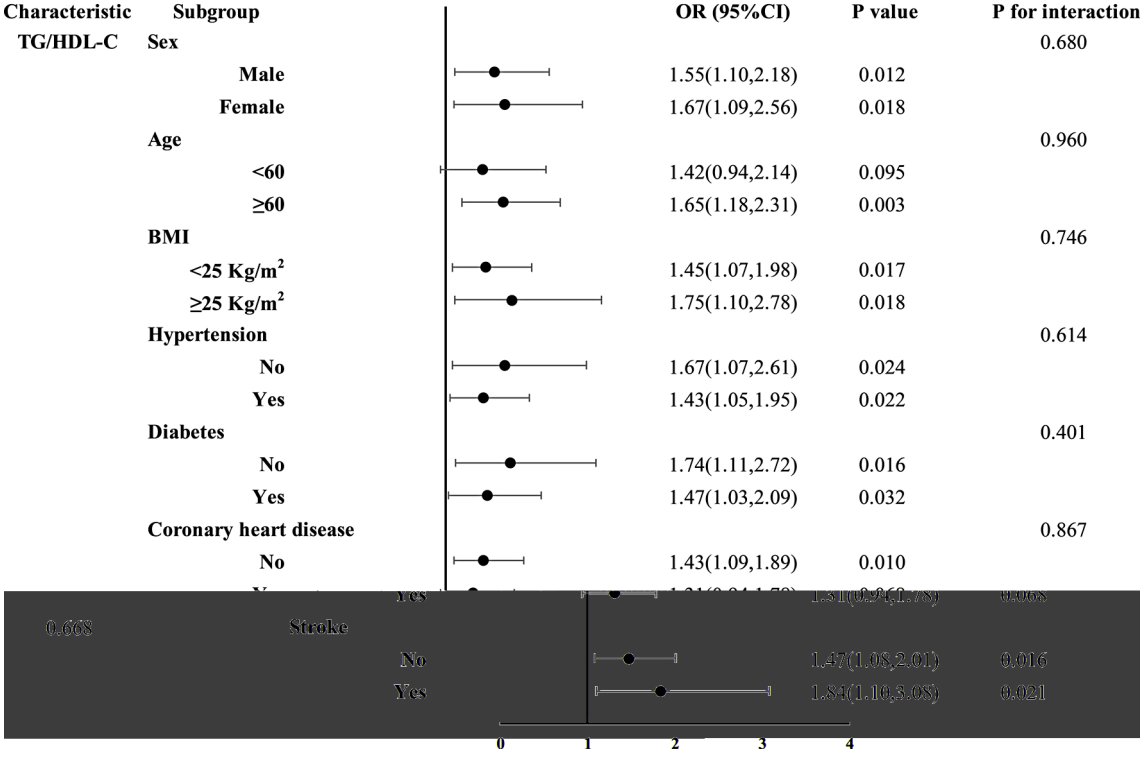

Fig. 5 Subgroup analysis results of the TG/HDL-C

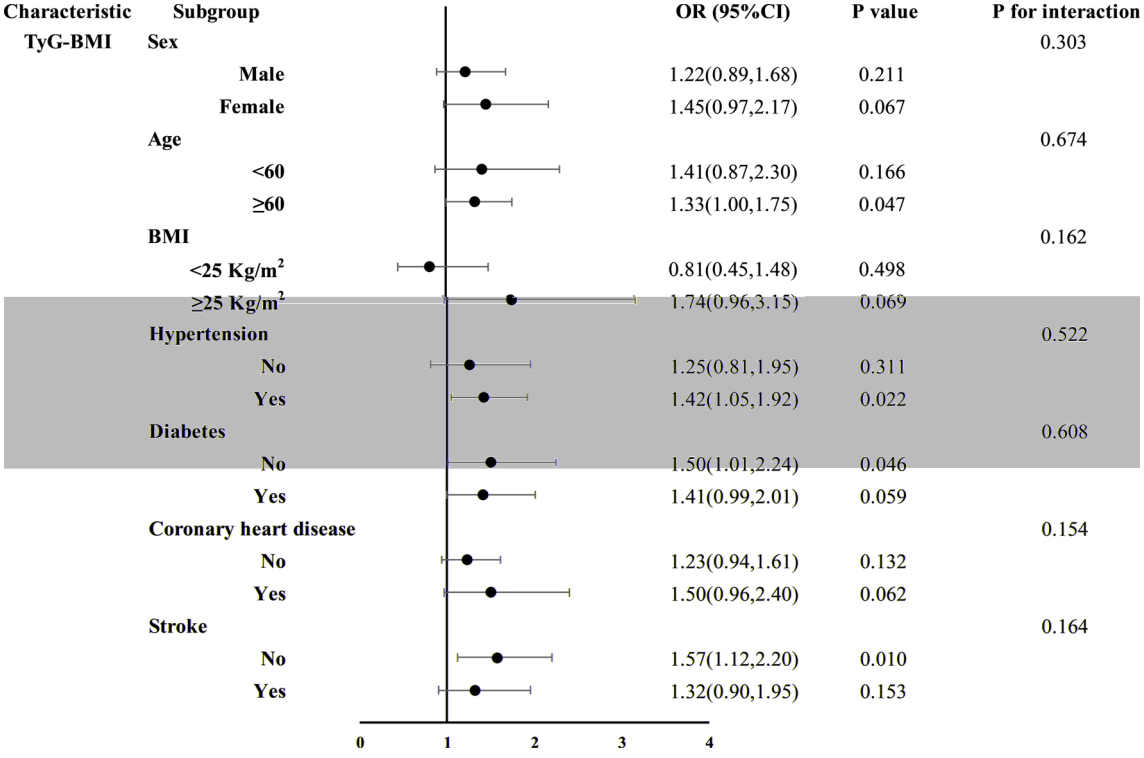

Fig. 6 Subgroup analysis results of the TyG-BMI index

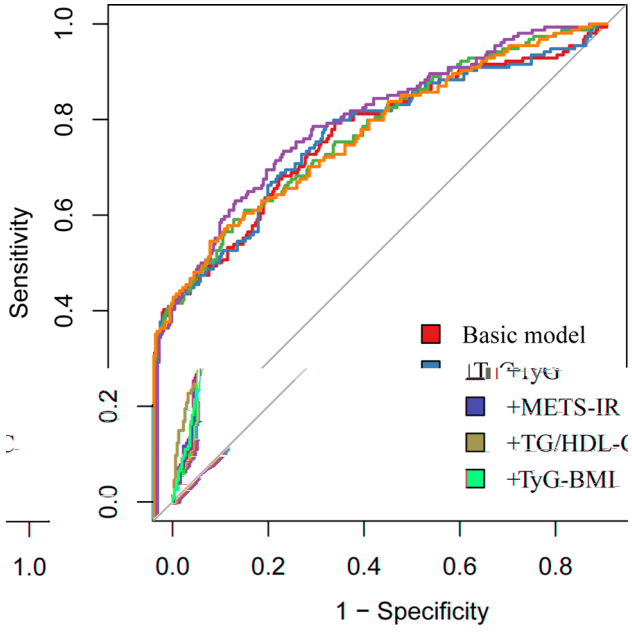

Fig. 7 ROC analysis of the basic model and IR indices. The basic model includes age, sex, smoking, hypertension, diabetes, coronary artery disease, stroke, and lesion site

We subsequently introduced different IR parameters to construct the composite model and observed its ability to predict postoperative restenosis. Figure 7; Table 5 display the ROC curves and related statistics of the different models. Among the four indices, the TG/HDL-C index significantly enhanced the predictive ability of the base model for restenosis following DCB angioplasty in ASO patients (AUC: 0.726 vs. 0.760, P=0.042). The P values for the NDI and IDI were 0.001 and 0.002, respectively, which indicated that the addition of the TG/HDL-C index significantly improved the base model after the addition of the TG/HDL-C index.

Discussion

Despite the widespread impact of atherosclerosis, PAD often receives less attention than coronary heart disease and stroke do. Specific vascular interventions, such as DCB angioplasty, and their impact on restenosis in lower limb arteries are under-researched. This study was designed to address these gaps by comprehensively assessing the relationship between four NI-IRIs and restenosis after DCB angioplasty in patients with ASO. The findings of this study provide valuable evidence for risk stratification in postoperative restenosis, potentially shaping follow-up strategies for ASO patients undergoing DCB treatment.

The application of NI-IRIs in vascular diseases

In insulin-resistant patients, normal plasma insulin levels fail to adequately suppress glucose production, reduce lipolysis, promote glucose uptake, and increase glycogen synthesis [15]. In the early stages of IR, triglycerides

Table 5 Postoperative restenosis risk prediction model performance analysis

Model	AUC (95%CI)	*P* value	NDI (95%CI)	*P* value	IDI (95%CI)	*P* value
Basic model	0.726(0.673–0.775)	Ref.	Ref.	Ref.	Ref.	Ref.
+ TyG	0.728(0.677–0.779)	0.453	0.151(-0.041-0.343)	0.124	0.024(-0.008-0.039)	0.063
+METS-IR	0.734(0.682–0.782)	0.476	0.182(-0.009-0.373)	0.062	0.027(0.010–0.043)	0.002
+TG/HDL-C	0.760(0.712–0.806)	0.042	0.422 (0.233–0.612)	0.001	0.035(0.016–0.054)	0.002
+TyG-BMI	0.731(0.683–0.780)	0.554	0.164(-0.028-0.356)	0.094	0.024(0.008–0.040)	0.003

stored in adipose tissue are released as free fatty acids into the bloodstream through lipolysis before an increase in plasma glucose levels occurs [16]. As early as thirty years ago, Reaven and others demonstrated that IR promotes de novo lipogenesis, leading to elevated triglyceride levels even in nonhypertriglyceridemic and nonobese populations [17]. On the basis of these mechanisms, the TyG index was proposed as a simple marker of IR. Numerous large-scale prospective cohort studies have confirmed a strong association between the TyG index and hypertension [18–20]. A meta-analysis suggested that the TyG index could be a reliable predictor of hypertension in the general population [21]. Additionally, studies by Ding and colleagues revealed that a higher TyG index is associated with an increased risk of ASCVD in individuals without a prior history of ASCVD [22]. Liu et al. reported that the TyG index is an independent predictor of peripheral artery disease complexity [23]. Park and Lee also reported associations between the TyG index, arterial stiffness, and coronary artery calcification in Korean adults [24, 25]. Gökalp et al. confirmed that a high TyG index is an independent risk factor for mitral annular calcification [26].

The TyG-BMI index, a combination of the TyG index and BMI, was recently introduced as a novel surrogate for insulin resistance. In an early study, Er and colleagues demonstrated that the TyG-BMI was superior to lipid parameters, glucose measures, and obesity-related metrics in reflecting insulin resistance [27]. Research has further confirmed its association with various metabolic disorders, reinforcing its association with insulin resistance [28–30]. Several studies have explored the relationship between the TyG-BMI and vascular diseases. For example, Zeng et al. reported a strong positive association between the TyG-BMI and blood pressure levels in a cross-sectional study of Chinese adults [31]. Similarly, Du and colleagues reported that the TyG-BMI is linearly and independently related to the incidence of ischaemic stroke in the general population [32].

METS-IR, introduced by Bello et al. in 2018, combines fasting blood glucose, triglycerides, HDL-C, and BMI, and has demonstrated high accuracy in detecting insulin resistance, with an AUC of 0.84 (95% CI: 0.78–0.90) [33]. Previous large studies have established strong associations between METS-IR and hypertension, coronary artery calcification, and ischaemic heart disease [34–37]. A retrospective study of 15,453 Japanese subjects revealed a significant positive correlation between METS-IR and the prevalence of prehypertension or hypertension [34]. Wang et al. further noted that in asymptomatic adults without a history of cardiovascular disease, METS-IR was a better predictor of coronary artery calcification than other insulin resistance indices [37]. METS-IR has also been shown to reliably predict the severity of coronary heart disease, and in a large longitudinal cohort study of nondiabetic Korean adults, higher METS-IR levels were significantly associated with an increased risk of ischaemic heart disease [38].

The TG/HDL-C ratio is a well-established marker of IR, and its elevation has been linked to an increased risk of PAD. In a large cohort of hypertensive patients, Ding et al. reported that each one-standard-deviation increase in the TG/HDL-C ratio was associated with a 14% increase in PAD risk [39].In the Atherosclerosis Risk in Communities (ARIC) study, higher TG levels combined with lower HDL-C levels were independently associated with PAD incidence [40].Other cross-sectional and longitudinal studies further support the strong association between the TG/HDL-C ratio and PAD risk [41]. Among the diabetic patients, PAD patients had significantly higher TG/HDL-C ratios than the controls did, suggesting that this ratio could aid in early PAD identification [42]. Moreover, the TG/HDL-C ratio has been proven to predict the complexity of PAD, offering new insights into clinical assessment and management [43].

Mechanism of IR in vascular restenosis

Previous research has demonstrated that IR significantly increases the risk of atherosclerotic cardiovascular diseases [44, 45]. The hyperglycaemic state induced by IR impairs vascular endothelial function, reduces vascular dilation capacity, and increases the risk of restenosis [46–48]. Intravascular ultrasound studies in nondiabetic coronary heart disease patients revealed that those with impaired glucose tolerance exhibited greater intimal hyperplasia after stent implantation than did patients with normal glucose tolerance [49]. Additionally, Piatti and colleagues reported that IR was prominent in coronary artery disease patients who experienced restenosis after stent surgery [50]. Babalik and others measured insulin levels one day before coronary stent implantation, and the results revealed that in nondiabetic patients,

hyperinsulinaemia was a strong predictor of restenosis at the six-month follow-up after stent surgery [51]. However, research on the role of insulin resistance in restenosis following DCB treatment remains scarce. Some previous studies have confirmed that DCBs are noninferior to first-generation drug-eluting stents (DESs) in treating coronary small vessel disease [52, 53]. A meta-analysis of DCBs in de novo coronary lesions in diabetic patients revealed that DCBs did not demonstrate a potential benefit over DESs in reducing vascular restenosis (OR: 0.42, 95% CI: 0.09–1.92; $p=0.26$) [54]. Regarding arterial type, insulin resistance also plays a significant role in restenosis of the carotid artery. Mark et al. reported that patients with elevated perioperative fasting glucose had significantly less resolution of restenosis at five years compared with those with normal fasting glucose [55]. Zhao et al. reported that an elevated preoperative TyG index was associated with a significantly increased risk of restenosis after carotid stent implantation [56].

The underlying mechanisms of these phenomena may involve IR stimulating the proliferation and migration of vascular smooth muscle cells through hyperinsulinaemia, enhancing lipoprotein metabolism, and promoting vascular disease [57]. Furthermore, elevated insulin levels increase sympathetic nerve activity and cardiac output, leading to hypertension and vascular damage [58]. The body's reduced response to insulin also hampers fat metabolism, increasing blood lipid concentrations. Hyperlipidaemia damages arterial endothelial function, increases platelet aggregation, and enhances inflammation, all of which contribute to the occurrence of vascular restenosis after surgery [15].

Nonlinear associations between IR indices and vascular restenosis

This study revealed a significant nonlinear association between insulin resistance indices and vascular restenosis. The threshold effect observed with METS-IR indicated that when the METS-IR value was below 48.10, the association with restenosis risk was not significant. However, when the value exceeded this threshold, the risk increased significantly. Based on the calculation of METS-IR, individuals below the threshold are generally lean, where insulin resistance plays a weaker role, resulting in a lower risk of restenosis [59]. In contrast, individuals above the threshold are more likely to be obese, and insulin resistance becomes more pronounced, thereby increasing the risk of restenosis. The TyG-BMI index, which is determined by a combination of the TyG score and BMI, offers a comprehensive assessment of insulin resistance. The threshold effect of the TyG-BMI may be due to the amplifying impact of obesity on insulin resistance. Obesity, an inflammatory state, exacerbates insulin resistance and accelerates the development of vascular disease [59]. When the TyG-BMI is less than 219.32, the adverse effects of obesity may not be sufficient to significantly increase the risk of restenosis. However, when it exceeds this threshold, the combined impact of obesity and insulin resistance results in substantial vascular damage and an elevated risk of restenosis. The saturation effect observed with the TG/HDL-C ratio may be due to the role of dyslipidaemia in vascular endothelial dysfunction [60]. At lower TG/HDL-C levels, dyslipidaemia promotes atherosclerosis by increasing oxidative stress, inflammation, and endothelial dysfunction. However, when TG/HDL-C exceeds 1.42, these effects may reach a biological saturation point, beyond which further increases in dyslipidaemia contribute minimally to restenosis risk.

The TG/HDL-C ratio is a strong predictor of restenosis

In this study, compared with the other three IR indices, the inclusion of the TG/HDL-C index in the basic vascular restenosis model yielded the greatest incremental predictive value for restenosis events after DCB angioplasty. Several factors may explain this finding: (1) The TG/HDL-C ratio is closely related to insulin resistance, which is itself associated with the development and progression of PAD, increasing the risk of restenosis. (2) Previous studies have shown that a high TG/HDL-C ratio reflects a relatively high load of atherogenic particles, closely linked to the total number of LDL particles and small LDL particles. Differences in LDL subcategories may explain the residual cardiovascular risk and unique lipoprotein characteristics of PAD patients [61–63]. (3) Small LDL particles possess greater atherogenic properties, are more likely to penetrate the arterial intima, and exhibit longer circulation times with lower LDL receptor affinity, promoting atherosclerosis and restenosis formation [62, 64]. (4) HDL-C is considered antiatherosclerotic. A higher TG/HDL-C ratio may indicate a decrease in large, mature HDL particles, which are crucial for reversing cholesterol transport and reducing atherosclerosis [65]. (5) The TG/HDL-C ratio is also associated with non-HDL cholesterol, a collective marker for all atherogenic lipoproteins and a strong predictor of atherosclerotic vascular diseases [66].

In subgroup analyses, the TG/HDL-C ratio showed a meaningful association with most subgroups, although the association was not statistically significant in patients under 60 years of age or those with CHD. However, in these subgroups, the trend remained evident ($P<0.1$). Among younger patients, the lack of a significant association may be due to confounding biological or lifestyle factors. Younger patients generally have higher metabolic rates, greater physical activity, and better disease management adaptability, which may influence their relationship with restenosis [67]. In patients with coronary

heart disease, various factors, such as myocardial infarction history, coronary artery disease severity, and medication use, could mask the direct association between TG/HDL-C and restenosis risk [68]. Nevertheless, the observed trend suggests that even in patients with coronary heart disease, TG/HDL-C may still have predictive value. Compared with other IR indices, TG/HDL-C consistently showed a significant association with restenosis in most subgroups, indicating its broader clinical applicability. The simplicity, cost-effectiveness, and direct relationship with lipid metabolism make TG/HDL-C an ideal indicator for use in diverse clinical settings.

Conclusion

The TG/HDL-C showed a saturating effect on restenosis within one year after DCB treatment in ASO patients, and METS-IR and TyG-BMI showed threshold effects. Compared with other IR indices, the TG/HDL-C index demonstrated a stable association with postoperative restenosis. The inclusion of the TG/HDL-C index significantly enhanced the predictive performance of the base model for restenosis in ASO patients who underwent DCB angioplasty.

Strengths and limitations

This study has several notable strengths. First, to our knowledge, this is the first study to investigate the relationship between noninsulin-dependent insulin resistance indices and restenosis following DCB angioplasty in lower limb arteries. These findings may have significant implications for the secondary prevention and postoperative management of restenosis in ASO patients. Second, the inclusion of the TG/HDL-C ratio significantly improved the predictive performance of traditional restenosis risk models. Given the ease of obtaining TG and HDL-C levels and their cost-effectiveness, the results of this study have the potential to enhance the scoring systems used by specialists for routine preoperative assessments of postoperative restenosis risk.

However, there are several limitations of this study that should not be overlooked. First, we acknowledge limitations due to the small sample size and the relatively short follow-up period. Future studies with larger sample sizes and longer follow-up durations are warranted to thoroughly elucidate the association between IR and restenosis following DCB procedures. Second, as a retrospective study, we were unable to control for the type of antiproliferative drugs carried by the DCBs or the technical proficiency of the surgeons, both of which may influence long-term outcomes and the occurrence of restenosis. Third, we only measured the values of various indices at a single time point, leaving the relationship between the longitudinal changes in these parameters and clinical outcomes unknown. Additionally, the study was conducted at a single centre, and given the potential differences in ethnicity, diet, and physical activity, these results should be validated in multicentre studies. Finally, as an observational study, there may be potential confounding factors that were not fully accounted for, which could affect the interpretation of the findings.

Abbreviations

ASO	Arterial sclerosis obliterans
DCB	Drug-coated balloon
IR	Insulin resistance
PAD	Peripheral artery disease
NI-IRIs	Non-insulin dependent insulin resistance indices
TyG	Triglyceride-glucose index
BMI	Body mass index
TG/HDL-C	Triglyceride-to-high-density lipoprotein cholesterol ratio
METS-IR	Metabolic score for insulin resistance
TASC	Transatlantic inter-society consensus
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
FBG	Fasting blood glucose
VIF	Variance inflation factor
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
AUC	Area under the curve
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
ARIC	Atherosclerosis risk in communities

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

Z.Q. and Y.Z. defined the study theme and methods, performed the data collection, data analyses and wrote the original manuscript. Z.W. checked the data. Z.Q., Y.Z. and Z.W. contributed to interpreted the results. All authors made critical revision of the manuscript for important intellectual content and approved the final manuscript.

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Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Ethics Approval Number: 2024-KY-1169-001).

Consent for publication
All authors have consent for publication.

Competing interests
The authors declare no competing interests.

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