Surrogate markers of insulin resistance and coronary artery disease in type 2 diabetes: U-shaped TyG association and insights from machine learning integration

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Abstract

Background Surrogate insulin resistance (IR) indices are simpler and more practical alternatives to insulin-based IR indicators for clinical use. This study explored the association between surrogate IR indices, including triglyceride-glucose index (TyG), triglyceride glucose-body mass index (TyG-BMI), triglyceride glucose-waist circumference (TyG-WC), triglyceride glucose-waist to height ratio (TyG-WHtR), metabolic score for insulin resistance (METS-IR), and the triglycerides/high-density lipoprotein cholesterol (TG/HDL-C) ratio, and coronary artery disease (CAD) in patients with type 2 diabetes (T2D).

Methods Patients with T2D were enrolled in this study and divided into two groups, matched for age and diabetes duration: those with CAD and those without CAD. The association between surrogate IR indices and CAD was evaluated using restricted cubic spline (RCS) and multivariable logistic regression and their discriminative ability was assessed via Receiver operating characteristic (ROC) curve analysis. Additionally, machine learning models, including Logistic Regression, Random Forest, eXtreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), and Support Vector Machine (SVM), were employed to predict CAD presence using multiple surrogate IR indices and their components.

Results All surrogate IR indices exhibited non-linear associations with CAD. TyG demonstrated a U-shaped relationship, where both extremely low and high levels were associated with higher odds of CAD compared to intermediate levels. The surrogate IR indices showed a relatively strong discriminative ability for CAD, with AUC values exceeding 0.708 across all indices. The TG/HDL-C ratio displayed the highest AUC (0.721), accuracy (68%), and sensitivity (71%), whereas TyG-WC showed the highest specificity (78%). Machine learning algorithms (except logistic regression) demonstrated greater discriminative power than individual IR indices. Random forest and XGBoost revealed the best performance when using either multiple surrogate IR indices or their components.

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Conclusions Surrogate IR indices could be used as valuable tools for evaluating cardiometabolic risk in patients with T2D, who are at high risk for CAD. Integrating machine learning models further improved CAD prediction, underscoring their potential for better risk stratification. The observed association between these indices and CAD in T2D may help clarify the complex pathophysiology of CAD and offer insights for future research.

Keywords Insulin resistance, Triglyceride-glucose index, Coronary artery disease, Diabetes mellitus, Lipids, Machine learning

Introduction

Diabetes is often accompanied by several cardiovascular risk factors, including hypertension, dyslipidemia, and obesity [1–6]. Patients with diabetes have a 2 to 4 times higher risk of developing coronary artery disease (CAD) compared to non-diabetics [7]. In addition, the clinical presentation of CAD in people with diabetes is milder and atypical, with an estimated 20–60% of patients with diabetes having asymptomatic CAD [8, 9]. The high prevalence of silent CAD in diabetes highlights the need for early prediction and appropriate screening to improve prognosis [9, 10]. Various non-invasive tests, such as functional tests for myocardial ischemia, coronary artery calcium (CAC) scans, and coronary computed tomography angiography (CTA), are employed to assess the presence and severity of CAD [11]. However, using these screening tests in asymptomatic individuals requires careful evaluation, considering their prognostic value, impact on treatment and outcomes, cost-effectiveness, and risks such as high radiation exposure [10, 12].

Insulin resistance (IR) is associated with the presence of CAD in individuals with diabetes [13]. Various methods are used to assess IR, including direct measures such as the hyperinsulinemic euglycemic glucose clamp and insulin-suppression test (IST), indirect measures such as the minimal model analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT) and the oral glucose tolerance test (OGTT), and surrogate IR indices [14]. While direct and indirect methods are difficult, time-consuming, and require specialized expertise, surrogate indices provide a more practical and accessible alternative for clinical use [15]. Moreover, given that many patients with diabetes are prescribed insulin, using insulin-based indicators may not be suitable for this population [16].

Earlier studies have investigated the association between surrogate IR indices and CAD in the general population. A meta-analysis found that higher triglyceride-glucose (TyG) index levels are linked to an increased risk of CAD, and TyG can aid in managing patients with CAD [17]. Yang et al. reported a linear relationship between triglyceride glucose-body mass index (TyG-BMI) and CAD severity in female patients with acute coronary syndromes [18]. In addition, a longitudinal study showed that metabolic score for insulin resistance (METS-IR) predicts ischemic heart disease (IHD)

in individuals without diabetes [19]. Furthermore, the triglycerides/high-density lipoprotein cholesterol (TG/HDL-C) ratio is significantly associated with CAD-related outcomes in both the general population and individuals with established CAD [20].

The association between surrogate IR indices and CAD in individuals with diabetes has been evaluated in a limited number of studies, with a primary focus on TyG [21, 22]. Additionally, the comparative advantage of these indices in predicting CAD in individuals with diabetes has yet to be determined. Clarifying these associations could provide valuable data for identifying a more accessible tool for screening CAD in diabetes. This study aimed to investigate the association of TyG, TyG-BMI, triglyceride glucose-waist to height ratio (TyG-WHtR), triglyceride glucose-waist circumference (TyG-WC), METS-IR, and TG/HDL-C ratio with CAD in patients with type 2 diabetes (T2D).

Methods

Study design

Individuals with T2D who were referred to the diabetes clinic of a tertiary hospital affiliated with Tehran University of Medical Sciences were enrolled in this study. Participants were divided into two groups based on CAD status, matched by age and duration of diabetes. Individuals were excluded if they had malignancies, thyroid disease, liver cirrhosis, pregnancy, smoked, or used antioxidant supplements or oral contraceptives. Participants were homogenous, had a middle to high school education level, and were mostly from the middle class of socio-economic status. The study population had access to medical care facilities and insurance coverage. The participants followed a regular diet and engaged in routine physical activity. The research ethics committee of Tehran University of Medical Sciences approved this study. All participants provided written informed consent before participating, and the study adhered to the declaration of Helsinki.

Data collection

Demographic characteristics of the study population, such as age, diabetes duration, and gender, were gathered. Additionally, a complete medical history, including acute or chronic diseases, diabetes complications, and medications, was taken. Well-trained nurses assessed weight,

height, waist circumference (WC), and blood pressure. Weight was measured to the nearest 0.1 kg using a digital scale (Tefal PP1100), with participants in light clothing and barefoot. Height and WC were measured using non-elastic tapes with an accuracy of 0.1 cm. Height was measured with the participant standing upright with their feet together. The WC was considered at the midpoint between the lower rib cage and the iliac crest [23]. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). The waist-to-height ratio (WHtR) was determined by dividing waist circumference (cm) by height (cm). After resting for at least 3–5 min while seated without talking or moving around, participants were asked to place their right hand on a surface at the level of the fourth intercostal space with their palms facing upwards and their back supported [24]. Blood pressure (BP), including systolic and diastolic measurements, was taken twice, ten minutes apart, and the median value was recorded. Measurements were only conducted if participants had avoided caffeine, exercise, and smoking for at least 30 min before admission [24]. A calibrated digital sphygmomanometer (Omron M7, Hoofddorp, The Netherlands) was used to assess BP.

Venous blood samples were collected from each individual after 12 h of fasting (only water was allowed) to measure fasting blood sugar (FBS), serum creatinine, hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). 2-hour postprandial blood glucose (2hpp) was analyzed from specimens collected two hours after the beginning of an adequate breakfast. FBS and 2hpp were measured using the glucose oxidase method with the Parsazmun auto-analyzer (BT-3000 (plus), Biotechnica). TC, TG, LDL-C, HDL-C, and creatinine were quantified using enzymatic techniques with the Parsazmun auto-analyzer (BT-3000 (plus), Biotechnica). HbA1c was measured via high-performance liquid chromatography (HPLC) using the DS5 analyzer (Drew, England). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [25]. Non-high-density lipoprotein cholesterol (non-HDL-C) was determined by subtracting HDL-C from TC.

Indices formulas

$TyG = Ln(TG \text{ (mg/dL)} \times FBS \text{ (mg/dL)})/2$
$TyG\text{-}BMI = TyG \times BMI \text{ (kg/m}^2)$
$TyG\text{-}WC = TyG \times WC \text{ (cm)}$
$TyG\text{-}WHtR = TyG \times WHtR$
$METS\text{-}IR = Ln\ [(2 \times FBS \text{ (mg/dL)}) + TG \text{ (mg/dL)}] \times BMI \text{ (kg/m}^2))/(Ln\ [HDL\text{-}C \text{ (mg/dL)}])$
$TG/HDL\text{-}C \text{ ratio} = TG \text{ (mg/dL)}/HDL\text{-}C \text{ (mg/dL)}$

Definitions

Diabetes was determined according to the American Diabetes Association (ADA) criteria as follows: FBS ≥ 126 mg/dL, 2hpp ≥ 200 mg/dL, or HbA1c ≥ 6.5% [26]. Hypertension was defined as BP ≥ 130/80 mmHg or being on antihypertensive therapy [27]. CAD was determined based on a positive medical history of myocardial infarction (MI), unstable angina, cardiac care unit admission, coronary revascularization procedures (percutaneous interventions or bypass graft surgery), or abnormal results of coronary angiography.

Medications

The study population was treated with oral anti-diabetic drugs (OADs), insulin, or a combination of both. Insulin glargine or NPH was used alongside mealtime insulin aspart or regular, respectively. Dyslipidemia medications included atorvastatin, rosuvastatin, and fibrates, with atorvastatin being the most commonly prescribed due to its availability and cost-effectiveness. The medication adherence among the study population was consistent. Several medications can impact surrogate IR indices by affecting glucose and lipid metabolism. For instance, insulin lowers blood glucose and suppresses lipolysis, leading to lower TG levels [28]. In addition, dyslipidemia drugs such as statins and fibrates reduce TG levels, a key component of the TyG [28]. To ensure reliable results, we have adjusted for these medications in the analysis.

Statistical analysis

Data analysis was performed using Python (version 3.12) along with libraries such as NumPy (1.26), Pandas (2.1.4), Matplotlib (3.8.1), Scikit-learn (1.4.0), SciPy (1.13.1), XGBoost (2.1.3), and Lightgbm (4.6.0), as well as SPSS (version 22.0, IBM Corporation, USA) [29–35]. To assess normality, the Kolmogorov-Smirnov test and visual inspections of P-P plots and histograms were used. Categorical variables were shown as frequencies and percentages. Continuous variables were presented as mean ± standard deviation (SD) or median (Q1–Q3). Student's t-test and Mann-Whitney U test were used for continuous variables, and the chi-squared test for categorical variables.

Restricted cubic spline (RCS) analysis with four knots at the 5th, 35th, 65th, and 95th percentiles was utilized to examine non-linear associations between CAD and surrogate IR indices, with the median of each index as the reference (odds ratio = 1).

To further examine the relationship between surrogate IR indices and CAD, multivariable logistic regression was performed. Each index was divided into quartiles, and the odds of having CAD were compared across quartiles, with the first quartile as the reference. This analysis began with an unadjusted model and was followed

by adjustments for confounding factors, including gender, hypertension, dyslipidemia drug, antihyperglycemic agents, LDL-C, systolic blood pressure, and BMI; variables that showed significant group differences and are well-established risk factors for CAD. The results were reported as odds ratios (ORs) with their 95% confidence intervals (CIs).

The predictive value of surrogate IR indices for CAD was assessed using a receiver operating characteristic (ROC) curve. The ROC curve analysis was adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, LDL-C, systolic blood pressure, and BMI. Cut-off values were determined based on the maximum Youden index. Statistical significance was defined as a *p*-value of less than 0.05.

Machine learning analysis

For data preprocessing, all variables were standardized to facilitate comparability. The data was subsequently divided into training and testing groups following a 70–30% split, assigning 70% of the data to the training group and 30% to the testing group. Five machine learning models, including Logistic Regression, Random Forest, eXtreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), and Support Vector Machine (SVM), were trained using the training subset, and their performance was assessed on the testing subset. Model performance was evaluated using the area under the curve (AUC) derived from ROC curves, reflecting each model's capability to distinguish between CAD and non-CAD cases. To evaluate potential multicollinearity among predictor variables, the variance inflation factor (VIF) was computed for each variable. Variables with a VIF exceeding 5 were eliminated from the analysis to reduce the risk of overfitting and enhance model stability.

To evaluate the robustness of the models, a 10-fold cross-validation was implemented. The dataset was partitioned into 10 subsets, with each subset acting as the test set one time, while the remaining 9 subsets were utilized for training. This procedure was repeated 10 times. In addition, hyperparameter tuning was conducted using the grid search embedded in the cross-validation process. A predefined set of hyperparameters was examined for each model to optimize performance. The AUC from the ROC curve was the primary performance metric. The mean and SD of AUC values across cross-validation folds were reported.

Results

Baseline characteristics

A total of 2702 patients with T2D were studied, comprising 1376 individuals with CAD and 1326 without CAD.

Table 1 presents the baseline characteristics of the study population, both overall and stratified by CAD status. Participants with CAD included a higher proportion of men, were more often hypertensive, and had higher WC and TG levels (all *p*-values < 0.001). Additionally, individuals with CAD showed higher systolic blood pressure (SBP) (*p*-value = 0.007), WHtR (*p*-value = 0.012), and BMI (*p*-value = 0.002) compared to those without CAD. TC, LDL-C, HDL-C, and non-HDL-C levels were higher among patients without CAD (all *p*-values < 0.001). Diastolic blood pressure (DBP), FBS, 2hpp, HbA1c, and eGFR did not significantly differ between the two groups (Table 1).

All surrogate IR indices, including TyG (4.98 vs. 5.05), TyG-BMI (139.98 vs. 144.73), TyG-WC (480.83 vs. 497.07), TyG-WHtR (2.98 vs. 3.05), METS-IR (45.29 vs. 47.60), and TG/HDL-C (2.79 vs. 3.44), were higher in patients with CAD compared to those without CAD (all *p*-values < 0.001) (Table 2).

Association between surrogate insulin resistance indices and CAD

In the RCS analysis, the association between surrogate IR indices and CAD in patients with T2D was assessed (Fig. 1). Four knots were applied at the 5th, 35th, 65th, and 95th percentile for each index distribution. The median of each distribution was used as the reference point, with its OR set to 1. The reference points for TyG, TyG-BMI, TyG-WC, TyG-WHtR, METS-IR, and TG/HDL-C were 4.99, 138.9, 485.9, 2.98, 45.50, and 3.13, respectively. Non-linear associations were observed between surrogate IR indices and CAD. The ORs with 95% CIs for the selected knots are provided in Table 3.

The findings indicate that as surrogate IR indices increased across percentiles, the odds of having CAD increased (Fig. 1). For TyG, the odds of CAD exhibited a U-shaped pattern. The ORs were higher than the reference point (TyG = 4.99) for values < 4.31. In the range of 4.31 < TyG < 4.99, the ORs of CAD were lower than the reference point, with the minimum OR observed at TyG = 4.56 (OR = 0.77, 95% CI:0.69–0.85). Beyond the reference point (TyG = 4.99), the ORs followed an increasing trend (Fig. 2).

Table 4 presents the odds ratios for CAD in patients with T2D across quartiles of each surrogate IR index, with the first quartile regarded as the reference. Results were adjusted for gender, hypertension, use of dyslipidemia drugs, antihyperglycemic agents, LDL-C, systolic blood pressure, and BMI. For all indices, the odds of CAD in patients with T2D increased significantly in the higher quartiles compared to the first quartile (Table 4).

Table 1 Baseline characteristics of the study population: patients with and without CAD

Variable		Total (N = 2702)	Patients without CAD (N = 1326)	Patients with CAD (N = 1376)	*P*-value
Age (years)		62.7 ± 9.3	62.6 ± 9.2	62.8 ± 9.4	-
Duration of Diabetes (years)		12 (6–20)	11 (6–18)	12 (6–20)	-
Gender	Men (N, %)	1380 (51.1%)	608 (45.9%)	772 (56.1%)	< 0.001
	Women (N, %)	1322 (48.9%)	718 (54.1%)	604 (43.9%)	
Hypertension (N, %)		1399 (51.8%)	573 (43.2%)	826 (60.0%)	< 0.001
SBP (mmHg)		132.4 ± 18.6	131.4 ± 17.9	133.3 ± 19.1	0.007
DBP (mmHg)		78.5 ± 9.7	78.7 ± 9.4	78.3 ± 10.0	0.186
WC (cm)		97.4 ± 10.2	96.4 ± 10.5	98.4 ± 9.8	< 0.001
WHtR		0.60 ± 0.07	0.59 ± 0.07	0.60 ± 0.06	0.012
BMI (kg/m^2)		28.3 ± 4.7	28.1 ± 4.7	28.6 ± 4.6	0.002
FBS (mg/dL)		170.9 ± 64.1	169.9 ± 63.0	171.9 ± 65.2	0.418
2hpp (mg/dL)		239.5 ± 91.9	237.9 ± 93.5	241.1 ± 90.4	0.359
HbA1c (%)		8.05 ± 1.72	8.01 ± 1.73	8.08 ± 1.70	0.252
eGFR (ml/min/1.73m^2)		73.9 ± 17.6	74.5 ± 17.2	73.4 ± 18.1	0.094
TG (mg/dL)		136 (100–192)	128 (96–180)	144 (106–206)	< 0.001
TC (mg/dL)		173.3 ± 44.3	181.2 ± 42.6	165.7 ± 44.6	< 0.001
LDL-C (mg/dL)		97.1 ± 34.3	103.3 ± 33.8	91.0 ± 33.6	< 0.001
HDL-C (mg/dL)		45.3 ± 11.7	47.3 ± 12.3	43.3 ± 10.7	< 0.001
Non-HDL-C (mg/dL)		128.0 ± 42.2	133.9 ± 40.6	122.4 ± 42.9	< 0.001
Medication					
Dyslipidemia drug N (%)	Atorvastatin	2359 (87.3%)	1227 (92.5%)	1132 (82.3%)	< 0.001
	Rosuvastatin	313 (11.6%)	92 (6.9%)	221 (16.1%)	
	Fibrates	30 (1.1%)	7 (0.5%)	23 (1.7%)	
Antihyperglycemic agents N (%)	Multiple Drug Therapy	1066 (39.5%)	431 (32.5%)	635 (46.1%)	< 0.001
	Insulin	16 (0.6%)	7 (0.5%)	9 (0.7%)	
	Metformin monotherapy	1436 (53.1%)	794 (59.9%)	642 (46.7%)	
	Any sulfonylurea	184 (6.8%)	94 (7.1%)	90 (6.5%)	

Data are presented as mean ± SD, median (Q1, Q3), or number (%)

CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; WHtR: waist-to-height ratio; BMI: body mass index; FBS: fasting blood sugar; 2hpp: 2-hour postprandial glucose; HbA1c: hemoglobin A1c; eGFR: estimated glomerular filtration rate; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol

Table 2 Comparison of surrogate insulin resistance indices by CAD status

Insulin resistance indices	Total	Patients without CAD	Patients with CAD	*P*-value
TyG	5.01 ± 0.33	4.98 ± 0.32	5.05 ± 0.34	< 0.001
TyG-BMI	142.40 ± 26.56	139.98 ± 25.86	144.73 ± 27.01	< 0.001
TyG-WC	489.10 ± 63.85	480.83 ± 63.32	497.07 ± 63.37	< 0.001
TyG-WHtR	3.02 ± 0.43	2.98 ± 0.42	3.05 ± 0.43	< 0.001
METS-IR	46.47 ± 8.77	45.29 ± 8.61	47.60 ± 8.78	< 0.001
TG/HDL-C	3.13 (2.16–4.71)	2.79 (1.98–4.17)	3.44 (2.41–5.27)	< 0.001

Data are presented as mean ± SD or median (Q1, Q3)

CAD: coronary artery disease; TyG: triglyceride–glucose index; TyG-BMI: triglyceride glucose-body mass index; TyG-WC: triglyceride glucose-waist circumference index; TyG-WHtR: triglyceride glucose-waist to height ratio index; METS-IR: metabolic score for insulin resistance; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol

Predictive performance of surrogate insulin resistance indices for CAD

The discriminative ability of surrogate IR indices for CAD in patients with T2D is presented in Fig. 3; Table 5. Using the maximum Youden index, optimal cut-off values for TyG, TyG-BMI, TyG-WC, TyG-WHtR, METS-IR, and TG/HDL-C were identified as 4.65, 113.94, 694.78, 2.78, 45.18, and 2.33, respectively. The AUC values for all indices ranged from 0.708 to 0.721 (all *p*-values < 0.001). Among these indices, TG/HDL-C demonstrated the highest AUC (0.721), accuracy (68%), and sensitivity (71%), while TyG-WC exhibited the highest specificity (78%). Detailed values for sensitivity, specificity, and AUC for each index are presented in Table 5.
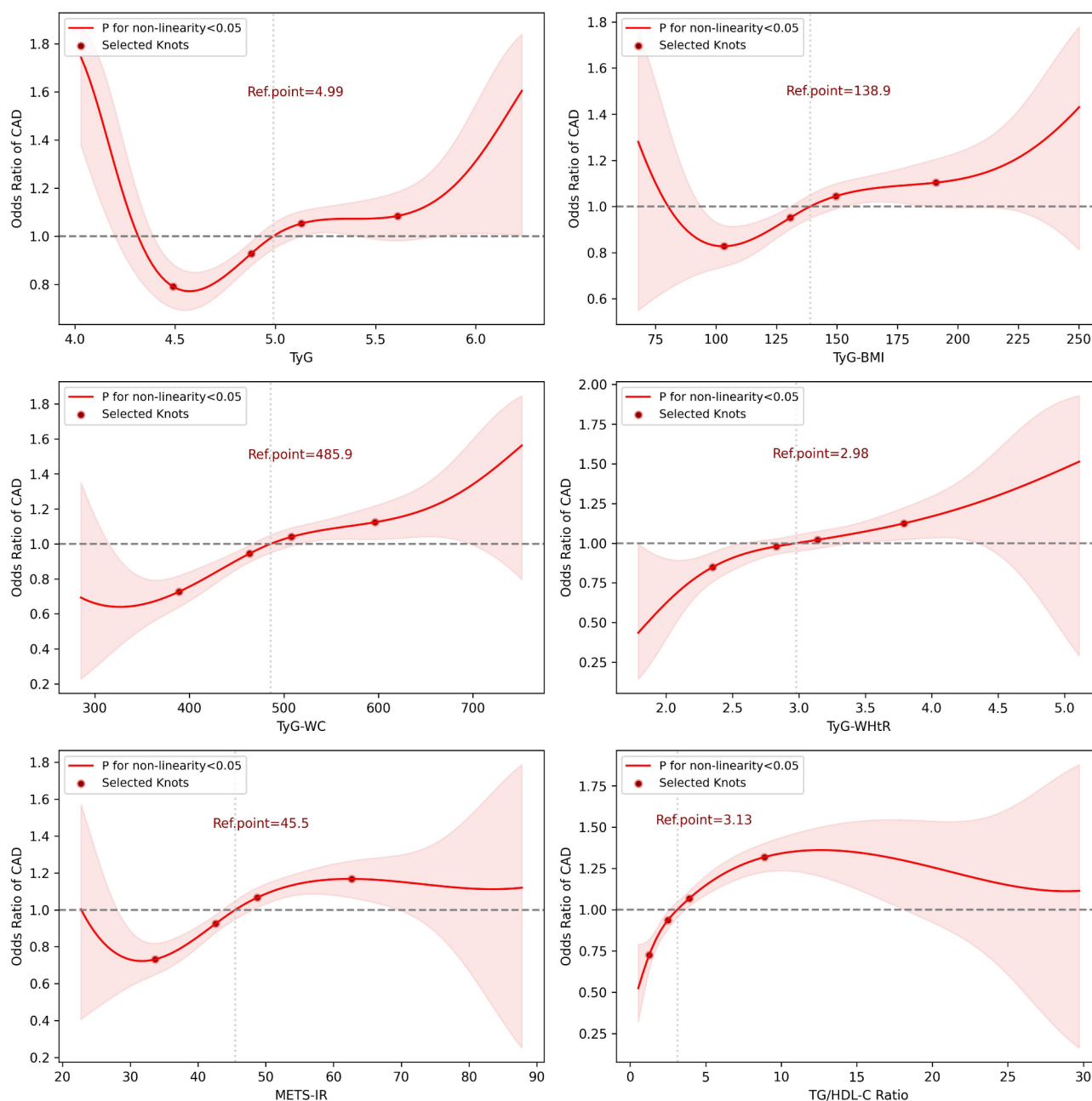
Fig. 1 Association between surrogate insulin resistance indices and CAD in patients with T2D: The RCS function employed four knots based on the distribution of each index (5th, 35th, 65th, 95th percentiles). The ORs for CAD were calculated relative to the median value of each index. CAD: coronary artery disease; T2D: type 2 diabetes; RCS: restricted cubic spline; OR: odds ratio; TyG: triglyceride-glucose index; TyG-BMI: triglyceride glucose-body mass; TyG-WC: triglyceride glucose-waist circumference; TyG-WHtR: triglyceride glucose-waist-to-height ratio; METS-IR: metabolic score for insulin resistance; TG/HDL: triglycerides/high-density lipoprotein cholesterol ratio

Performance of machine learning algorithms in discriminating CAD using surrogate insulin resistance indices

Five machine learning models, including logistic regression, random forest, XGBoost, LightGBM, and SVM, were employed to predict the presence of CAD using multiple surrogate IR indices such as TyG, TyG-WHtR, and the TG/HDL-C ratio (Fig. 4). Other IR indices (TyG-BMI, TyG-WC, and METS-IR) were excluded due to high multicollinearity. AUCs across the models ranged from 0.716 to 0.792. The ROC curves (Fig. 4) show that XGBoost had the highest AUC (0.792; 95% CI: 0.763–0.822), along with the highest sensitivity (79%), specificity (67%), and accuracy (73%). All models, except for logistic regression, demonstrated higher AUCs and greater potential for discriminating CAD compared to each

Table 3 Odds ratios for CAD at selected knots (5th, 35th, 65th, 95th percentiles) in the RCS analysis

Insulin resistance indices	Knots							
	5th percentile		35th percentile		65th percentile		95th percentile	
	Value	OR (95% CI)	Value	OR (95% CI)	Value	OR (95% CI)	Value	OR (95% CI)
TyG	4.49	0.72 (0.62, 0.83)	4.88	0.98 (0.90, 1.05)	5.13	1.01 (0.93, 1.07)	5.61	1.15 (1.03, 1.26)
TyG-BMI	103.3	0.81 (0.70, 0.92)	130.7	0.98 (0.91, 1.05)	149.6	1.03 (0.96, 1.10)	191.0	1.16 (1.03, 1.28)
TyG-WC	389.1	0.78 (0.67, 0.90)	463.7	0.97 (0.90, 1.04)	508.1	1.05 (0.98, 1.12)	596.3	1.19 (1.07, 1.30)
TyG-WHtR	2.35	0.79 (0.68, 0.91)	2.83	0.97 (0.90, 1.04)	3.14	1.02 (0.95, 1.09)	3.79	1.19 (1.04, 1.29)
METS-IR	33.69	0.78 (0.68, 0.89)	42.59	0.92 (0.85, 0.99)	48.76	1.11 (1.04, 1.17)	62.68	1.19 (1.06, 1.31)
TG/HDL-C	1.26	0.70 (0.59, 0.81)	2.50	0.91 (0.85, 0.97)	3.92	1.10 (1.04, 1.15)	8.89	1.21 (1.08, 1.33)

CAD: coronary artery disease; RCS: restricted cubic spline; OR: odds ratio; CI: confidence interval; TyG: triglyceride–glucose index; TyG-BMI: triglyceride glucose-body mass index; TyG-WC: triglyceride glucose-waist circumference index; TyG-WHtR: triglyceride glucose-waist to height ratio index; METS-IR: metabolic score for insulin resistance; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol
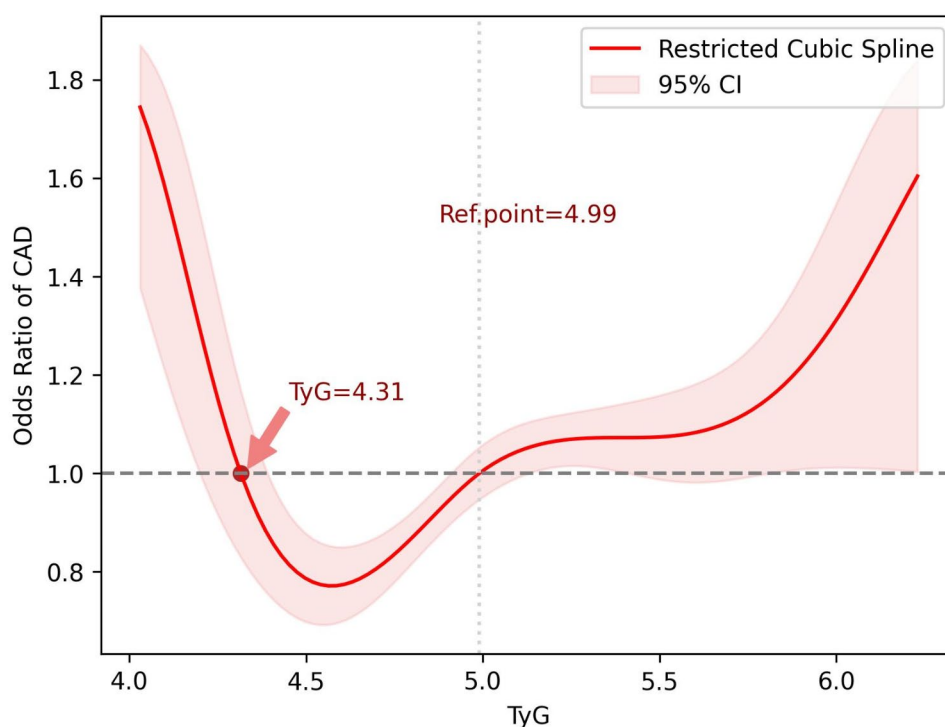
Fig. 2 U-shaped association between TyG and the odds of CAD in patients with T2D. TyG: triglyceride-glucose index; CAD: coronary artery disease; T2D: type 2 diabetes

individual IR index (Table 6). To evaluate the robustness of predictive models, a 10-fold cross-validation was conducted. The mean AUC values (±SD) across the folds were as follows: logistic regression: 0.699±0.028, random forest: 0.790±0.014, XGBoost: 0.787±0.014, LightGBM: 0.783±0.018, and SVM: 0.716±0.018. Random forest exhibited the highest mean AUC, followed by XGBoost, affirming their superior predictive capabilities among the evaluated models.

Furthermore, we incorporated the components used to calculate the surrogate IR indices, including TG, FBS, HDL-C, BMI, and WHtR, into the machine learning models to predict CAD (Fig. 5). Other components, such as WC, were excluded due to high multicollinearity.

Similar to the models based on the combination of surrogate IR indices, AUCs were higher than those for each individual surrogate IR index (except logistic regression), ranging from 0.734 to 0.791 (Table 6). The random forest model demonstrated the highest AUC (0.791; 95% CI: 0.763–0.819), along with the highest sensitivity (78%), specificity (67%), and accuracy (73%) (Fig. 5). To assess the robustness of our predictive models, we performed 10-fold cross-validation. The mean (±SD) AUC values across folds were as follows: logistic regression: 0.703±0.028, random forest: 0.788±0.015, XGBoost: 0.787±0.023, LightGBM: 0.785±0.018, and SVM: 0.716±0.017. Of all the models, random forest displayed the highest mean AUC, followed by XGBoost.

Table 4 Odds ratios for CAD in patients with T2D across quartiles of surrogate insulin resistance indices

Insulin resistance indices quartiles		OR (95% CI) [a]	
		Unadjusted	Adjusted
TyG	Q1	Ref	-
	Q2	1.38 (1.12–1.71)	1.49 (1.19–1.88)
	Q3	1.40 (1.13–1.73)	1.52 (1.20–1.91)
	Q4	1.77 (1.43–2.20)	2.06 (1.62–2.61)
TyG-BMI	Q1	Ref	-
	Q2	1.33 (1.08–1.65)	1.53 (1.11–2.11)
	Q3	1.36 (1.10–1.68)	1.78 (1.18–2.68)
	Q4	1.68 (1.35–2.08)	3.04 (1.83–5.06)
TyG-WC	Q1	Ref	-
	Q2	1.13 (0.91–1.40)	1.13 (0.88–1.44)
	Q3	1.56 (1.26–1.93)	1.51 (1.16–1.96)
	Q4	1.94 (1.56–2.41)	1.93 (1.43–2.62)
TyG-WHtR	Q1	Ref	-
	Q2	1.18 (0.96–1.47)	1.13 (0.87–1.45)
	Q3	1.02 (0.83–1.27)	1.06 (0.80–1.40)
	Q4	1.60 (1.29–1.98)	1.77 (1.28–2.45)
METS-IR	Q1	Ref	-
	Q2	1.24 (0.99–1.53)	1.43 (1.07–1.91)
	Q3	1.63 (1.31–2.02)	2.27 (1.61–3.20)
	Q4	2.13 (1.71–2.65)	3.78 (2.48–5.76)
TG/HDL-C	Q1	Ref	-
	Q2	1.21 (0.97–1.50)	1.25 (0.99–1.57)
	Q3	1.88 (1.51–2.33)	1.95 (1.54–2.45)
	Q4	2.29 (1.84–2.85)	2.44 (1.93–3.08)

[a]: adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, low-density lipoprotein cholesterol, systolic blood pressure, and body mass index

CAD: coronary artery disease; T2D: type 2 diabetes; OR: odds ratio; CI: confidence interval; TyG: triglyceride–glucose index; TyG-BMI: triglyceride glucose-body mass index; TyG-WC: triglyceride glucose-waist circumference index; TyG-WHtR: triglyceride glucose-waist to height ratio index; METS-IR: metabolic score for insulin resistance; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol

Discussion

The current study found a non-linear association between CAD in patients with T2D and surrogate IR indices including, TyG, TyG-BMI, TyG-WC, TyG-WHtR, METS-IR, and TG/HDL-C ratio. The TyG exhibited a U-shaped association with CAD. The surrogate IR indices demonstrated a relatively strong discriminative ability for CAD, with AUC values exceeding 0.708 for all indices. Among them, the TG/HDL-C ratio showed the highest AUC (0.721) and sensitivity (71%), followed by METS-IR (AUC = 0.713). In addition, TyG-WC exhibited the highest specificity (78%). Machine learning algorithms (except logistic regression) outperformed individual IR indices in discriminative power. Random forest and XGBoost revealed the best performance when using either multiple surrogate IR indices or their individual components.

IR has been found to promote atherosclerosis and the formation of lipid lesions which has been considered an important risk factor for CAD in patients with diabetes

[36, 37]. The current study identified a non-linear association between surrogate IR indices and CAD. The pathophysiology behind this correlation can be explained by several factors. IR induces the secretion of non-esterified fatty acids and pro-inflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and leptin, which exacerbate inflammation [38]. Hyperglycemia linked to IR leads to metabolic disturbances, including dyslipidemia, hypertension, oxidative stress, endothelial dysfunction, and myocardial fibrosis, impairing cardiac function [39–43]. Additionally, chronic hyperglycemia induces the generation of advanced glycation end products (AGEs), which disrupt the extracellular matrix, damage endothelium, and inhibit nitric oxide (NO) activity [44–47]. Enhanced glycosylation initiated by IR increases the secretion of pro-coagulant factors, facilitating platelet aggregation and further impairing endothelial function [48, 49]. Moreover, IR-associated hyperinsulinemia further accelerates lipid plaque progression and promotes arterial wall remodeling, worsening CAD outcomes [50].

This study identified a U-shaped association between TyG levels and odds of CAD in patients with T2D, suggesting that both extremely high and low TyG levels may negatively impact health outcomes. In addition, a TyG cut-off of 4.65 demonstrated predictive value for CAD, with an AUC of 0.709, sensitivity of 58%, and specificity of 76%. Elevated TyG levels likely increase CAD risk due to hyperglycemia and hyperlipidemia, well-known CAD risk factors [51]. Conversely, low TyG levels may elevate CAD risk through hypoglycemic conditions, which can trigger sympathetic activation, increased adrenaline, and vasoconstriction [51]. Nonetheless, the current evidence regarding the association between TyG and CAD remains inconsistent. A prior study on National Health and Nutrition Examination Survey (NHANES) data between 2001 and 2018, reported an inverse relationship between TyG levels below 8.84 and CVD-related death and a positive correlation when TyG exceeded this threshold [52]. Another study using NHANES between 1999 and 2018, found that an intermediate TyG range (8.72–9.15) was associated with reduced CVD mortality risk [53]. Similar to our findings, a study that used data from NHANES between 2003 and 2018, observed a U-shaped association between TyG and CVD risk in the general population, although without an obvious non-linear association [54]. However, Da Silva et al. reported a direct association between TyG and symptomatic CAD in patients receiving secondary CVD care in Brazil [55]. Additionally, a dose-response relationship between cumulative TyG and CAD risk was demonstrated in China between 2018 and 2021, particularly among men and older individuals [56]. Thai et al. identified a TyG threshold above 10 as a predictor of coronary artery stenosis of >70% in patients
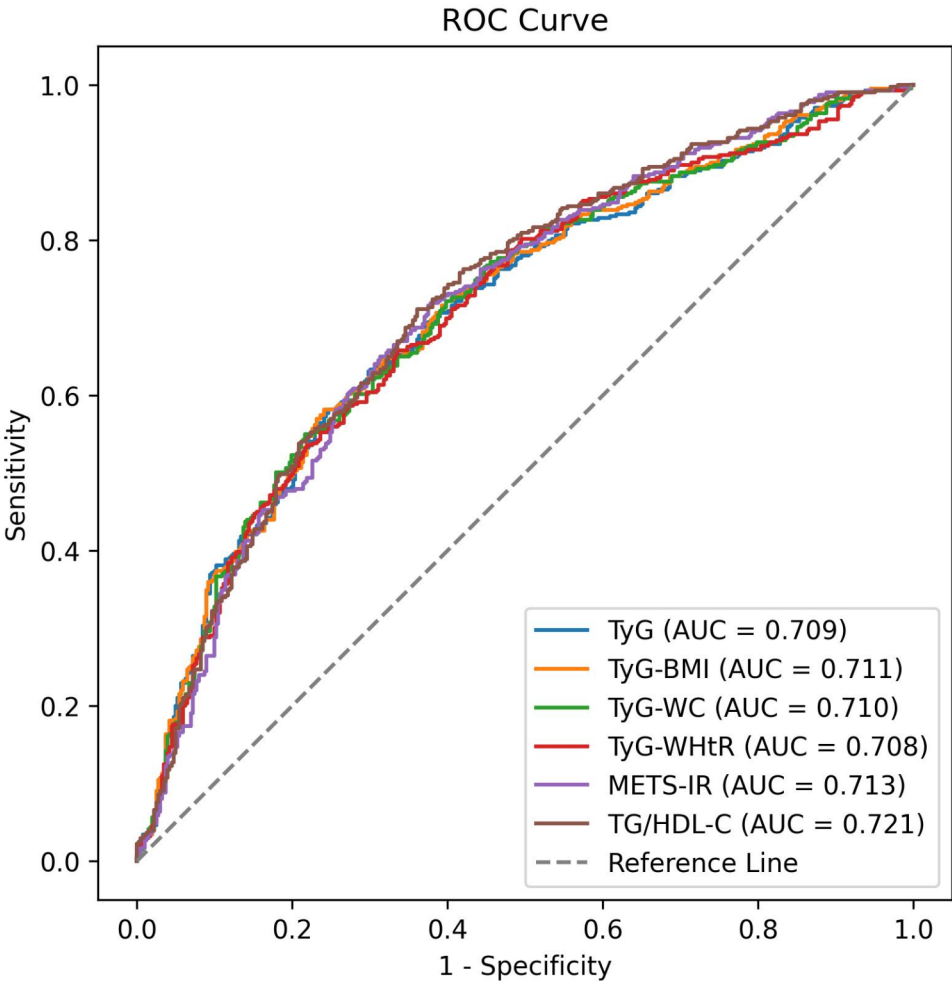
Fig. 3 ROC curve showing the AUC, sensitivity, and specificity of surrogate insulin resistance indices for discriminating CAD in patients with T2D; adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, low-density lipoprotein cholesterol, systolic blood pressure, and body mass index. ROC: Receiver operating characteristic; AUC: area under curve; CAD: coronary artery disease; T2D: type 2 diabetes; TyG: triglyceride-glucose index; TyG-BMI: triglyceride glucose-body mass; TyG-WC: triglyceride glucose-waist circumference; TyG-WHtR: triglyceride glucose-waist-to-height ratio; METS-IR: metabolic score for insulin resistance; TG/HDL: triglycerides/high-density lipoprotein cholesterol ratio

Table 5 ROC analysis of surrogate insulin resistance indices for discriminating CAD status in patients with T2D

Insulin resistance indices	Cutoff	AUC (95% CI) [a]	Sensitivity	Specificity	Accuracy
TyG	4.65	0.709 (0.674–0.744)	58%	76%	67%
TyG-BMI	113.94	0.711 (0.676–0.745)	58%	76%	67%
TyG-WC	694.78	0.710 (0.675–0.747)	55%	78%	67%
TyG-WHtR	2.78	0.708 (0.673–0.743)	65%	67%	66%
METS-IR	45.18	0.713 (0.677–0.747)	67%	67%	67%
TG/HDL-C	2.33	0.721 (0.687–0.757)	71%	64%	68%

[a]: adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, low-density lipoprotein cholesterol, systolic blood pressure, and body mass index

ROC: receiver operating characteristic; CAD: coronary artery disease; T2D: type 2 diabetes; AUC: area under the curve; CI: confidence interval; TyG: triglyceride–glucose index; TyG-BMI: triglyceride glucose-body mass index; TyG-WC: triglyceride glucose-waist circumference index; TyG-WHtR: triglyceride glucose-waist to height ratio index; METS-IR: metabolic score for insulin resistance; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol

with diabetes in Vietnam between 2017 and 2018, with a sensitivity of 57% and a specificity of 75% [21]. Moreover, TyG has been shown to predict cardiovascular events in patients with acute coronary syndrome and diabetes in China [57, 58]. These findings highlight the valuable role of the TyG as a comprehensive tool for cardiometabolic risk evaluation. However, further research is required to clarify the association between TyG and CAD,
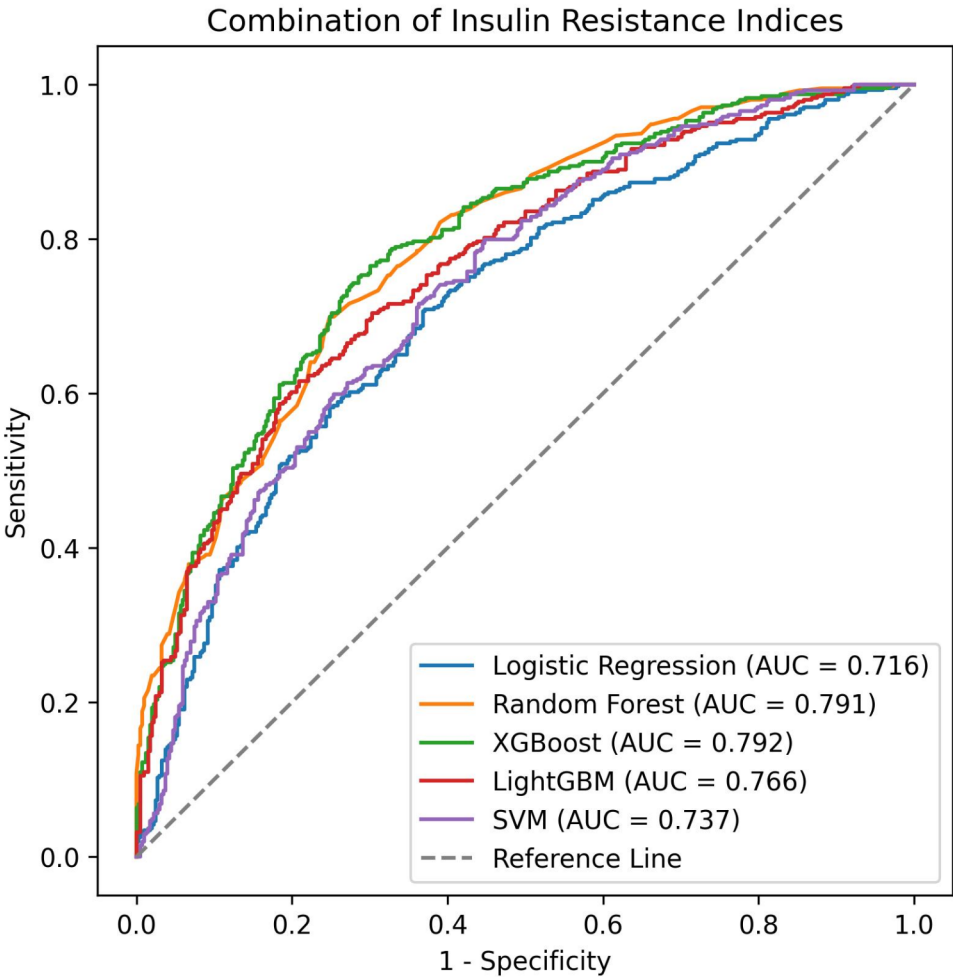
Combination of Insulin Resistance Indices

Fig. 4 ROC curves for various machine learning models predicting CAD in patients with T2D using the combination of multiple surrogate insulin resistance indices (TyG, TyG-WHtR, and TG/HDL-C). ROC: Receiver operating characteristic; CAD: coronary artery disease; T2D: type 2 diabetes; TyG: triglyceride-glucose index; TyG-WHtR: triglyceride glucose-waist-to-height ratio; TG/HDL: triglycerides/high-density lipoprotein cholesterol ratio; AUC: area under the curve; SVM: support vector machine

Table 6 Comparison of machine learning models for discriminating CAD status using surrogate insulin resistance indices and their components

Machine learning models	AUC (95% CI) [a]	Sensitivity	Specificity	Accuracy
Combination of IR indices[a]				
Logistic Regression	0.716 (0.681–0.751)	70%	63%	67%
Random Forest	0.791 (0.760–0.820)	78%	64%	71%
XGBoost	0.792 (0.763–0.822)	79%	67%	73%
LightGBM	0.766 (0.733–0.798)	74%	64%	69%
SVM	0.737 (0.704–0.773)	74%	61%	68%
Components of IR indices[b]				
Logistic Regression	0.715 (0.677–0.749)	70%	62%	66%
Random Forest	0.791 (0.763–0.819)	78%	67%	73%
XGBoost	0.766 (0.733–0.797)	74%	64%	69%
LightGBM	0.758 (0.727–0.791)	71%	66%	68%
SVM	0.734 (0.698–0.768)	76%	59%	67%

[a]: adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, low-density lipoprotein cholesterol, systolic blood pressure, and body mass index

[b]: adjusted for gender, hypertension, dyslipidemia drug, antihyperglycemic agents, low-density lipoprotein cholesterol, and systolic blood pressure

CAD: coronary artery disease; AUC: area under the curve; CI: confidence interval; IR: insulin resistance; SVM: support vector machine
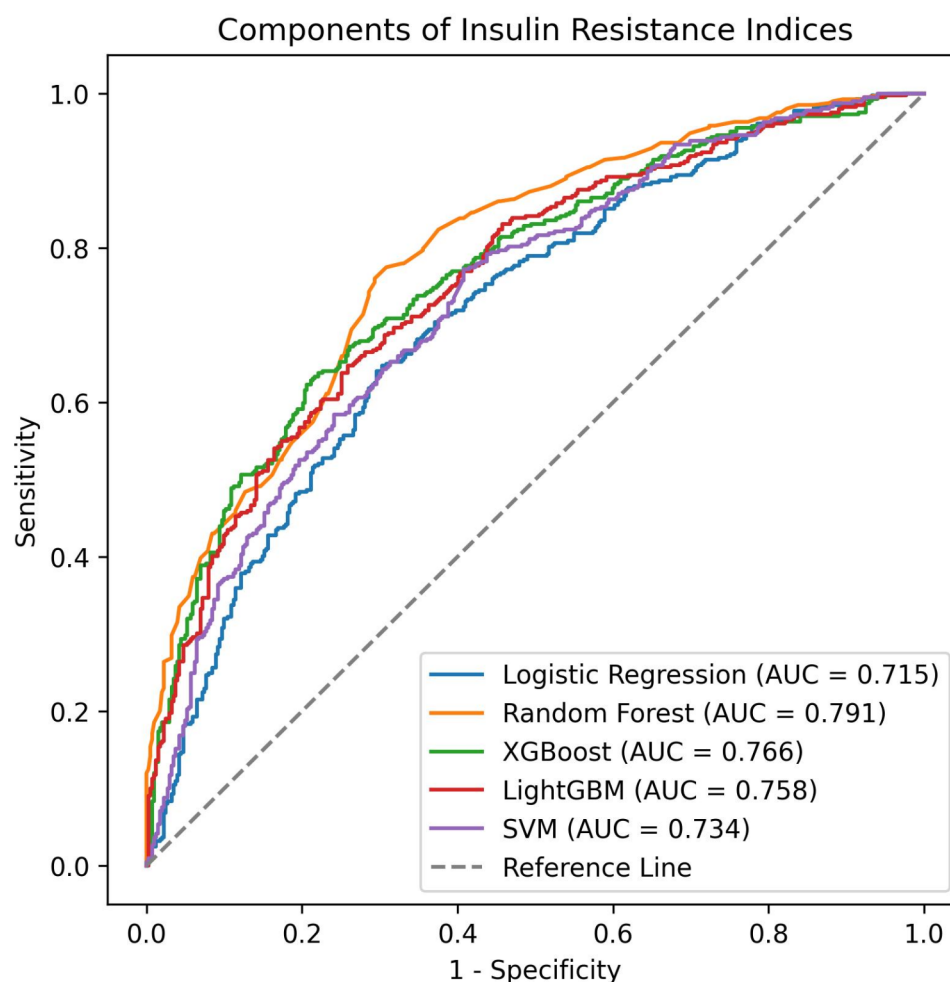
Fig. 5 ROC curves illustrate the performance of different machine learning models in predicting CAD in patients with T2D based on components of surrogate insulin resistance indices (TG, FBS, HDL-C, BMI, and WHtR). ROC: Receiver operating characteristic; CAD: coronary artery disease; T2D: type 2 diabetes; TG: triglycerides; FBS: fasting blood sugar; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; WHtR: waist-to-height ratio; AUC: area under the curve; SVM: support vector machine

particularly in patients with T2D. On the other hand, Chen et al. found a U-shaped association between TyG-BMI, TyG-WC, and TyG-WHtR with all-cause mortality in Poland, while TyG and TyG-WHR showed a J-shaped pattern [59]. They suggested that low TyG-BMI or TyG-WC may indicate malnutrition and weakened immunity, increasing infection risk and mortality. Contrarily, high levels reflect greater IR, metabolic disorders, and fat accumulation, contributing to inflammation, oxidative stress, and atherosclerosis, ultimately increasing mortality risk [59].

A non-linear relationship was observed in this study between TyG-derived markers (TyG-BMI, TyG-WC, and TyG-WHtR) and the odds of having CAD in patients with T2D. Similar to TyG, evidence on the association of these markers with CAD remains inconclusive. Chen et al. analyzed the NHANES (2005–2018) dataset and reported a non-linear relationship between

TyG-BMI and heart failure in patients with diabetes [22]. Park et al. showed a higher risk of CVD associated with TyG-BMI, TyG-WC, and TyG-WHtR in individuals without diabetes in Korea [60]. Wang et al. found a linear relationship between TyG-BMI and CAD risk in China between 2021 and 2024 [61]. Furthermore, a positive correlation between TyG-WC and myocardial infarction was reported based on the NHANES (2011–2018) [62]. In contrast, Xiao et al. identified a U-shaped relationship between TyG-BMI and CVD mortality in patients with diabetes using the NHANES (2001–2018) dataset [63]. Another study based on NHANES (2011–2018), highlighted a U-shaped association between TyG-WHtR and coronary heart disease [62]. These inconsistencies underscore the complex nature of the association between TyG-derived markers and CAD, necessitating further research to clarify their role.

Research on the association between METS-IR and CAD in patients with T2D is limited. Qian et al. found a positive correlation between METS-IR and CVD risk in middle-aged and elderly individuals in China between 2011 and 2018 [64]. Yoon et al. reported that elevated METS-IR predicts IHD in non-diabetic participants in Korea [19]. Furthermore, Wang et al. demonstrated a linear relationship between METS-IR and coronary artery calcification in Korea [65]. Zhang et al. highlighted METS-IR as a marker for risk assessment and prognosis in individuals with ischemic cardiomyopathy and diabetes in China from 2013 to 2019 [66]. Additionally, Zhang et al. showed that METS-IR is associated with CAD severity in China [67]. This study further identified a non-linear association between METS-IR and CAD in patients with T2D.

There is a controversy regarding the prognostic role of TG/HDL-C in cardiovascular events among patients with diabetes. Consistent with this study, Wu et al. showed that the TG/HDL-C ratio was an independent predictor of CAD presence in China from 2016 to 2017 [68]. In addition, Chen et al. analyzed the NHANES (2005–2018) dataset and reported a non-linear relationship between TG/HDL-C and heart failure in patients with diabetes [22]. Eeg Olofsson et al. found a positive association between TG/HDL-C and CVD risk in obese individuals with T2D in Sweden [69]. Additionally, TG/HDL-C has been identified as a predictor of major adverse cardiovascular events (MACEs) in patients with CAD and diabetes in China [70]. However, Tohidi et al. reported that the TG/HDL-C was not a significant independent predictor of cardiovascular events in individuals with diabetes without CVD in Iran [71]. These discrepancies may be due to the variations in participant characteristics, differences in follow-up durations, and the influence of unmeasured confounding factors across studies.

In the current analysis, TG/HDL-C demonstrated the highest predictive power for CAD among the indices studied, with a cut-off of 2.33 (AUC = 0.721, sensitivity = 71%, specificity = 64%), followed by METS-IR (cut-off = 45.18, AUC = 0.713, sensitivity = 67%, specificity = 67%). Wu et al. conducted a study in China from 2016 to 2017 and reported that METS-IR had the strongest predictive power for CAD compared to TyG and TG/HDL-C, with a cut-off of 42.1 (AUC = 0.636, sensitivity = 37.7%, specificity = 82.6%), followed by TG/HDL-C, which showed a cut-off of 2.9 (AUC = 0.567, sensitivity = 43.6%, specificity = 69.8%) [68]. In contrast, Wang et al. found that TyG-BMI was the most powerful predictive marker for CAD in patients with diabetes and hypertension in China, with an AUC of 0.699 (sensitivity = 70.8%, specificity = 62.4%) [61]. Additionally, Zhang et al. demonstrated that METS-IR had the highest predictive value for CAD severity in China

(AUC = 0.726, sensitivity = 44.4%, specificity = 92.2%), followed by TyG-BMI (AUC = 0.704, sensitivity = 70%, specificity = 58.6%), and TG/HDL-C (AUC = 0.652, sensitivity = 52%, specificity = 75%) [67]. These findings indicate that surrogate IR indices, particularly TG/HDL-C and METS-IR, are valuable predictors for CAD. However, their relative performance may differ among various populations and study settings, highlighting the need for customized risk assessment approaches.

In this study, the machine learning models exhibited superior discriminative power compared to individual surrogate IR indices. Random forest and XGBoost demonstrated the highest performance when utilizing either various surrogate IR indices (TyG, TyG-WHtR, and TG/HDL-C) or their components (TG, FBS, HDL-C, BMI, and WHtR). Research on the integration of surrogate IR indices into machine learning models for predicting cardiovascular disease in patients with T2D is limited. However, our results are consistent with earlier research assessing machine learning methods for predicting cardiovascular disease in individuals with T2D using alternative predictors. Hossain et al., incorporating social network-based features (such as comorbidity prevalence, transition patterns, and clustering membership) and demographic characteristics in Australia, reported that all tested models, including logistic regression, SVM, decision tree, random forest, K-nearest neighbors, and naïve bayes, achieved AUCs above 0.70, with the random forest model demonstrating the highest performance (AUC = 0.83) for cardiovascular disease prediction [72]. Fan et al., included demographic characteristics, anthropometric features (such as BMI), biochemical data (including FBS and lipid profile), and insulin secretion indices in their study in China. Their random forest model achieved an AUC of 0.77 in the training dataset, 0.80 in the testing dataset, and 0.71 in an independent validation dataset for predicting coronary heart disease in patients with T2D [73]. Additionally, Dinh et al. utilized survey data and laboratory results from the NHANES dataset and showed that random forest and XGBoost models outperformed others in predicting cardiovascular diseases in the general population. The AUC values for these models ranged from 0.816 to 0.839 [74]. These results emphasize the capability of machine learning models, especially tree-based algorithms, to improve cardiovascular disease prediction in individuals with T2D, irrespective of the specific predictors used.

Strengths and limitations
To the best of our knowledge, this is one of the first studies to comprehensively evaluate the association between various surrogate indices of IR and CAD in a relatively large number of patients with T2D.

The current study provided a detailed examination of these associations by employing diverse analytical approaches, including RCS, multivariable logistic regression, ROC curve analysis, and machine learning models. In addition, adjustments for potential confounders were performed to enhance the robustness of the results. Nonetheless, there were some limitations. This study was cross-sectional, which limits the establishment of causal relationships between the assessed indices and CAD. As this study was conducted at a single center, its findings may not be fully generalizable to larger populations. Additionally, the indices used were surrogate markers and may not accurately represent the actual IR. Despite adjustments for confounding variables, unmeasured factors such as diet preferences, hereditary factors, and social determinants of health could have impacted the results. While 10-fold cross-validation was used to improve the reliability of machine learning models, there is still a risk of overfitting. Furthermore, the models were developed using just one dataset, highlighting the need for external validation. In addition, due to the lack of longitudinal data, the ability of machine learning models to predict causal associations between surrogate IR indices and CAD was restricted. Future prospective cohort studies are needed to address these limitations.

Conclusion

This study highlights the non-linear association and predictive value of TyG, TyG-BMI, TyG-WHtR, TyG-WC, METS-IR, and the TG/HDL-C ratio as surrogate indices of insulin resistance for CAD in patients with T2D, with the TG/HDL-C ratio demonstrating the highest predictive accuracy. The findings emphasize the usefulness of these indices in assessing cardiometabolic risk, particularly in high-risk individuals. In addition, integrating machine learning models enhanced CAD prediction, emphasizing their capabilities for better risk stratification. Further longitudinal studies are essential to validate these indices and establish specific thresholds for optimal risk assessment and clinical use.

Declarations

Ethics approval and consent to participate
The research ethics committee of Tehran University of Medical Sciences approved this study. All participants provided written informed consent before participating, and the study adhered to the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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