

The Predictive Value of TyG Index and NLR for Risk of CHD and the Severity of Coronary Artery Lesions in Patients with Type 2 Diabetes Mellitus

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Background: There is a paucity of research examining the Triglyceride-glucose (TyG) index and Neutrophil-to-lymphocyte ratio (NLR) in relation to the onset and severity of coronary heart disease (CHD) in individuals with type 2 diabetes mellitus (T2DM). This study aims to explore the relationship between these biomarkers and the risk of CHD in T2DM patients and clarify their association with the CHD severity.

Methods: A total of 518 patients with T2DM who underwent coronary angiography (CAG) were included and categorized into either the T2DM group or the T2DM combined with CHD group based on the angiographic findings. The association of the TyG index and NLR with CHD and its severity were validated by logistic regression analyses. The predictive efficacy of both biomarkers, individually and in combination, for CHD was evaluated using receiver operating characteristic (ROC) curves.

Results: Among the 518 patients with T2DM, 396 individuals were identified as having a combination of CHD of varying severity. Multifactorial logistic regression analysis showed that after adjusting for age, sex, smoking, hypertension, and history use of glucose- and lipid-lowering medications, both TyG index and NLR were risk factors for CHD in T2DM patients (TyG index: OR:3.89, 95% CI:2.60–5.82; NLR: OR:1.44, 95% CI:1.22–1.71; all $P<0.05$). The odds ratios(OR) for the highest tertile compared to the lowest tertile of TyG index and NLR were 3.61(95% CI:2.41–5.40) and 1.62(95% CI:1.25–2.09).The TyG index exhibited a significant correlation with CHD severity in T2DM patients (OR:2.96, 95% CI:1.19–7.32; $P=0.019$). The areas under the curve for TyG index and NLR alone, and in combination, to predict CHD were 0.717, 0.692, and 0.761, respectively (all $P<0.001$).

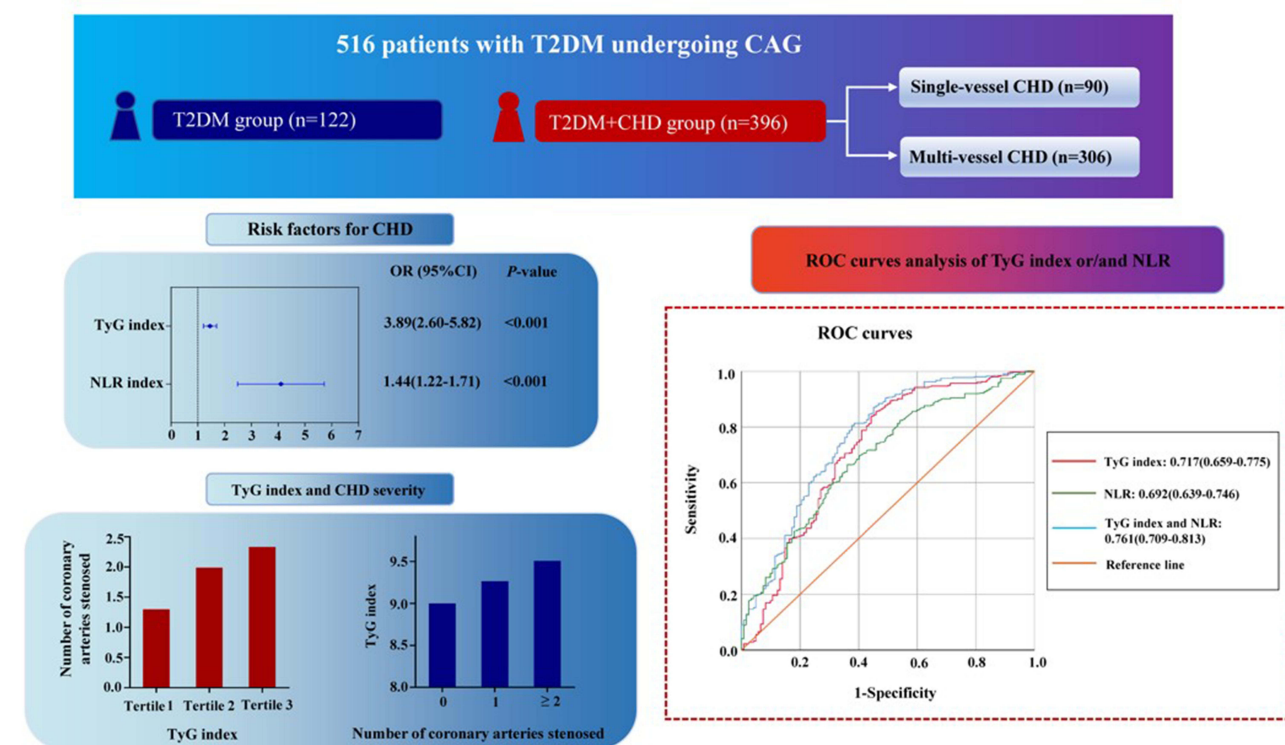
Conclusion: The TyG index and NLR were significantly associated with the occurrence of CHD in the T2DM population. The combined use of these two biomarkers enhances diagnostic accuracy, which is beneficial for the prevention of CHD.

Keywords: triglyceride-glucose index, neutrophil-to-lymphocyte ratio, type 2 diabetes, coronary heart disease, coronary heart disease severity

Background

Coronary heart disease (CHD) is a chronic ischemic condition caused by the narrowing of the coronary arteries, with acute coronary syndrome (ACS) being one of its most serious manifestations.¹ With an aging population and the prevalence of unhealthy lifestyles, the morbidity and mortality of CHD are increasing, seriously jeopardizing global public health.² Diabetes mellitus (DM) is considered a serious risk factor for CHD.³ In diabetic patients, coronary arteries exhibit larger necrotic cores and heightened infiltration of inflammatory macrophages and T cells, resulting in more extensive coronary artery damage.⁴ An established link exists between hyperglycemia, coronary artery calcification(CAC), and glycated hemoglobin(HbA1c), which

Graphical Abstract



serves as a predictor of cardiovascular disease.⁵ Prior research⁶ has demonstrated that an abnormal elevation in blood glucose levels is associated with an increased risk of CHD. Data from the survey indicate that for each 1% increment in HbA1c, there is an estimated increase in cardiovascular events ranging from 11% to 16%. Patients with CHD and comorbid glucose metabolism abnormalities often have multibranch vasculopathy and a higher risk of subsequent adverse cardiovascular events.⁷

Insulin resistance (IR) is a classic marker of type 2 diabetes mellitus (T2DM).⁸ IR patients are prone to a range of metabolic disorders, including abnormalities in blood lipids, blood pressure, and blood glucose levels.⁹ IR has been widely recognised as a serious risk factor for cardiovascular disease.^{10,11} The high insulin-glucose clamp test (HIEC) is currently the gold standard for the detection of IR, but its clinical use is limited by the complexity of the test procedure.¹² The Triglyceride-Glucose (TyG) index, calculated from fasting blood glucose (FBG) and triglycerides (TG), has been increasingly recognized as a reliable indicator of IR. Numerous studies have validated the TyG index against the hyperinsulinemic-euglycemic clamp (HIEC) and the homeostasis model assessment of estimated insulin resistance (HOMA-IR).^{13,14} There is substantial evidence that the Triglyceride-Glucose (TyG) index is associated with various cardiovascular diseases, including coronary atherosclerosis, stenosis, and ACS.^{15,16} Additionally, TyG index has been shown to be an independent predictor of future adverse cardiovascular events in patients with DM and ACS, highlighting its potential for clinical use.¹⁷ Neutrophil-to-lymphocyte ratio (NLR) is a novel inflammatory marker used to reflect the severity of systemic inflammation.¹⁸ It has been shown that NLR is strongly associated with CHD progression, and that patients with higher ratios are also at higher risk of cardiovascular events and mortality.^{19,20} In addition, chronic inflammation plays a crucial role in the pathogenesis of DM. Chronic inflammation can affect adipose tissue and mitochondrial function by impairing normal lipid accumulation, which leads to IR. Conversely, IR can exacerbate the chronic inflammatory response.²¹ The two interact to form a vicious circle.

The severity of CHD is a critical factor in the development and prognosis of cardiovascular disease. Patients with CHD combined with multibranched coronary artery disease represent a high-risk group for mortality, particularly within the DM population.²² Both the TyG index and NLR are associated with atherosclerosis and IR. However, the combined value of the TyG index and NLR in predicting CHD and its severity remains uncertain. Therefore, this study aims to provide clinical insights for the early prevention of coronary heart disease in patients with T2DM by investigating the associations between the TyG index, NLR, and CHD and its severity.

Methods

Study Population

This retrospective study selected 720 patients with T2DM who attended the People's Hospital of Pingxiang City, Jiangxi Province, from January 2021 to December 2023, all of whom underwent coronary angiography (CAG) during hospitalisation. All patients were divided into T2DM and T2DM+CHD groups based on CAG results, and the following patients were excluded: (1) patients with severe arrhythmias, cardiomyopathy, valvular disease, and congenital heart disease; (2) patients with previous coronary artery bypass grafting (CABG) or cardiogenic shock; (3) patients with severe hepatic or renal insufficiency; (4) patients with severe infections, thyroid function disorders, hematological disorders, autoimmune diseases, and tumours; (5) patients who have recently suffered severe trauma or major surgery; (6) pregnant or breastfeeding women; and (7) patients lacking NLR, FBG, TG and CAG data. Finally 518 patients were included in the analysis and the enrolment process is shown in Figure 1. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Pingxiang People's Hospital. The requirement for informed consent was waived due to the retrospective nature of the study. Furthermore, the confidentiality of all patient data was guaranteed.

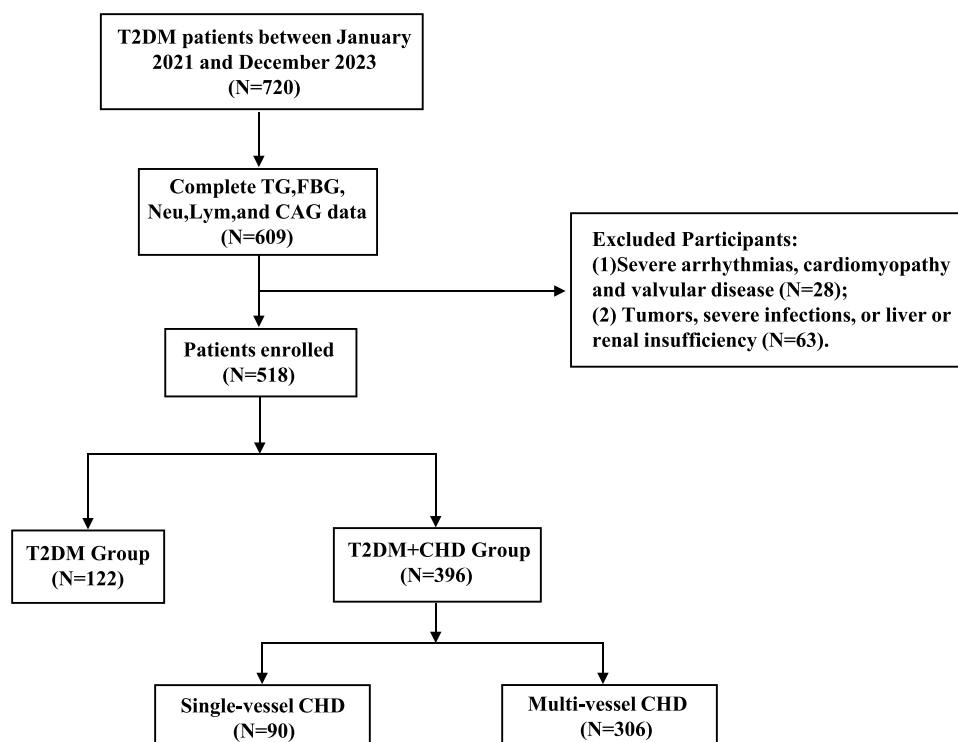


Figure 1 Flow chart of patient recruitment.

Abbreviations: T2DM, type 2 diabetes mellitus; TG, triglyceride; FPG, fasting plasma glucose; Neu, Neutrophils; Lym, lymphocyte; CAG, coronary angiography; CHD, coronary heart disease.

Data Collection

Clinical data of the enrolled patients during hospitalisation were collected through the electronic medical record system, including (1) general information such as: gender, age, body mass index (BMI), admission systolic blood pressure (SBP) and diastolic blood pressure (DBP), history of smoking, hypertension, oral hypolipidemic and hypoglycaemic drugs. (2) Laboratory test indications: fasting elbow vein blood was collected the next morning and placed in anticoagulant tubes for examination. These include: total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), serum creatinine (Scr), neutrophil (NE) count, lymphocyte (LY) count. (3) CAG was performed by at least two cardiovascular interventional experts who were blinded to the study protocol via radial or femoral artery and the results were recorded.

Definitions

(1) TyG index and NLR are calculated as follows: $TyG = \ln(TG[mg/dL] \times FBG[mg/dL]/2)$; ¹³ $NLR = (NE \text{ counts} \times 10^9/L) / LY \text{ counts} \times 10^9/L$. ²³ (2) BMI was calculated by dividing weight (kg) by the square of height (m), expressed in kg/m^2 . (3) Diagnostic criteria for hypertension included a documented history of hypertension, current use of antihypertensive medications, or systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. (4) According to the American Diabetes Association criteria, ²⁴ T2DM is defined as: FBG ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$, or oral glucose tolerance test shows that 2-hour postprandial blood glucose ≥ 11.1 mmol/l, or a previous diagnosis of T2DM and received hypoglycemic drug treatment. (5) CHD was defined as the stenosis of at least one major coronary artery (left main artery, left anterior descending artery, left circumflex artery and right coronary artery) assessed by CAG $\geq 50\%$. The number of diseased vessels with stenosis $\geq 50\%$ can reflect the severity of CHD. ²² Patients with only one major coronary artery involved were defined as single vessel CHD, and patients with two or more major coronary arteries involved were defined as multi vessel CHD.

Statistical Analysis

Continuous variables following a normal distribution are presented as mean $\pm$ standard deviation, while non-normally distributed variables are presented as median and interquartile range. Categorical variables are shown as frequencies and percentages (%). The unpaired samples *t*-test and Mann–Whitney *U*-test were used to compare two continuous variables with normal and non-normal distributions, respectively. The χ^2 -test or Fisher's exact test was used to compare categorical variables. Logistic regression models, including odds ratios (ORs) and corresponding 95% confidence intervals (CIs), were used to validate the correlation of the TyG index and NLR with CHD. The interaction of TyG index and NLR with CHD was examined by building three models: model I, unadjusted for status; model II, adjusted for age and sex by including them as covariates; and model III, refined by introducing the variables of model II and incorporating smoking status, history of hypertension, and history of glucose-lowering and lipid-lowering medications. In addition, to examine the association between TyG index and NLR with CHD and its severity, the same three models were again built for logistic regression analysis separately. The predictive validity of these two indices individually as well as jointly for CHD was determined by calculating the area under the curve (AUC) and the corresponding 95% confidence interval (CI) from the receiver operating characteristic (ROC) curve. All statistical analyses were performed using SPSS 26.0 (IBM, USA) and GraphPad Prism 8.0 (San Diego, California, USA). A two-sided *P* value of <0.05 was considered significant.

Results

Clinical and Biochemical Characteristics of T2DM and T2DM+CHD Groups

Data from this study were obtained from 518 individuals with T2DM (285 males and 233 females), including 396 CHD participants and 122 non-CHD participants. The mean age of individuals in the T2DM with and without CHD groups was 63.7 ± 9.5 years and 61.6 ± 9.8 years, respectively. Table 1 shows the demographic and clinical characteristics of the two groups. There were no significant differences between the two groups of participants in terms of BMI, SBP, DBP, TC, LDL-C, HDL-C, history of smoking, hypertension, antihypertensive and glucose-lowering medication use ($P > 0.05$). The

Table 1 Demographic and Clinical Characteristics of Included Patients

	T2DM (n=122)	T2DM+CHD (n=396)	P
General information			
Male (n,%)	54(44.3)	231(58.3)	0.006
Age (years)	61.6±9.8	63.7±9.5	0.035
BMI (kg/m ²)	24.9±4.6	24.1±4.1	0.080
SBP(mmHg)	139.0±18.6	140.1±21.9	0.580
DBP(mmHg)	82.4±12.7	80.9±13.7	0.298
Smoking	39 (32.0)	140 (35.4)	0.492
Past medical history (n,%)			
Hypertension	81 (66.4)	255(64.4)	0.603
Hypoglycemic drugs	94(77.0)	322(81.3)	0.474
Dyslipidemia medications	17(13.9)	90(22.7)	0.036
Antiplatelets drugs	21(17.2)	362(91.4)	<0.001
Antihypertensive drugs	42(34.4)	154(38.9)	0.434
Heart failure	5(4.1)	47(11.9)	0.020
Laboratory indicators			
TG (mmol/L)	1.4(1.0–2.2)	1.9(1.4–2.7)	<0.001
TC (mmol/L)	4.4±1.2	4.5±1.3	0.366
LDL-C (mmol/L)	3.0±0.8	3.1±1.0	0.291
HDL-C (mmol/L)	1.1±0.3	1.1±0.4	0.152
Scr (mmol/L)	67.5 (56.1–80.1)	74.2 (60.8–83.8)	0.003
FPG (mmol/L)	6.5(5.4–7.4)	7.8(6.8–9.1)	<0.001
HbA1c (%)	6.9±1.6	7.7±1.5	<0.001
TyG index	8.8(8.5–9.4)	9.4(9.0–9.8)	<0.001
Neutrophils (×10 ⁹ /L)	3.8(2.9–4.9)	4.7(3.7–6.4)	<0.001
Lymphocyte (×10 ⁹ /L)	1.6(1.2–2.0)	1.5(1.2–1.9)	0.041
NLR	2.2(1.7–3.1)	3.1(2.3–4.6)	<0.001

Notes: Data are presented as the IQR, mean ± SD or n (%).

Abbreviations: T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio.

T2DM combined with CHD group had a higher mean age, a higher proportion of male, heart failure, antiplatelets and lipid-lowering medication-using patients; and higher levels of TG, FBG, HbA1c, TyG index, and NLR, with statistically significant differences ($P < 0.05$).

Univariate and Multivariate Analysis of Factors Associated with CHD in T2DM

Univariate logistic regression analysis showed that TG, FBG, HbA1c, TyG index and NLR were associated with the development of CHD in patients with T2DM ($P < 0.05$). Hypoglycemic and lipid-lowering medications play a pivotal role in the prevention and management of CHD. Their administration has been shown to mitigate the risk of cardiovascular disease and to lower both the incidence and mortality rates of cardiovascular events among patients with T2DM.^{25,26} Consequently, we have controlled for these medications to account for their potential confounding effects. After correcting for confounders such as age, sex, smoking, hypertension, and history of taking hypoglycaemic and dyslipidemia medications, multifactorial logistic regression analysis suggested that TyG index (OR, 3.89; 95% CI, 2.60–5.82; $P < 0.001$) and NLR (OR, 1.44; 95% CI, 1.22–1.71; $P < 0.001$) remained risk factors for CHD in T2DM patients (Table 2).

Table 2 Univariate and Multivariate Analysis of Factors Associated with CHD in T2DM

	Model I		Model II		Model III	
	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
SBP (mmHg)	1.00(0.99–1.01)	0.611				
DBP (mmHg)	0.99(0.98–1.01)	0.298				
BMI (kg/m ²)	0.96(0.92–1.01)	0.085				
Scr (mmol/L)	1.00(1.00–1.00)	0.199				
TC (mmol/L)	1.08(0.91–1.28)	0.365				
LDL-C (mmol/L)	1.12(0.91–1.40)	0.291				
HDL-C (mmol/L)	0.70(0.41–1.19)	0.188				
TG (mmol/L)	1.19(1.01–1.39)	0.037	1.04(1.01–1.06)	0.018	1.02(0.99–1.05)	0.064
FBG (mmol/L)	1.67(1.44–1.94)	<0.001	1.09(0.87–1.37)	0.446	1.11(0.88–1.40)	0.369
TyG index	3.51(2.38–5.17)	<0.001	3.53(2.39–5.23)	<0.001	3.89(2.60–5.82)	<0.001
HbA1c (%)	1.55(1.31–1.84)	<0.001	1.04(0.82–1.30)	0.774	1.00(0.79–1.26)	0.969
NLR	1.50(1.27–1.76)	<0.001	1.42(1.20–1.67)	<0.001	1.44(1.22–1.71)	<0.001

Notes: Model I: unadjusted. Model II: adjusted for age and sex. Model III: adjusted for age, sex, smoking status, hypertension, status of antidiabetic drugs and status of antilipidemic drugs.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; Scr, serum creatinine; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio; OR, odd ratio; CI: confidence interval.

Clinical and Biological Characteristics According to TyG Index Tertiles

To understand the relationship between different TyG levels and the development of CHD in patients with T2DM, all participants were divided into three groups based on the TyG index tertiles: T1(n=171; 7.91≤ TyG index ≤ 9.03), T2(n=174; 9.04≤ TyG index ≤ 9.57), and T3(n=173; 9.58≤ TyG index ≤ 11.48). The median TyG index for the three groups were 8.7, 9.3 and 10.0, respectively. Compared with patients in the lowest tertile of the TyG index (T1), the highest tertile of the TyG index (T3) had higher proportions of male patients, heart failure, TC, TG, LDL-C, FPG, and HbA1c, and lower rates of HDL-C, hypoglycaemic, and dyslipidemia medication use (*P*<0.05). In addition, the prevalence of CHD and the risk of developing multiple coronary lesions were higher in the T3 group compared with the T1 group (*P*<0.001, Table 3).

Table 3 Demographic and Clinical Characteristics of Participants by TyG Index Tertiles

	T1(n=171)	T2(n=173)	T3(n=174)	P
General information				
Male (n,%)	92(53.8)	85(49.1)	108(62.1)	0.049
Age (years)	63.0±9.6	64.7±9.1	62.1±10.0	0.034
BMI (kg/m ²)	24.8±4.7	23.8±4.4	24.3±3.6	0.080
SBP(mmHg)	139.7±20.3	142.2±21.4	137.5±21.5	0.116
DBP(mmHg)	81.4±13.8	80.6±14.3	81.8±12.4	0.679
Smoking	59(34.5)	55(31.8)	65(37.4)	0.552
Past medical history (n,%)				
Hypertension	111(64.9)	111(64.2)	116(66.7)	0.881
Hypoglycemic drugs	139(81.3)	151(87.3)	126(72.4)	0.004
Dyslipidemia medications	44(25.7)	37(21.4)	26(14.9)	0.045
Antiplatelets drugs	125(73.1)	128(73.9)	130(74.7)	0.943
Antihypertensive drugs	60(35.1)	63(36.4)	73(41.9)	0.379
Heart failure	5(2.9)	12(6.9)	35(20.1)	<0.001

(Continued)

Table 3 (Continued).

	T1(n=171)	T2(n=173)	T3(n=174)	P
Laboratory indicators				
TG (mmol/L)	1.2(1.0–1.3)	1.8(1.6–2.1)	3.2(2.5–4.3)	<0.001
TC (mmol/L)	4.1±1.2	4.5±1.2	4.8±1.2	<0.001
LDL-C (mmol/L)	2.8±0.9	3.0±1.0	3.3±0.9	<0.001
HDL-C (mmol/L)	1.1±0.5	1.1±0.2	1.0±0.3	0.015
Scr (mmol/L)	67.5(55.9–84.5)	74.8(61.4–90.8)	75.2(61.1–92.5)	0.016
FBG (mmol/L)	6.1(5.4–7.4)	7.5(6.7–8.4)	8.2(7.4–10.1)	<0.001
HbA1c (%)	6.8±1.4	7.5±1.3	8.2±1.7	<0.001
TyG index	8.7(8.5–8.9)	9.3(9.2–9.4)	10.0(9.7–10.3)	<0.001
Neutrophils ($\times 10^9/L$)	4.5(3.1–5.8)	4.5(3.4–6.1)	4.5(3.8–6.1)	0.183
Lymphocyte ($\times 10^9/L$)	1.5(1.2–1.9)	1.5(1.1–2.0)	1.6(1.2–2.0)	0.236
NLR	2.7(2.0–4.1)	2.8(2.1–4.2)	2.9(2.1–4.2)	0.763
CHD (n,%)	98(57.3)	144(83.2)	154(88.5)	<0.001
Number of vessels with stenosis (n,%)				<0.001
0	73(42.7)	29(16.8)	20(11.5)	
1	32(18.7)	33(19.1)	25(14.4)	
≥ 2	66 (38.6)	111 (64.1)	129(74.1)	

Note: Data are presented as the IQR, mean $\pm$ SD or n (%). The groups were stratified by the tertiles of the TyG index (T1, $7.91 \leq \text{TyG index} \leq 9.03$; T2, $9.04 \leq \text{TyG index} \leq 9.57$; T3, $9.58 \leq \text{TyG index} \leq 11.48$).

Abbreviations: T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio.

Association of TyG Index and NLR with CHD in T2DM

Logistic regression modelling showed a significant association between TyG index and the occurrence of CHD in the T2DM population after adjusting for relevant cardiovascular risk factors and pharmacological treatment. Logistic regression analyses of the risk of developing CHD in the T2 and T3 groups were performed using TyG index as a categorical variable and T1 as a control group. The results showed that, after adjusting for age, sex, smoking, hypertension, and history of taking hypoglycaemic and dyslipidemia medications, each 1-unit increase in TyG index was associated with a 1.86-fold increase in the risk of CHD in the T2 group (OR, 1.86; 95% CI, 1.13–3.05; $P=0.014$); whereas in the T3 group, the risk of CHD increased by 3.61-fold (OR, 3.61; 95% CI, 2.41–5.40; $P<0.001$; Table 4).

Similarly, using NLR as a categorical variable, all participants were categorised into three groups based on the tertiles of NLR: T1($0.54 \leq \text{NLR} \leq 2.31$), T2($2.32 \leq \text{NLR} \leq 3.64$) and T3($\text{NLR} \geq 3.65$). After multifactorial correction, the results showed the same correlation between NLR and CHD. Among them, the risk of CHD in the T2 and T3 groups was 1.34 times (OR, 1.34; 95% CI, 1.14–1.58, $P=0.001$) and 1.62 times (OR, 1.62; 95% CI, 1.25–2.09, $P<0.001$; Table 5) higher than that in the T1 group, respectively.

Table 4 Association Between the TyG Index and CHD

TyG index	Model I		Model II		Model III	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
T 1	Ref.		Ref.		Ref.	
T 2	1.77(1.11–2.83)	0.017	1.71(1.06–2.76)	0.028	1.86(1.13–3.05)	0.014
T 3	3.37(2.29–4.94)	<0.001	3.37(2.28–4.96)	<0.001	3.61(2.41–5.40)	<0.001

Notes: Model I: unadjusted; Model II: adjusted for age and sex; Model III: adjusted for age, sex, smoking status, hypertension, status of antidiabetic drugs and status of antilipidemic drugs. T1, $7.91 \leq \text{TyG index} \leq 9.03$; T2, $9.04 \leq \text{TyG index} \leq 9.57$; T3, $9.58 \leq \text{TyG index} \leq 11.48$.

Abbreviations: TyG index, triglyceride-glucose index; OR, odd ratio; CI: confidence interval. Ref, reference.

Table 5 Association Between the NLR and CHD

NLR	Model I		Model II		Model III	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
N1	Ref.		Ref.		Ref.	
N2	1.35(1.15–1.59)	<0.001	1.35(1.14–1.59)	<0.001	1.34(1.14–1.58)	0.001
N3	1.64(1.28–2.09)	<0.001	1.60(1.25–2.04)	<0.001	1.62(1.25–2.09)	<0.001

Notes: Model I: unadjusted; Model II: adjusted for age and sex; Model III: adjusted for age, sex, smoking status, hypertension, status of antidiabetic drugs and status of antilipidemic drugs. N1, $0.54 \leq \text{NLR} \leq 2.31$; N2, $2.32 \leq \text{NLR} \leq 3.64$; N3, $\text{NLR} \geq 3.65$.

Abbreviations: NLR, neutrophil/lymphocyte ratio; OR, odd ratio; CI: confidence interval; Ref, reference.

In addition, we performed a sensitivity analysis based on the risk factors included in Model III. Initially, we conducted propensity score matching(PSM) for all enrolled patients at a 1:2 and 1:3 ratio, respectively, and determined that the TyG index and NLR remained significant risk factors for CHD (Sensitivity Analysis I, [Table S1](#)). Subsequently, we adjusted BMI, TC, LDL, and HDL and found that, consistent with the main model, TyG and NLR were risk factors for CHD (Sensitivity Analysis II, [Table S1](#)). Ultimately, we stratified the enrolled patients based on estimated glomerular filtration rate (eGFR), categorizing those with $\text{eGFR} < 60 \text{ mL/min}$ as having reduced renal function. Further sensitivity analysis confirmed that the outcomes were consistent with those of the primary model(Sensitivity Analysis III, [Table S1](#)).

Correlation Between TyG Index and CHD Severity in T2DM

Patients with T2DM combined with CHD were classified into single-vessel CHD (group V1) and multivessel CHD (group V2 including 2 coronary stenoses and group V3 with greater than 2 coronary stenoses) based on CAG results. Baseline clinical characteristics are shown in [Table 6](#). TG, LDL-C, Scr, HBA1c, heart failure, antihypertensive drugs and TyG index were higher in the V3 group than in the V1 group, whereas HDL-C was lower than in the V1 group, and the difference was statistically significant ([Table 6](#), $P < 0.05$).

Correlation analyses between CHD severity with BMI, TG, FGB, HBA1c, TyG index and NLR index showed no correlation between CHD severity and BMI ($r = -0.077$, $P = 0.079$); and with TG ($r = 0.145$, $P = 0.001$), HBA1c ($r = 0.244$, $P < 0.001$), FPG ($r = 0.261$, $P < 0.001$), NLR ($r = 0.250$, $P < 0.001$), and TyG index ($r = 0.315$, $P < 0.001$) were weakly correlated with each other ([Table 7](#)). [Figure 2](#) presents the CHD severity in TyG subgroups and TyG index in CHD severity subgroups among patients in the T2DM+CHD group, which showed a positive correlation with a statistically significant difference ($P < 0.001$).

Table 6 Clinical and Biological Characteristics According to CHD Severity

	V1(n=90)	V2(n=82)	V3(n=224)	P
General information				
Male (n,%)	48(53.3)	43(52.4)	140(62.5)	0.157
Age (years)	63.0 $\pm$ 10.3	63.9 $\pm$ 9.8	64.0 $\pm$ 9.1	0.737
BMI (kg/m ²)	24.5 $\pm$ 5.3	24.0 $\pm$ 3.9	24.0 $\pm$ 3.7	0.606
SBP(mmHg)	140.0 $\pm$ 20.7	139.3 $\pm$ 21.0	140.4 $\pm$ 22.7	0.934
DBP(mmHg)	82.6 $\pm$ 14.3	79.0 $\pm$ 12.9	81.0 $\pm$ 13.7	0.223
Smoking	30(33.3)	26(31.7)	84(37.5)	0.580
Past medical history (n,%)				
Hypertension	65(72.2)	45(54.9)	146(65.2)	0.058
Hypoglycemic drugs	73 (81.1)	66(80.5)	183(81.7)	0.927
Dyslipidemia medications	22(24.4)	20(24.4)	48(21.4)	0.781
Antiplatelets drugs	86(95.6)	78(95.1)	219(97.8)	0.408
Antihypertensive drugs	29(32.2)	38(46.3)	129(57.6)	<0.001
Heart failure	3(3.3)	7(8.5)	37(16.5)	0.001

(Continued)

Table 6 (Continued).

	V1(n=90)	V2(n=82)	V3(n=224)	P
Laboratory indicators				
TG (mmol/L)	1.7(1.2–2.3)	2.0(1.5–2.7)	2.0(1.5–3.0)	0.003
TC (mmol/L)	4.3±1.1	4.3±1.3	4.6±1.3	0.059
LDL-C (mmol/L)	2.9±0.9	2.9±1.0	3.2±1.0	0.011
HDL-C (mmol/L)	1.1±0.2	1.1±0.7	1.0±0.3	0.033
Scr (mmol/L)	65.9(57.1–85.5)	72.2(58.6–91.0)	77.2(64.5–98.0)	0.015
FBG (mmol/L)	7.5(6.6–8.4)	7.8(6.7–9.2)	7.8(6.9–9.1)	0.180
HbA1c(%)	7.4±1.4	7.5±1.5	7.9±1.5	0.023
TyG index	9.1(8.9–9.6)	9.3(9.0–9.8)	9.5(9.1–9.9)	0.001
Neutrophils (×10 ⁹ /L)	4.2(3.2–5.8)	5.2(3.7–7.0)	4.8(3.8–6.5)	0.022
Lymphocyte (×10 ⁹ /L)	1.4(1.2–2.0)	1.4(1.0–2.1)	1.5(1.2–1.8)	0.478
NLR	2.7(2.2–3.8)	3.5(2.3–5.3)	3.1(2.3–4.6)	0.125

Notes: Data are presented as the IQR, mean ± SD or n (%). The groups were stratified by the severity of CHD (V1: single-vessel CHD; V2: stenosis of two main coronary arteries; V3, stenosis of three or more major coronary arteries).

Abbreviations: T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio.

Table 7 Relationship Between the Severity of CHD with BMI, TG, FGB, HbA1c, TyG and NLR

Variable	r	p
FBG (mmol/L)	0.261	<0.001
HbA1c (%)	0.244	<0.001
BMI (kg/m ²)	−0.077	0.079
TG (mmol/L)	0.145	0.001
TyG index	0.315	<0.001
NLR	0.250	<0.001

Notes: correlation analysis was used to analyze the relationship between the severity of CHD and various indicators.

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; BMI, body mass index; TG, triglyceride; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio.

Associations of the TyG Index and NLR with CAD Severity in T2DM

Logistic regression modelling showed a significant association between TyG index and CHD severity. Using TyG index as a categorical variable and T1 as the control group, after adjusting for risk factors such as age, sex, smoking, hypertension, and history of taking hypoglycaemic and dyslipidemia medications, the risk of multivessel CHD was 2.02 times (OR, 2.02; 95% CI, 1.29–3.17; $P=0.002$) and 2.96 times (OR, 2.96; 95% CI, 1.19–7.32; $P=0.019$; Table 8), a statistically significant difference. In contrast, in the NLR tertile subgroup, the results showed no statistically significant difference between NLR and CHD severity ($P>0.05$, Table 9).

Predictive Value of TyG Index and NLR for the Development of CHD in T2DM

ROC curves were used to evaluate the diagnostic value of TyG index, NLR and their combinations for the occurrence of CHD in the T2DM population. As shown in Table 10, the AUCs of TyG index and NLR for predicting CHD were 0.717 (95% CI, 0.659–0.775) and 0.692 (95% CI, 0.639–0.746), respectively; the sensitivities were 85.6% and 66.4%,

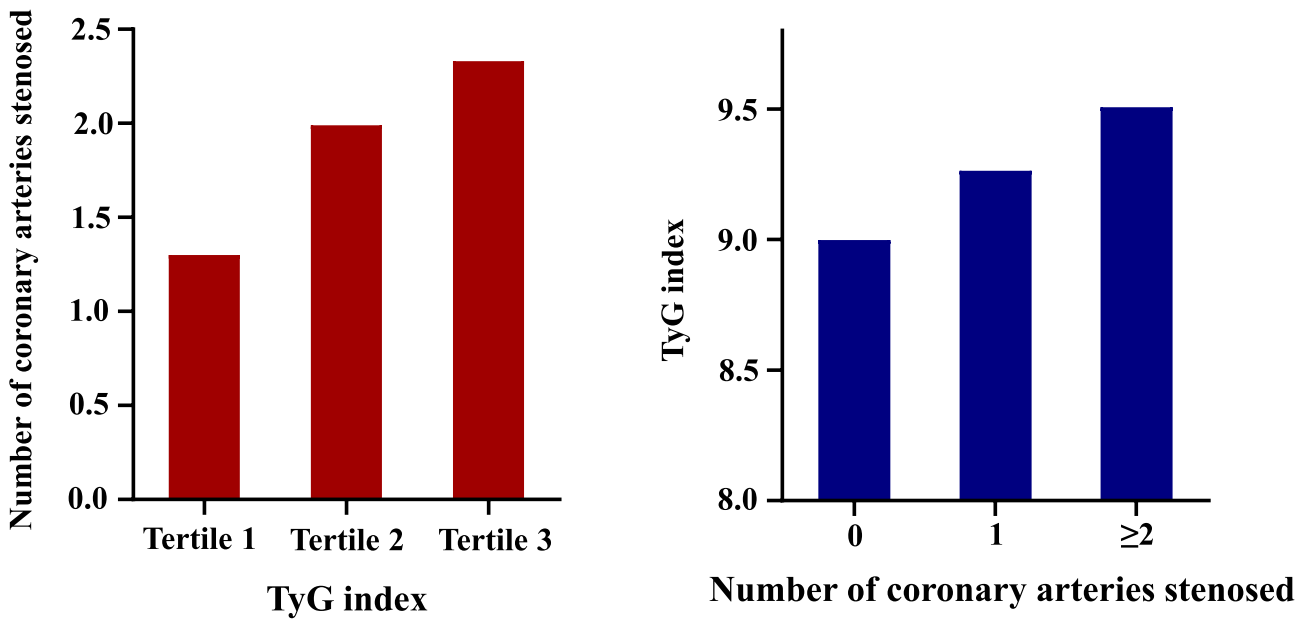


Figure 2 The relationship between TyG index and severity of CHD in T2DM+CHD patients. The red bar chart illustrates the number of coronary artery stenoses within the three-segment TyG index group of T2DM+CHD patients. Conversely, the blue bar chart represents the TyG index values corresponding to the number of three-segment coronary artery stenoses in this patient cohort.
Abbreviations: TyG index, triglyceride-glucose index; CHD, coronary heart disease.

respectively; and the specificities were 54.1% and 63.9%, respectively. The combined predictive value of TyG index and NLR was 0.761(95% CI, 0.709–0.813); sensitivity was 87.1%; and specificity was 54.9%. The optimal cut-off values of TyG index, NLR and their combination for the diagnosis of CHD were 8.858, 2.542 and 0.687, respectively(all $P<0.001$).

Table 8 Association Between TyG Index and CHD Severity

TyG index	Model I		Model II		Model III	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
T 1	Ref.		Ref.		Ref.	
T 2	1.98(1.28–3.05)	0.002	2.00(1.29–3.09)	0.002	2.02(1.29–3.17)	0.002
T 3	2.93(1.24–6.89)	0.014	2.99(1.26–7.08)	0.013	2.96(1.19–7.32)	0.019

Notes: Model I: unadjusted. Model II: adjusted for age and sex. Model III: adjusted for age, sex, smoking status, hypertension, status of antidiabetic drugs and status of antilipidemic drugs. T1, $7.91 \leq \text{TyG index} \leq 9.03$; T2, $9.04 \leq \text{TyG index} \leq 9.57$; T3, $9.58 \leq \text{TyG index} \leq 11.48$.
Abbreviations: TyG index, triglyceride-glucose index; OR, odd ratio; CI: confidence interval; Ref, reference.

Table 9 Association Between NLR and CHD Severity

NLR	Model I		Model II		Model III	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
N1	Ref.		Ref.		Ref.	
N2	1.08(0.97–1.20)	0.178	1.07(0.97–1.19)	0.195	1.06(0.95–1.18)	0.278
N3	1.15(0.96–1.36)	0.126	1.13(0.95–1.35)	0.157	1.14(0.95–1.35)	0.154

Notes: Model I: unadjusted. Model II: adjusted for age and sex. Model III: adjusted for age, sex, smoking status, hypertension, status of antidiabetic drugs and status of antilipidemic drugs. N1, $0.54 \leq \text{NLR} \leq 2.31$; N2, $2.32 \leq \text{NLR} \leq 3.64$; N3, $\text{NLR} \geq 3.65$.
Abbreviations: NLR, neutrophil/lymphocyte ratio; OR, odd ratio; CI: confidence interval; Ref, reference.

Table 10 ROC Curves Analysis of TyG Index or/and NLR to Predict CHD

Variable	AUC	95% CI	P	sensitivity	specificity	Youden's index	Cut-off
TyG index	0.717	0.659–0.775	<0.001	0.856	0.541	0.397	8.858
NLR	0.692	0.639–0.746	<0.001	0.664	0.639	0.303	2.542
TyG index +NLR	0.761	0.709–0.813	<0.001	0.871	0.549	0.420	0.687

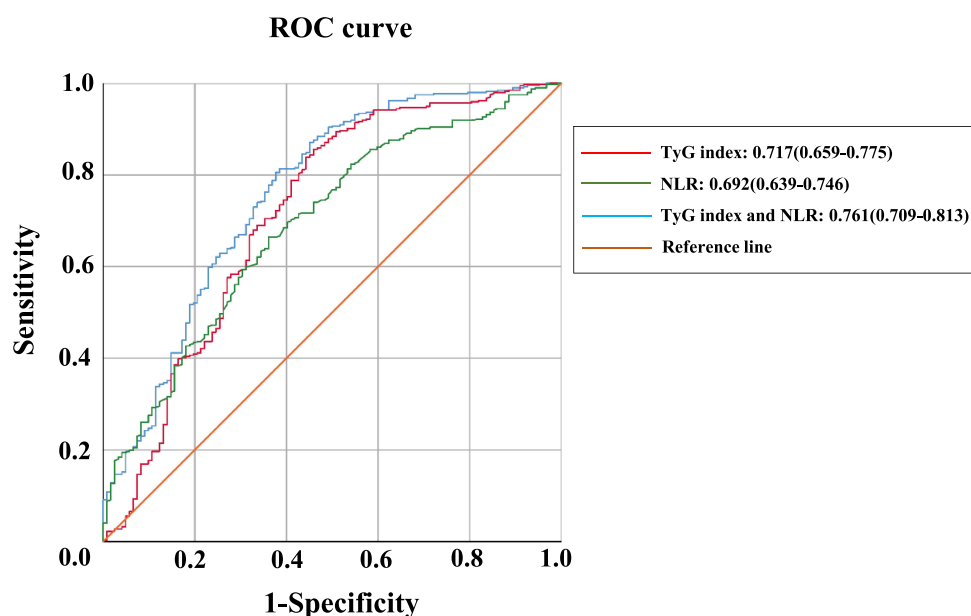
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CHD, coronary heart disease; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio;

The TyG index combined with the NLR enhanced the predictive strength and diagnostic ability of CHD, and all results were statistically significant (Figure 3, $P<0.001$).

The AUC for the combined TyG index and NLR model exceeds that of either individual model. To ascertain the model's efficacy, we conducted additional interaction analyses. As shown in Table S2, in the analysis of additive interaction, the relative excess risk due to interaction (RERI) is 0.089 (95% CI, 0.022–0.156). The attributable proportion due to interaction (APAB) is estimated at 0.054 (95% CI, 0.027–0.081). The synergy index (SI) is calculated to be 1.157 (95% CI, 1.117–1.198). A value of SI greater than 1 signifies the presence of a synergistic effect, and a 95% CI above 1 indicates that this synergistic effect is statistically significant. Thus, the additive interaction analysis has elucidated the synergistic effect between the TyG index and NLR, revealing that their combined effect surpasses the sum of their individual effects. Additionally, we executed net reclassification index(NRI) and integrated discrimination improvement(IDI) analyses for both combined and individual indicators. The results demonstrated that NRI was greater than 0, suggesting that the combined model can more accurately differentiate between distinct risk groups. Additionally, an IDI value greater than 0 indicates that the joint model has enhanced the overall predictive accuracy. Furthermore, the 95% CI for both NRI and IDI did not include 0, which further confirms the statistical significance of the combined effect (Table S3). This finding underscores the importance of considering both factors concurrently in clinical practice.

Discussion

This study investigated the correlation between TyG index and NLR with CHD and its severity in T2DM patients. The main findings were as follows: (1) TyG index and NLR were significantly associated with the occurrence of CHD in patients with T2DM, and this association persisted after adjusting for many confounding risk factors; (2) In the T2DM

**Figure 3** ROC curve analysis of TyG index or/and NLR to predict CHD.

Abbreviations: ROC, receiver operating characteristic; TyG index, triglyceride-glucose index; NLR, neutrophil/lymphocyte ratio.

combined CHD population, TyG index was significantly correlated with multivessel CHD, whereas there was no significant difference in NLR; (3) In the T2DM population, TyG index and NLR are a promising set of biomarkers for predicting CHD, and the combination of the two increases diagnostic efficacy.

IR is defined as a decrease in glucose uptake and utilization mediated by insulin and compensatory excess insulin secretion by the body.²⁷ Previous studies have revealed a strong and statistically significant correlation between IR and the risk of cardiovascular disease in different populations, especially among people diagnosed with T2DM and insulin-resistant coronary artery disease.²⁸ Chronic hyperglycemia and dyslipidemia, which result from IR, significantly contribute to the pathogenesis of cardiovascular disease.¹¹ Hyperglycemia substantially elevates the risk of microvascular dysfunction, the no-reflow phenomenon, and mortality following ACS and percutaneous coronary intervention (PCI), by triggering inflammatory responses, atherosclerosis, and oxidative stress.²⁹ Atherosclerosis is the main pathophysiological basis of CHD, and IR tends to cause body inflammation, vascular endothelial dysfunction, oxidative stress, disorders of glucose metabolism, lipid metabolism, and the formation of prothrombotic states, which ultimately accelerate the formation of atherosclerosis.^{30,31} In recent years, many studies have shown that IR is not only involved in atherosclerosis formation at an early stage, but can also play an important role in late plaque progression by promoting apoptosis of macrophages, vascular endothelial cells, and vascular smooth muscle cells.^{32,33} This may be a potential mechanism causing the development of CHD in patients with T2DM. The homeostasis model assessment estimated insulin resistance (HOMA-IR) index is a commonly used method for evaluating IR, but is of limited value in patients who have been treated with insulin or have severely impaired pancreatic β -cell function.^{12,34} The high insulin positive glucose clamp test is considered the gold standard for diagnosing IR, but its clinical use is limited by the high cost of the test, the complexity of the procedure, and the time-consuming nature of the test.¹³ The TyG index was first proposed as an alternative to the HOMA-IR by Simal-Mendía et al to assess IR.³⁵ Recently, a growing number of studies have shown that the TyG index is a simple and reliable index for estimating IR and is comparable to the HOMA-IR.³⁶ A large retrospective cohort study demonstrated that an elevated TyG index was significantly associated with an increased risk of adverse cardiovascular events, including fatal and nonfatal CHD, in an elderly population.³⁷ This is similar to the results of the present study, where the risk of CHD increased as the TyG index increased. This was a significant difference despite adjusting for risk factors such as age, sex, smoking history, hypertension, and history of taking glucose and lipid-lowering medications (Table 4). Previous studies have shown a correlation between TyG index and the number and severity of coronary stenoses.³⁸ Multivessel CHD has a higher prognosis and incidence of adverse cardiovascular events compared with single-vessel CHD, even with percutaneous coronary intervention.³⁹ The number of coronary artery stenoses maps the severity of CHD, and multivessel CHD increases the difficulty of coronary intervention, bringing it into greater focus in clinical practice. A recent study showed that TyG index was significantly associated with the occurrence of multivessel CHD in the DM population.²² Consistent with the results of previous studies, the present study demonstrated that the larger the TyG index, the greater the number of coronary stenoses and the higher the severity of CHD in the group, and the difference was statistically significant (Table 8 and Figure 2). There is growing epidemiologic evidence that IR constitutes an independent prognostic predictor of CHD, but IR or its surrogate markers have not yet been incorporated into any risk prediction tools such as the global registry of acute coronary events (GRACE) score or the synergy between percutaneous coronary intervention (SYNTAX) score. The study by Wang L et al concluded that the TyG index is independent of currently known cardiovascular risk factors and can be used to predict the future risk of major adverse cardiovascular events (MACE) in patients with DM and CHD.¹⁷ Park et al also concluded that the TyG index remains a valid marker for the early detection of subclinical coronary atherosclerosis even in the absence of traditional cardiovascular disease risk factors.⁴⁰ This study found that the TyG index will hopefully become a very clinically promising biomarker for early identification of high-risk CHD risk groups in T2DM patients, and that it can predict the severity of coronary artery lesions before CAG, enabling more targeted prevention and treatment.

Inflammation plays a central role in the pathogenesis of atherosclerosis, and elevated inflammatory markers indicate activation of vascular damage.⁴¹ Neutrophils are important inflammatory cells, and high levels of circulating neutrophils can cause hypercoagulability by increasing blood viscosity and releasing large amounts of pro-oxidants and prothrombotic substances, leading to platelet aggregation and vascular endothelial cell injury.⁴² In contrast, lymphocytes with immunomodulatory functions have anti-atherosclerotic effects.⁴³ As the understanding of the immune response in

the pathogenesis of CHD has deepened, researchers have turned their attention to the NLR, which reflects the dynamic balance between inflammatory activation and inflammatory regulation in the body and is more stable compared to absolute counts of neutrophils and lymphocytes.⁴⁴ In the inflammatory state, the number of CD8⁺ T-lymphocytes decreases, and with the imbalance in the ratio of lymphocyte subpopulations as well as their function, the body's immunity appears to be reduced. The persistent chronic inflammatory hold ultimately leads to IR and insulin secretion dysfunction, which promotes T2DM and its complications.⁴⁵ A large cohort study from China showed that the risk of future CHD in DM patients was 2–4 times higher than in non-DM patients, and about 75% of them died from coronary ischemia.⁴⁶ Compared to other inflammatory biomarkers such as hsCRP and TNF- α , NLR is more convenient and accessible for daily clinical use. NLR has been suggested as a diagnostic and prognostic marker for CHD.⁴⁷ In our study, NLR was independently associated with the development of CHD in T2DM patients, but the relationship with CHD severity has not been confirmed. The results remained statistically significant after correction for potential confounders (Tables 5–9). NLR is considered one of the markers of systemic inflammatory response and is valuable in predicting the occurrence and prognosis of CHD. This simple marker can help physicians make better clinical decisions.

The TyG index and NLR, as indicators of IR as well as inflammation, have become important predictors of CHD and MACE. The results of the ROC curves in this study showed that the AUC of TyG index and NLR for predicting the risk of CHD in T2DM patients was 0.717 and 0.692, respectively. The AUC of the two parameters combined for predicting CHD in patients with T2DM was 0.761. A prior study⁴⁸ identified the optimal cut-off value for TyG index in predicting CHD as 9.22, with the maximum AUC reaching 0.702, a sensitivity of 0.590, and a specificity of 0.784. Similar to our results, the optimal cut-off value of TyG is 8.86, the AUC is 0.717, and the sensitivity and specificity are 0.856, 0.541, respectively. Consistent with previous findings, a prior prospective study⁴⁹ determined the optimal cut-off value of NLR for predicting CHD to be 2.15, whereas in our analysis, the optimal cut-off value was found to be 2.54. The predictive value of TyG index combined with NLR was significantly higher than that of either TyG index or NLR. Our interaction analysis, along with NRI and IDI assessments, has substantiated the validity of our conclusions (Table S2-3).

Our findings have significant clinical implications for the management and risk stratification of CHD. By conducting a comprehensive evaluation of TyG index and NLR, healthcare providers can identify high-risk individuals with T2DM and implement more targeted and personalized prevention strategies. The objective of lowering blood glucose and lipid levels can be realized by adopting a healthier lifestyle, which includes dietary modifications and regular physical activity. Furthermore, for individuals at high risk, physicians should actively consider managing cardiovascular risk factors, including hypertension, hyperglycemia, and dyslipidemia, within this demographic. In clinical practice, the integration of the TyG index and NLR with established CHD risk factors enhances the predictive accuracy for unfavorable CHD outcomes. Thus, employing the combination of TyG index and NLR to identify the T2DM population at high cardiovascular risk can facilitate timely prevention and management of CHD onset and progression. This approach can reduce the incidence of multivessel coronary disease, enhance patient survival rates, and improve long-term prognoses for those with CHD, as well as elevate their quality of life.

Strengths and Limitations

The strength of this study lies in the fact that it was conducted in patients with T2DM, which is a chronic disease population with a very large base size. In addition, our study is the first to investigate the value of TyG index combined with NLR in predicting CHD and CHD severity in a T2DM population. There are also some limitations to this study. First, due to the inherent limitations of retrospective studies, we were unable to determine the existence of a causal relationship. Second, the final results of observational studies are always affected by confounding factors and statistical results may be biased. Finally, the study population was single-center and relatively small. Future multi-center, large sample and prospective studies are needed to further explore this.

Conclusion

Our study found that TyG index and NLR were significantly higher in T2DM patients combined with CHD than in patients with T2DM alone, and that TyG index was positively correlated with CHD severity. The combination of TyG index and NLR was superior to TyG index or NLR in predicting CHD. The TyG index and NLR may be complementary

to traditional cardiovascular disease risk factors, and their relevance may be higher especially in T2DM, a population at high risk of MACE. It can be widely used in primary and community hospitals due to its simplicity, inexpensiveness and convenience, but this needs to be further confirmed in larger studies.

Abbreviations

TyG Index, triglyceride glucose index; NLR, neutrophil/lymphocyte ratio; T2DM, type 2 diabetes mellitus; CAC, coronary artery calcification; CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IR, Insulin resistance; PSM, propensity score matching; PCI, percutaneous coronary intervention; HOMA-IR, homeostasis model assessment for IR; MACE, major adverse cardiovascular events; GRACE Score, global registry of acute coronary events score; SYNTAX Score, the synergy between percutaneous coronary intervention score; OR, odd ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the curve; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index. NRI, net reclassification index; IDI, integrated discrimination improvement.

Data Sharing Statement

Due to privacy and ethical constraints, the data generated and analyzed in this study are not publicly available. All data about the patients was anonymized or maintained confidentially.

Consent for Publication

All the authors agree to publish.

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We thank all participants in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest.

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