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ORIGINAL RESEARCH

Association Between Triglyceride–Glucose Index and Carotid Plaque Stability in Different Glycemic Status: A Single-Center Retrospective Study

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BACKGROUND: The triglyceride–glucose (TyG) index has been proposed as a reliable marker of insulin resistance. However, its value in patients with carotid plaque stability remains unclear. This study investigated the association between the TyG index and unstable carotid plaque.

METHODS: A total of 12 068 participants were enrolled. Carotid ultrasound was used to determine the stability of carotid plaque. Logistic regression was used to analyze the relationship between the TyG index and unstable carotid plaque. The relationship between the TyG index and unstable carotid plaque was evaluated according to sex, age, and glucose metabolism states. Further, the dose–response relationship between the TyG index and unstable carotid plaque was also determined by restrictive cubic splines.

RESULTS: Of the 12 068 participants, 11 601 had stable carotid plaque and 467 had unstable carotid plaque. In several different adjustment models, the TyG index is significantly related to the risk of unstable carotid plaque. The association between the TyG index and an unstable carotid plaque was similar between men and women, despite the fact that the odds ratio (OR) tended to be higher in men (OR, 2.80 [95% CI, 2.04–3.83]) than women (OR, 2.07 [95% CI, 1.51–2.82]), and higher in older patients (aged >60 years; (OR, 3.59 [95% CI, 2.74–4.70]) than middle-aged patients (aged ≤60 years) (OR, 2.00 [95% CI, 1.36–2.95]). The TyG index of patients with different glycemic status was significantly correlated with the risk of unstable carotid plaque, among which the OR value of diabetes (OR, 2.51 [95% CI, 1.87–3.36]) was the highest. The restrictive cubic spline analysis indicated a nonlinear relationship between the TyG index and unstable carotid plaque, with TyG index >8.63 identified as an independent risk factor for unstable carotid plaque.

CONCLUSIONS: The TyG index has a significant association with unstable carotid plaque. The association between the TyG index and unstable carotid plaque is similar between men and women, and the association in older patients is higher than that in middle-aged patients. In different glycemic status, the association between the TyG index and unstable carotid plaque is highest in patients with diabetes.

Key Words: carotid plaque stability ■ fasting plasma glucose ■ triglyceride ■ TyG index ■ unstable carotid plaque

Stroke is a leading cause of death and disability in adults worldwide, and the risk of stroke in the Chinese population ranks first in the world.[1,2] About 7% to 18% of ischemic strokes are related to carotid atherosclerosis.[3,4] At present, it is believed that the occurrence of stroke is closely related not only to

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CLINICAL PERSPECTIVE

What Is New?

- This is the first large-scale study to explore the relationship between the triglyceride–glucose index and unstable carotid plaque in different glycemic statuses.
- The research revealed a strong association between the triglyceride–glucose index and unstable carotid plaque; this relationship is similar for both men and women, but it is notably stronger in older patients compared with middle-aged patients.
- In different glycemic status, those with diabetes exhibit the most significant connection between the triglyceride–glucose index and unstable carotid plaque.

What Are the Clinical Implications?

- The results of this study emphasize the need for risk management strategies for different sexes, ages, and glycemic statuses to prevent patients from developing unstable carotid plaque.

Nonstandard Abbreviations and Acronyms

FPG	fasting plasma glucose
IR	insulin resistance
RCS	restrictive cubic spline
TyG	triglyceride–glucose

the degree of carotid artery stenosis but also to the stability of carotid plaque.[5,6] The rupture of unstable carotid plaque is more likely to lead to ischemic stroke in clinic.[7] Therefore, early identification of unstable carotid plaque and intervention and management are essential to reduce the occurrence of stroke events.

Insulin resistance (IR) refers to the weakening of the physiological effect of insulin in the body, which is a common pathological mechanism of a variety of metabolic-related diseases, and is closely related to the occurrence and development of atherosclerosis.[8–10] The triglyceride–glucose (TyG) index was proposed and has become a reliable alternative biomarker for IR.[11,12] More and more evidence shows that there is a significant association between carotid unstable plaque and stroke events, and there is also a significant association between the TyG index and stroke events.[13–15] Although it has been reported in the literature that the TyG index is significantly correlated with unstable carotid plaque in patients without diabetes.[16] However, the current evidence on the relationship between the TyG index and unstable plaques is limited. Moreover, there is no relevant research to explore the relationship between the TyG index and unstable carotid plaque according to the patient's different glycemic status. Therefore, further evidence is needed to better understand the complex relationship between the TyG index and unstable carotid plaque in different glycemic statuses.

Therefore, the purpose of this study is to clarify the association between the TyG index and unstable carotid plaque in different glycemic statuses, and further explore the association between the TyG index and unstable carotid plaque in different sexes and ages. Finally, the dose–response relationship between TyG index and unstable carotid plaque is discussed by using restricted cubic splines (RCSs).

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This retrospective study complied with the Declaration of Helsinki and was approved by the Affiliated Suzhou Hospital of Nanjing Medical University Ethical Committee, and all subjects gave informed consent. This retrospective study included 30 869 patients who underwent carotid artery ultrasonography from January 2020 to January 2024 in the Affiliated Suzhou Hospital of Nanjing Medical University. Exclusion criteria included the following: (1) The data of triglyceride and fasting plasma glucose (FPG) are incomplete; and (2) carotid ultrasound showed that there was no carotid plaque. A total of 12 068 participants were eventually included in the study. This study was conducted in accordance with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology.[17] The flowchart of patient screening is shown in Figure 1.

Data Collection and Definition

Fasting blood samples were taken from all participants, and biochemical measurements were analyzed. The following clinical data were obtained, including sex, age, low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL), high-density lipoprotein cholesterol (HDL-C), urea, uric acid (UA), total bilirubin, direct bilirubin, indirect bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol (TC), triglyceride, FPG, hemoglobin A_{1c} (HbA_{1c}), white blood cell count (WBC), CRP (C-reactive protein), neutrophils, lymphocytes, red blood cell count (RBC), creatinine, blood platelet count (PLT), hemoglobin, and TyG index. Serum biochemical

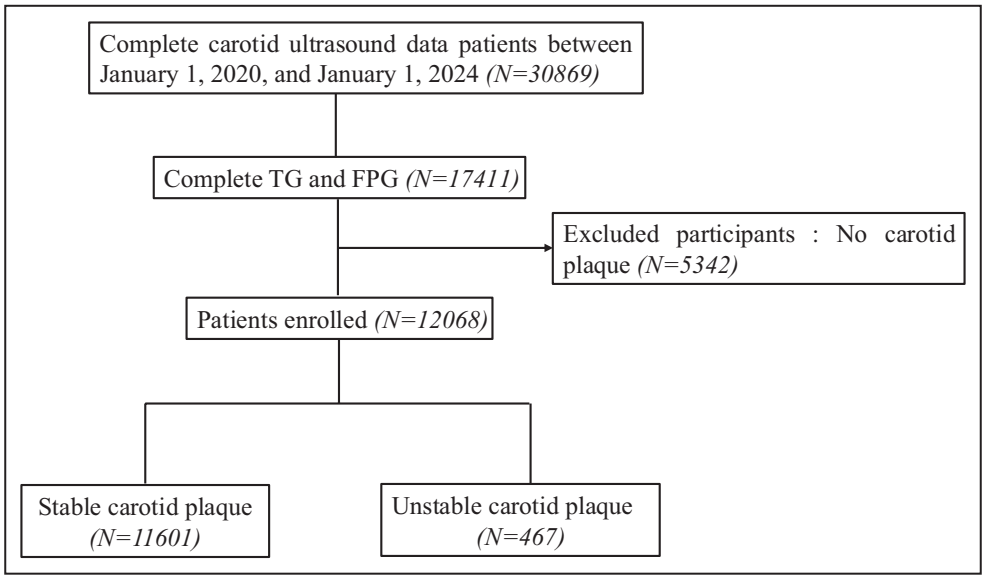

Figure 1. Flowchart of patient recruitment.
FPG indicates fasting plasma glucose; and TG, triglyceride.

parameters were determined with a biochemical autoanalyzer (Hitachi 7600, Tokyo, Japan). Blood routine parameters were determined with an automatic blood cell analyzer (BC-6800Plus, Mindray, Guangdong, China). LDL-C is measured by using catalase LDL-C assay, HDL-C is measured by using polyanion polymer/detergent HDL-C assay, and VLDL is calculated using the formula: VLDL=TC–HDL-C–LDL-C.[18–20] The TyG index was calculated as ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. Glycemic statuses are classified as normal glucose regulation, prediabetes, and diabetes. Normal glucose regulation was defined as FPG <5.6 mmol/L or HbA_{1c} <5.7%. Prediabetes was defined as FPG of 5.6 to 6.9 mmol/L or HbA_{1c} of 5.7% to 6.4%. Diabetes was defined as FPG ≥7.0 mmol/L or HbA_{1c} ≥6.5%.[21]

Assessment of Stability of Carotid Plaque

Carotid ultrasound is performed by certified professional technicians using an ultrasound diagnostic system (Resona7, Mindray). The common carotid artery, internal carotid artery, and carotid bifurcation were scanned. Stable carotid plaque has a uniform texture, smooth and regular surface, and high level or even plaque echo. Unstable carotid plaque was defined as low level or heterogeneous echogenic plaque according to plaque echo density, and as incomplete fibrous cap plaque or ulcerative plaque according to plaque morphology.[22,23] Carotid artery ultrasound results are reviewed by 2 independent technicians, and a consistent result is obtained. When the results of 2 technicians are inconsistent, a third technician is sought for consistent verification, and the consistent result shall prevail.

Statistical Analysis

Quantitative variables were expressed as mean±SE, differences between groups were analyzed by independent sample *t* test. Categorical variables were expressed as numbers and percentages and were compared using the χ^2 test. The relationship between the TyG index and carotid plaque stability was evaluated using a logistic regression by calculating odds ratios (ORs) and 95% CIs. Sex, age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, HbA_{1c}, total bilirubin, ALT, and AST were considered as potential confounders in this association. The collinearity of the different models was tested before logistic regression. Four models are established by adjusting different covariates. In the unadjusted model, no covariates were adjusted. In model 1, data were adjusted for sex, age, WBC, CRP, neutrophil, RBC, PLT, and hemoglobin. In model 2, data were adjusted for sex, age, LDL-C, VLDL, TC, HDL-C, UA, direct bilirubin, indirect bilirubin, ALT, and AST. In model 3, data were adjusted for sex, age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, direct bilirubin, indirect bilirubin, ALT, and AST. The receiver operating characteristic curves were established to assess the predictive value of FPG, triglyceride, and the TyG index on incidence of unstable carotid plaque, and the area under the curve was used to quantify. Sex, age, and glycemic status were analyzed in subgroups. The missing values are interpolated by the k-nearest neighbor method. The dose–response relationship between TyG and unstable carotid plaque was determined by RCSs. All statistical analyses were performed using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population Characteristics

A total of 12 068 participants were included in this study. Of these, 467 had unstable carotid plaque, and 11 601 had stable carotid plaque. The median age was 66.09 years, and 6328 (52.44%) participants were women. Among them, 5317 (44.06%) patients with diabetes accounted for the highest proportion. Participants with unstable carotid plaque are generally men, are older, and have diabetes; have a higher level of WBC, CRP, neutrophils, RBC, hemoglobin, LDL-C, VLDL, TC, triglyceride, FPG, TyG, UA, total bilirubin, direct bilirubin, indirect bilirubin, ALT, and AST; and have a lower level of HDL-C and PLT. The demographic and clinical characteristics of all patients are shown in Table 1.

TyG Index Is an Independent Predictor of Unstable Carotid Plaque

This study used multivariate logistic regression to examine the relationship between the TyG index and unstable carotid plaque and carefully adjust the potential

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Carotid plaque stability			*P* value
	Overall (N=12 068)	Stable carotid plaque (N=11 601)	Unstable carotid plaque (N=467)	
Sex, n (%)				<0.001
Male	5740 (47.56)	5479 (47.23)	261 (55.89)	
Female	6328 (52.44)	6122 (52.77)	206 (44.11)	
Age, y	66.09±13.72	66.03±13.76	67.46±12.61	0.017
WBC, 10^9/L	6.84±2.68	6.83±2.68	7.18±2.61	0.004
Neutrophil	4.18±2.22	4.17±2.22	4.49±2.37	0.004
Lymphocytes, 10^9/L	1.79±0.91	1.79±0.92	1.85±0.73	0.064
RBC, 10^{12}/L	4.25±0.65	4.25±0.65	4.34±0.70	0.010
Hemoglobin, g/L	128.92±19.64	128.82±19.57	131.36±21.27	0.012
PLT, 10^9/L	211.35±68.74	211.72±68.89	202.14±64.32	0.001
CRP, mg/L	5.34±4.12	5.32±4.16	5.77±3.02	0.002
FPG, mmol/L	6.30±2.27	6.21±2.11	8.55±4.27	<0.001
HbA_{1c}, %	7.02±1.90	6.98±1.86	8.32±2.49	<0.001
TC, mmol/L	4.35±1.18	4.34±1.16	4.80±1.42	<0.001
Triglyceride, mmol/L	1.64±1.33	1.54±1.00	4.09±3.86	<0.001
HDL-C, mmol/L	1.19±0.34	1.19±0.34	1.01±0.30	<0.001
LDL-C, mmol/L	2.70±1.04	2.67±1.03	3.28±1.04	<0.001
VLDL, mmol/L	0.49±0.30	0.47±0.23	0.99±0.86	<0.001
UA, mmol/L	329.63±101.39	328.32±100.66	362.00±113.44	<0.001
Urea, mmol/L	6.83±4.36	6.82±4.37	7.18±3.95	0.056
Creatinine, μmol/L	76.24±56.59	76.10±56.76	79.74±52.28	0.143
Indirect bilirubin, μmol/L	8.36±4.63	8.34±4.63	9.07±4.60	<0.001
Direct bilirubin, μmol/L	4.02±2.416	3.99±2.37	4.99±3.31	<0.001
Total bilirubin, μmol/L	12.30±9.35	12.27±9.46	12.90±5.83	0.029
ALT, U/L	23.14±16.87	23.02±16.77	25.96±18.99	0.001
AST, U/L	21.68±14.84	21.60±14.68	23.72±18.32	0.014
TyG index	8.78±0.69	8.74±0.64	9.71±1.10	<0.001
Glucose regulation state, n (%)				<0.001
Normal glucose tolerance	2399 (19.88)	2348 (20.24)	51 (10.92)	
Prediabetes	4352 (36.06)	4266 (36.77)	86 (18.42)	
Diabetes	5317 (44.06)	4987 (42.99)	330 (70.66)	

ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

Table 2. Multivariable Logistic Regression Analysis of the Relationship Between TyG Index and the Risk of Unstable Carotid Plaque

Variables	OR	95% CI	*P* value
Unadjusted	5.71	5.01–6.51	<0.001
Adjusted model I	5.77	5.05–6.60	<0.001
Adjusted model II	2.71	2.20–3.34	<0.001
Adjusted model III	2.64	2.12–3.27	<0.001

Model I was adjusted for sex, age, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.

Model II was adjusted for sex, age, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.

Model III was adjusted for sex, age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

confounding variables. Four models were developed to evaluate the association between the TyG index and unstable carotid plaque. After adjusting for multiple confounding factors, the TyG index was associated with a risk of unstable carotid plaque (OR, 2.64 [95% CI, 2.12–3.27]). The research results, including ORs and its corresponding 95% CI, have been analyzed in detail in Table 2. We further evaluated the predictive value of the TyG index for unstable carotid plaque and compared it with that of FPG and triglyceride. The results showed that the area under the curve of FPG, triglyceride, and the TyG index were 0.523 (95% CI, 0.505–0.541), 0.579 (95% CI, 0.561–0.597), and 0.637 (95% CI, 0.620–0.654), respectively (Figure 2). Compared with FPG and triglyceride, the TyG index showed better diagnostic performance. As shown in Table 3, this relationship remained statistically significant after subgroup analysis for sex. After multivariate adjustment, the OR tended to be higher in men (OR, 2.80 [95% CI, 2.04–3.83]) than women (OR, 2.07 [95% CI, 1.51–2.82]). Interaction analysis showed that there was no interaction between the TyG index and unstable carotid plaque in the group of sex (*P* for interaction=0.227). Therefore, the association between the TyG index and unstable carotid plaque was similar between men and women.

As shown in Table 4, after subgroup analysis for different age groups and multivariate adjustment, the TyG index is significantly correlated with unstable carotid plaque in different age groups. Interaction analysis showed that there was interaction between the TyG index and unstable carotid plaque in group of age (*P* for interaction<0.001). Therefore, the association between the Tyg index and unstable carotid plaque in older patients (aged >60 years) (OR, 3.59 [95% CI, 2.74–4.70]) was significantly higher than that in middle-aged patients (aged ≤60 years) (OR, 2.00 [95% CI, 1.36–2.95]). Regardless of sex and age, the TyG index is related to the increased risk of unstable carotid plaque, and this relationship remains stable after multifactor adjustment.

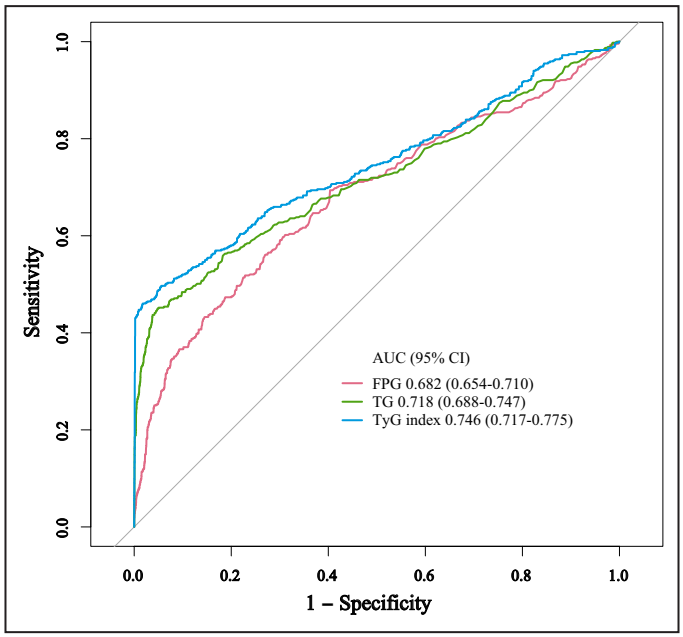

Figure 2. Receiver operating characteristic curves of FPG, triglyceride, and TyG index.
Compared with FPG and TG, the TyG index showed better diagnostic performance. AUC indicates area under the curve; FPG, fasting plasma glucose; TG, triglyceride; and TyG, triglyceride–glucose.

Table 3. Association Between the TyG Index and the Risk of Unstable Carotid Plaque According to Sex

Variables	Male		Female		*P* for interaction
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
Unadjusted	6.33 (5.29–7.59)	<0.001	4.94 (4.07–5.98)	<0.001	0.064
Adjusted model I	6.94 (5.75–8.37)	<0.001	4.66 (3.84–5.67)	<0.001	0.058
Adjusted model II	2.64 (1.94–3.59)	<0.001	2.40 (1.78–3.23)	<0.001	0.226
Adjusted model III	2.80 (2.04–3.83)	<0.001	2.07 (1.51–2.82)	<0.001	0.227

Model I was adjusted for age, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.
Model II was adjusted for age, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.
Model III was adjusted for age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

Association Between the TyG Index and Unstable Carotid Plaque According to Glycemic Status

As shown in Table 5, after multifactor adjustment, the TyG index of patients with different glycemic statuses was significantly correlated with the risk of unstable carotid plaque, among which the OR value of diabetes (OR, 2.51 [95% CI, 1.87–3.36]) was the highest. Interaction analysis showed that there was interaction between the TyG index and unstable carotid plaque in the group of glycemic status (*P* for interaction=0.012). Therefore, the relationship between the Tyg index and unstable carotid plaque was the highest in patients with diabetes. As shown in Table 6, in male patients, there was a significant association between the TyG index and unstable carotid plaque risk in patients with prediabetes (OR, 2.66 [95% CI, 1.10–6.70]) and diabetes (OR, 2.71 [95% CI, 1.79–4.11]). The association between the TyG index and unstable carotid plaque was similar in male with prediabetes and diabetes (*P* for interaction=0.076), despite the OR tended to be higher in diabetes than prediabetes. In female patients, this study observed a significant association between the TyG index and unstable carotid plaque risk in patients with normal glucose regulation (OR, 0.29 [95% CI, 0.11–0.78]) and diabetes (OR, 2.43 [95% CI, 1.55–3.83]). The association between the TyG index and the risk of unstable carotid plaque was highest in patients with diabetes (*P* for interaction <0.001). It is worth mentioning that a higher TyG index was associated with more stable carotid plaque in women with normal glucose regulation. Regardless of sex, the TyG index is significantly related to the increased risk of unstable carotid plaque in patients with diabetes.

As shown in Table 7, in patients aged ≤60 years, there was a significant association between the TyG index and unstable carotid plaque risk in patients with diabetes (OR, 2.25 [95% CI, 1.30–3.91]). In patients aged >60 years, we also observed a significant association between the TyG index and unstable carotid plaque risk in patients with diabetes (OR, 2.81 [95% CI, 1.97–4.01]). Regardless of age, the TyG index is significantly related to the increased risk of unstable carotid plaque in patients with diabetes.

Restricted Cubic Spline Regression Analysis

The RCS curve indicates that the TyG index and unstable carotid plaque have a nonlinear relationship (*P*<0.001). The results of the RCS curve showed that for a TyG index >8.63, the prevalence of unstable carotid plaque increased rapidly with the increase of TyG index (Figure 3).

Table 4. Association Between the TyG Index and the Risk of Unstable Carotid Plaque According to Age

Variables	Age ≤60		Age >60		*P* for interaction
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
Unadjusted	3.64 (2.96–4.47)	<0.001	7.51 (6.32–8.94)	<0.001	<0.001
Adjusted model I	3.75 (3.03–4.64)	<0.001	7.57 (6.35–9.02)	<0.001	<0.001
Adjusted model II	2.03 (1.40–2.94)	<0.001	3.58 (2.74–4.66)	<0.001	<0.001
Adjusted model III	2.00 (1.36–2.95)	<0.001	3.59 (2.74–4.70)	<0.001	<0.001

Model I was adjusted for sex, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.
Model II was adjusted for sex, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.
Model III was adjusted for sex, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

Table 5. Association Between TyG Index and the Risk of Unstable Carotid Plaque According to Glycemic Status

Variables	Normal glucose regulation		Prediabetes		Diabetes	*P* value	*P* for interaction
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)		
Unadjusted	3.57 (2.43–5.22)	<0.001	3.38 (2.44–4.67)	<0.001	6.67 (5.59–7.97)	<0.001	<0.001
Adjusted model I	3.55 (2.40–5.27)	<0.001	3.44 (2.47–4.78)	<0.001	6.78 (5.66–8.13)	<0.001	<0.001
Adjusted model II	1.52 (0.84–2.75)	0.166	1.79 (1.06–3.03)	0.028	2.49 (1.87–3.31)	<0.001	0.011
Adjusted model III	1.47 (0.80–2.69)	0.215	1.76 (1.03–3.02)	0.040	2.51 (1.87–3.36)	<0.001	0.012

Model I was adjusted for sex, age, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.
Model II was adjusted for sex, age, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.
Model III was adjusted for sex, age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

DISCUSSION

This is the first large-scale study to reveal a significant association between the TyG index and unstable carotid plaque, and this relationship was assessed according to sex, age, and glycemic status. In several different adjustment models, TyG index is significantly related to the risk of unstable carotid plaque. The association between the TyG index and an unstable carotid plaque was similar between men and women and higher in older patients than in middle-aged patients. The TyG index of patients with different glycemic statuses was significantly correlated with the risk of unstable carotid plaque, and the association was highest in patients with diabetes. Further analysis showed that regardless of sex and age, under different glycemic statuses, the TyG index is significantly related to the increased risk of unstable carotid plaque in patients with diabetes. It is worth mentioning that a higher TyG index was associated with more stable carotid plaque in women with normal glucose regulation. The restricted cubic spline analysis indicated a nonlinear relationship between the TyG index and unstable carotid plaque, with a TyG index >8.63 identified as an independent risk factor for unstable carotid plaque. These findings underscore the usefulness of this simple and easily calculated measure for early identification of patients with unstable carotid plaque.

The typical features of unstable carotid plaques are a large lipid-rich core and a thin fibrous cap, intraplaque hemorrhage, and ulceration.[24] The rupture of unstable carotid plaque is more likely to lead to stroke events.[25] Therefore, the detection of biomarkers for unstable carotid plaque may be even more important for stroke prevention. In recent years, the research shows that the prediction value of the TyG index for IR is better than homeostatic model assessment for IR.[26] A prospective cohort study reported that the TyG index was positively correlated with the prevalence of carotid plaque and could be used as a marker of carotid plaque.[27] In addition, studies have reported that the TyG index is correlated with carotid intima-media thickness, plaque burden, and carotid artery stenosis.[28,29] However, there are few reports on the relationship between TyG and carotid plaque stability. This study included 12 068 participants, and it was found that an increase of the TyG index was significantly associated with the risk of unstable carotid plaque formation, which was still significant even after adjusting multiple models.

Previous studies have shown that men and older patients have a higher risk of cardiovascular and cerebrovascular disease compared with women and middle-aged patients.[30,31] Wang et al enrolled 4748 participants without diabetes and used ultrasound to examine carotid plaque stability. The results showed that the prevalence of unstable carotid plaques increased significantly with an increase of the TyG index, which is consistent with the results of this study.[32] This study shows that the association between the TyG index and an unstable carotid plaque was similar between men and women, despite the fact that the OR tended to be higher in men than women, and compared with middle-aged people, the TyG index of older patients has a higher association with unstable carotid plaques, this suggests that in the same situation, older patients need more attention. At the same time, this study further conducted stratified analysis of TyG and unstable carotid plaque under different glycemic statuses, and the results showed that TyG was significantly correlated with unstable carotid plaque under different glycemic statuses, suggesting that to prevent the formation of unstable carotid plaque, the TyG index should be reduced as far as possible within a reasonable range. In different glycemic statuses, the association between the TyG index and unstable carotid plaque is highest in patients with diabetes. This suggests that clinicians need to pay more attention to patients with diabetes and dynamically monitor TyG

Table 6. Association Between the TyG Index and the Risk of Unstable Carotid Plaque According to Different Glycemic Status and Sex

Variables	Men						Women					
	Normal glucose regulation		Prediabetes		Diabetes		N ormal glucose regulation		Prediabetes		Diabetes	
	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	*P* for interaction
Unadjusted	5.72 (3.48–9.38)	<0.001	4.68 (3.16–6.95)	<0.001	6.85 (5.36–8.76)	<0.001	0.267	1.34 (0.64–2.80)	0.467	1.54 (0.85–2.78)	0.310	6.38 (4.93–8.26)	<0.001	<0.001
Adjusted Model I	5.74 (3.43–9.53)	<0.001	4.92 (3.26–7.44)	<0.001	7.69 (5.95–9.93)	<0.001	0.199	1.32 (0.62–2.80)	0.467	1.55 (0.86–2.79)	0.310	5.97 (4.59–7.76)	<0.001	<0.001
Adjusted Model II	1.82 (0.63–5.29)	0.285	3.24 (1.15–6.18)	0.028	2.50 (1.67–3.74)	<0.001	0.126	0.28 (0.11–0.75)	0.001	0.69 (0.30–1.55)	0.364	2.64 (1.73–4.01)	<0.001	<0.001
Adjusted Model III	1.91 (0.59–6.19)	0.298	2.66 (1.10–6.70)	0.034	2.71 (1.79–4.11)	<0.001	0.076	0.29 (0.11–0.78)	0.001	0.62 (0.27–1.42)	0.351	2.43 (1.55–3.83)	<0.001	<0.001

Model I was adjusted for age, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.
Model II was adjusted for age, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.
Model III was adjusted for age, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

levels. Regardless of sex, age, and glycemic status, the TyG index is significantly related to an increased risk of unstable carotid plaque.

After further analysis of the relationship between sex and different glycemic statuses, the results showed that the association between the TyG index and unstable carotid plaque was similar in men with prediabetes and diabetes. This suggests that for male patients, we should control the level of TyG at a relatively low level, especially patients with prediabetes and diabetes. In female patients, an increase in the TyG index was associated with unstable carotid plaques in patients with diabetes. Current studies show that unstable carotid plaque is closely related to the occurrence of stroke events[33,34] In China, the prevalence of stroke in men is significantly higher than that in women.[35] There is growing evidence that biological sex has a significant impact on the development of metabolic disorders, with women being more protected than men. This protection appears to be driven by the estrogens; it will disappear with the onset of menopause.[36,37] Bonora's research results show that diabetes is a risk factor for atherosclerosis, and there is no obvious correlation between early atherosclerosis and insulin resistance in patients without diabetes.[38] Therefore, in female patients with normal glucose regulation, the increase of the TyG index is related to stable carotid plaques; it may be that estrogen levels partially counteract the effects of insulin resistance. Therefore, for female patients, the TyG index level should be regulated according to their different glycemic status. The results also showed that the TyG index of patients with diabetes had the highest association with unstable carotid plaque in men and women, which required us to strengthen the early intervention and management of patients with diabetes. Subsequently, the TyG index and unstable carotid plaque in middle-aged and older people under different glycemic statuses were further analyzed. The results reveal that regardless of age, the TyG index is significantly related to the increased risk of unstable carotid plaque in patients with diabetes. Therefore, regardless of age, in patients with diabetes, we should control the TyG level at a relatively low level and dynamically monitor the TyG index to prevent the formation of unstable carotid plaque. Finally, the RCS curve showed that the TyG index presented a nonlinear relationship with unstable carotid plaque. When the TyG index was >8.63, the risk of unstable carotid plaque increased rapidly. Therefore, to avoid the formation of unstable carotid plaque, it is necessary to reduce the TyG index to <8.63. As far as we know, this study represents a groundbreaking analysis to explore the association between the TyG index and unstable carotid plaque.

Although the specific mechanism of the TyG index and unstable carotid plaque is still unclear, it may be

Table 7. Association Between the TyG Index and the Risk of Unstable Carotid Plaque According to Different Glycemic Statuses and Ages

Variables	Age ≤60						Age >60					
	Normal glucose regulation		Prediabetes		Diabetes		Normal glucose regulation		Prediabetes		Diabetes	
	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	*P* for interaction	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	OR (95% CI)	*P* adjusted	*P* for interaction
Unadjusted	3.05 (1.80–5.17)	<0.001	2.23 (1.35–3.70)	0.004	4.62 (3.42–6.23)	<0.001	0.035	4.16 (2.38–2.35)	<0.001	4.79 (3.10–7.39)	<0.001	7.79 (6.38–9.95)	<0.001	0.024
Adjusted model I	3.18 (1.81–5.57)	<0.001	2.52 (1.51–4.22)	0.003	4.64 (3.41–6.31)	<0.001	0.055	4.21 (2.35–7.52)	<0.001	4.62 (2.97–7.21)	<0.001	8.05 (6.42–10.09)	<0.001	0.015
Adjusted model II	1.22 (0.22–6.84)	0.746	1.37 (0.51–3.70)	0.704	1.96 (1.17–3.28)	0.007	0.003	1.80 (0.72–4.55)	0.445	1.92 (0.95–3.86)	0.167	2.79 (1.97–3.97)	<0.001	0.832
Adjusted model III	0.43 (0.04–4.37)	0.680	1.16 (0.40–3.42)	0.785	2.25 (1.30–3.91)	0.002	0.003	1.48 (0.56–3.93)	0.740	1.78 (0.86–3.70)	0.248	2.81 (1.97–4.01)	<0.001	0.655

Model I was adjusted for sex, WBC, CRP, neutrophils, RBC, PLT, and hemoglobin.
Model II was adjusted for sex, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST.
Model III was adjusted for sex, WBC, CRP, neutrophils, RBC, PLT, hemoglobin, LDL-C, VLDL, TC, HDL-C, UA, DBIL, IBIL, ALT, and AST. ALT indicates alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; DBIL, direct bilirubin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IBIL, indirect bilirubin; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBIL, total bilirubin; TC, total cholesterol; TyG, triglyceride–glucose; UA, uric acid; VLDL, very-low-density lipoprotein; and WBC, white blood cell count.

explained through the following aspects. First, the TyG index is a reliable indicator to evaluate IR, which can cause the formation of atherosclerosis and then lead to the occurrence of unstable carotid plaque.[39,40] Second, the TyG index is related to inflammation, oxidative stress, and metabolic changes, leading to damage of the vascular endothelium, which is one of the important mechanisms for the formation of unstable carotid plaque.[41,42] Third, patients with IR often have other comorbidities, including hypertension, diabetes, and obesity, and IR can lead to blood sugar and lipid disorders, which are high-risk factors for unstable carotid plaque formation.[43,44] Therefore, it seems reasonable to assume that patients with higher TyG index levels are experiencing more carotid damage and have a higher incidence of unstable carotid plaques. In clinical practice, our findings can guide clinicians to control the TyG index within the target range, which is beneficial to prevent the occurrence of unstable carotid plaques.

This study elucidates the role of the TyG index in unstable carotid plaque across sex, age, and glucose metabolic status, thereby combining previous evidence to provide a comprehensive approach for clinical decisionmaking. Globally, the number of patients with unstable carotid plaque is increasing, especially those with diabetes, who are more prone to stroke events.[34,45] Therefore, it is necessary to identify high-risk patients with unstable carotid plaque in time. In clinical practice, assessing the TyG index in patients with carotid stenosis can enhance the overall assessment of the disease and help develop more effective and personalized treatment and management strategies. In addition, understanding the association between TyG and carotid plaque stability and stroke events can help doctors better assess the risk of patients and timely detect and manage potential complications.

Although this study is the first to innovatively study the relationship between the TyG index and unstable carotid plaque under different glycemic statuses, there are still many limitations in this study. First, this is a cross-sectional study, and more prospective studies are needed to establish a causal relationship. Second, although the known risk factors have been adjusted, the inherent nature of observational design means that not all confounding variables can be taken into account and the influence of some selection bias cannot be ruled out. Third, ultrasound may not be as accurate as magnetic resonance imaging results in judging the stability of carotid plaque. In the future, with the accumulation of carotid magnetic resonance imaging data, the use of carotid magnetic resonance imaging results for analysis will be more valuable to a certain extent. However, it is undeniable that ultrasound is more universal and popular at present. Fourth, this study lacks

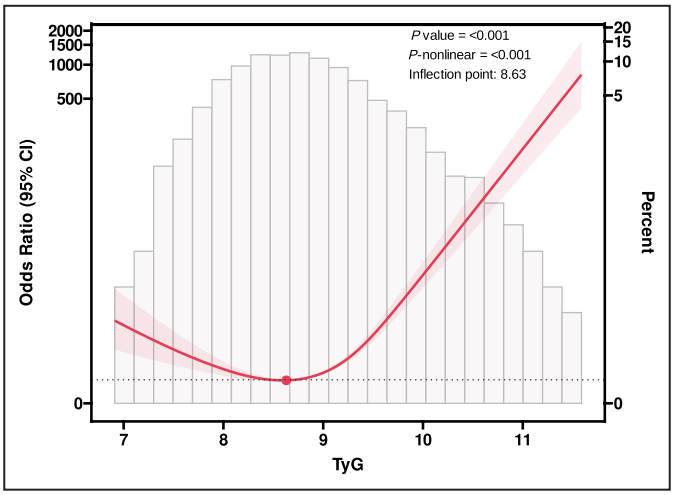

Figure 3. Restricted cubic spline regression analysis showed that there was a nonlinear relationship between TyG index and unstable carotid plaque.
TyG indicates triglyceride–glucose.

information about medications for lowering blood lipids, hypertension, and diabetes, as well as information about stroke, which is a limitation of this study. Finally, the participants in the study are all from a hospital, which may not be suitable for other ethnic groups, so multicenter and multiethnic participation is needed in the future.

CONCLUSIONS

In summary, the TyG index has a significant association with unstable carotid plaque. The association between the TyG index and an unstable carotid plaque was similar between men and women, and the association in older patients is higher than that in middle-aged patients. In patients with diabetes, the association between the TyG index and carotid plaque was higher. The results of this study may emphasize the need for risk management strategies for different sexes, ages, and glycemic statuses to prevent patients from developing unstable carotid plaque.

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Disclosures

None.

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