

Relationship Between the Triglyceride-Glucose Index and Type 2 Diabetic Macroangiopathy: A Single-Center Retrospective Analysis

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Purpose: The research explores the relationship between the triglyceride-glucose index (TyG index) and the macroangiopathy risk in single-center hospitalized type 2 diabetes mellitus (T2DM) patients and develops a risk prediction nomogram model.

Patients and Methods: A total of 858 patients with T2DM were studied retrospectively. Lasso regression was used to eliminate unimportant factors, and multivariate logistic regression analysis was used to investigate the association between the TyG index and macrovascular disease in T2DM. A nomogram model was constructed to predict macrovascular disease in T2DM and tested using the bootstrap technique, and the efficacy of the nomogram model was investigated using ROC curves. The multivariate Cox proportional hazards model estimated the association between the TyG index and all-cause mortality.

Results: TyG index, high-density lipoprotein, red blood cell count, hypertension, history of taking ACEI/ARB drugs, and aortic calcification were closely related to macrovascular complications. In Cox proportional hazard model, the HRs of TyG index were 1.89 (95% confidence interval (CI) 1.29–2.76, $p < 0.001$) after adjusting for covariates. The risk of all-cause mortality in T2DM with macrovascular complications was significantly higher than in diabetic patients without vascular disease. In the ROC curve analysis, the cut-off value of the TyG index for macrovascular complications of T2DM was 9.31 (AUC: 0.702, 95% CI 0.67–0.74, $p < 0.001$).

Conclusion: TyG index predicts future macrovascular disease in diabetic patients independently of known cardiovascular risk factors, suggesting that TyG index may be a useful marker for prognosis in diabetic patients.

Keywords: diabetes, cardiovascular events, vascular complications, risk factors, triglyceride-glucose index

Introduction

Diabetes is one of the most common chronic diseases in the world. The 2019 International Diabetes Federation survey data shows that there are currently about 463 million diabetic patients globally. China is already the leading country with a prevalence of adult diabetes as high as 10.9%.¹ According to the 2017 Global Burden of Disease Research report, diabetes is the fourth leading disability disease globally and is expected to become the seventh leading disease of premature death by 2024.^{2,3}

The continuous progression of diabetes can cause complications, such as cardiovascular and cerebrovascular disease, kidney disease, peripheral neuropathy, and ocular disease. Type 2 diabetic macroangiopathy, whose main pathological change is atherosclerosis, is the primary reason for the decline in the patient's quality of life, leading to death. The UK prospective diabetes study (UKPDS) showed that diabetic macroangiopathy caused 59% of deaths in type 2 diabetic patients. The development of diabetic macrovascular disease is an extremely complex dynamic process. In its complex pathological mechanism, insulin resistance (IR) plays an extremely important role in developing atherosclerosis.⁴ It puts the body in a systemic inflammatory environment, blocking atherosclerotic calcification. Hyperinsulinemic-positive

glucose clamps are considered the gold standard for measuring insulin sensitivity. However, this method is costly, time-consuming, complicated, and difficult to perform clinically.⁵

In recent years, the triglyceride glucose index (TyG) calculated from $\text{Ln} [\text{fasting triglyceride (mg/dl)} \times \text{fasting glucose (mg/dl)} / 2]$ has been proven to be an alternative to IR,^{6,7} and its effect is better than that of homeostasis model assessment- insulin resistance (HOMA-IR).⁸ Previous studies have shown that the TyG index may help identify individuals at risk of DM in the future in order to provide early intervention.⁹ Not only in diabetes but also in vascular diseases, more and more evidence shows that the TyG index can be used as an independent predictor of vascular injury^{10,11} and cardiovascular disease mortality,¹² indicating that it has a potential clinical role in predicting cardiovascular risk.

However, it is worth noting that most of the previous research groups were asymptomatic patients or patients with cardio-cerebrovascular diseases. There are few studies on the prognosis of individuals with type 2 diabetes or cardio-cerebrovascular diseases, and these inpatients are more unstable in metabolism. Their serum glucose and blood lipid levels are usually poorly controlled. It is unclear whether the TyG index remains a substantial risk predictor of diabetic complications in this group of patients with a high incidence of chronic complications. This study discussed the relationship between the TyG index and diabetic macroangiopathy, and provided a clinical reference for long-term treatment and prognosis prediction of diabetic patients.

Materials and Methods

Participants

This study recruited 1565 patients with diabetic patients who were hospitalized at the affiliated hospital of Jiangsu University from January 2017 to November 2018. All patients meet the diagnostic standards for diabetes in 1999. Exclusion criteria: (1) Patients with diabetes other than type 2 (including type 1 diabetes, gestational diabetes, and secondary diabetes)(n=126); (2) Patients with organ insufficiency (n=36); (3) Patients with autoimmune diseases or blood diseases (n=19); (4) Patients with malignant tumors (n=27); (5) Patients with severe infections in the previous three months (n=58); (6) Patients with congenital heart disease (n=2); (7) Incomplete patients with baseline data (n=364). All patients follow -up through telephone, mail, and outpatient follow-up. In the end, 858 (92%) patients completed clinical follow-up. The flow diagram (Figure 1) summarizes the recruitment process. This retrospective study protocol was approved by the Scientific Research Ethics Committee of the Affiliated Hospital of Jiangsu University. This study was registered in the Chinese Clinical Trials Registry (registration website: www.chictr.org.cn; registration number: ChiCTR2100045875). This study is a retrospective study, strictly complying with all provisions of the Helsinki Declaration, and obtaining the written/oral informed consent of all participants.

Assessment of Macrovascular Complications

The study divided patients into two groups according to their macrovascular disease: patients with T2DM without macroangiopathy (simple T2DM group) and those with T2DM with macroangiopathy. The diagnostic criteria for macroangiopathy were as follows: (1) Coronary atherosclerotic heart disease: the patient has a history of related diseases (angina pectoris, myocardial infarction). The diagnosis could be confirmed by related auxiliary examinations (coronary angiography, electrocardiogram, heart, and radionuclide imaging); (2) Ischemic cerebrovascular disease: a previous related medical history (cerebral infarction). Head CT¹³ or head MRI/MRA and cerebral blood flow map can confirm the diagnosis; (3) The thickness of the arterial intima-media>1.2mm was judged as atherosclerotic plaque formation according to the color Doppler ultrasound of the lower extremity arteries and carotid arteries.¹⁴ The arteries of the lower extremities form lumen stenosis (diameter <3mm) or related clinical symptoms (rest pain, claudication, aberrant epidermal temperature, decreased arterial pulsation, and other symptoms).

Data Collection and Definitions

Trained clinical doctors recorded data from the population statistics and clinical characteristics of the participants in the case system, including gender, weight, height, medical history, and drug treatment. The calculation method of the weight

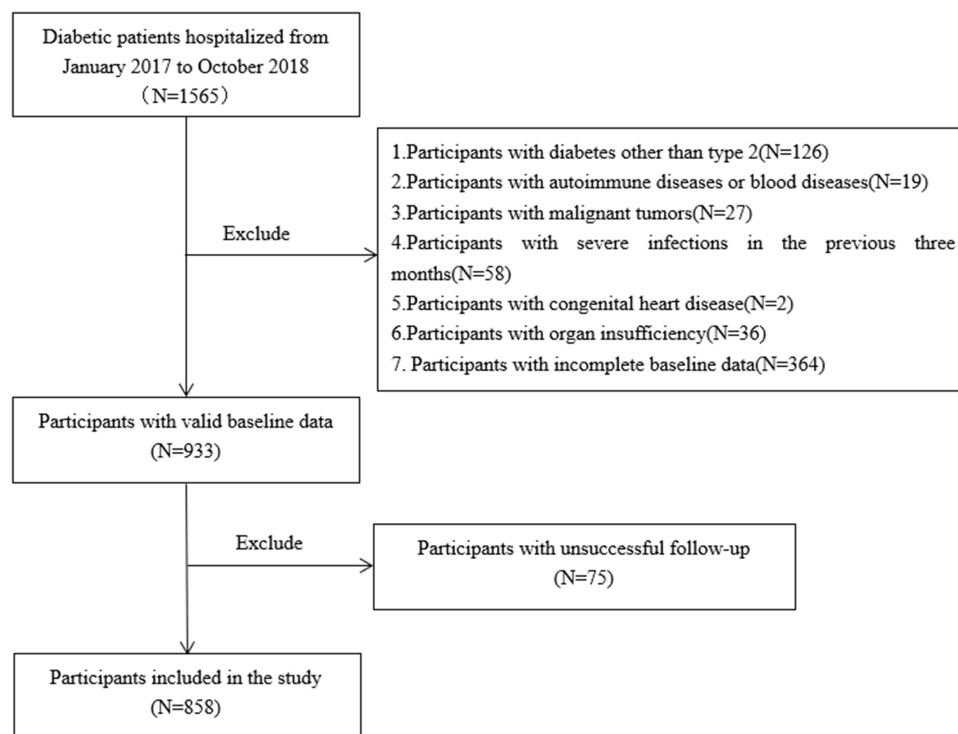


Figure 1 Flow chart for inclusion of participants in this study.

Notes: A total of 1565 participants were recruited at baseline, and all patients were screened according to exclusion criteria. Of these, 216 participants were diagnosed with diabetes other than type 2 (including type 1 diabetes, gestational diabetes, secondary diabetes), 36 participants had organ insufficiency, and 19 participants had autoimmune disease or blood disease, 27 participants had malignancy, 58 had severe infection within the last three months, 2 had congenital heart disease, 364 had incomplete baseline data, and 75 had incomplete follow-up information. After excluding the above participants, a total of 858 subjects were included in the study.

index (BMI) is to divide the weight (KG) with the height (M²). Use a mercury blood pressure meter to measure blood pressure in the sitting position, and record the average results of the three measured values of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension is defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, any history of hypertension that uses antihypertensive drugs or self-reporting. On the morning of the admission, after fasting for 10–12 hours, the venous blood sample was collected. The routine hematological and biochemical parameters of all samples were detected by an automatic biochemical analyzer (BECKMAN AU2700, USA) in the central laboratory of the affiliated Hospital of Jiangsu University. The biochemical indicators tested included white blood cells (WBC), neutrophils, red blood cells (RBC), hemoglobin (HB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, serum creatinine (Scr), blood urea nitrogen (BUN), fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C). Using automatic coagulometer analyzer (CA-7000, Xisenmekang) to detect international standardized ratio (INR).

The existence of active artery calcification may not be reviewed by 2 experienced radiologists. The radiographs were reviewed by 2 radiologists who were blinded to the real situation.

Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as frequencies or percentages (n, %). Mann–Whitney U, *t*-tests, and chi-square tests were used to compare the characteristics of subgroups according to whether T2DM was associated with macrovascular complications. To compare baseline characteristics, patients were sorted by TyG index quartile levels as follows: Q1 group (≤ 8.70), Q2 (8.70–9.20), Q3 (9.20–9.67), and Q4 (≥ 9.67). ANOVA and Kruskal–Wallis tests were used to compare the TyG index quartiles' characteristics. The Spearman's rank correlation test or Pearson correlation test was used to evaluate the correlations between the TyG index and cardiovascular risk factors when appropriate. The Pearson correlation test

was applied to evaluate the correlation between two continuous variables with normal distribution, while the Spearman's rank correlation test was used to analyze one or more variables that are non-normally distributed continuous variables or categorical variables. Since the TyG index is a comprehensive index of triglyceride and fasting blood glucose levels, fasting blood glucose and triglyceride variables are not included in the correlation analysis. Lasso regression analysis was used to screen the influencing factors of T2DM with macrovascular complications and to filter out unnecessary variables. The logistic regression model was used to screen the variables that had a strong relationship with T2DM with macrovascular complications. The factors closely related to macrovascular complications screened by multivariate Logistic regression analysis were included in the line chart risk model. Using a nomogram to visualize this risk model, the nomogram model was internally validated using the Bootstrap method (100 replicates of the original data), and the concordance index (C-index, CI) was calculated. The clinical diagnostic performance of the TyG index and other important variables was assessed by receiver operating characteristic (ROC) curve analysis, and the Youden index was calculated to determine the cutoff value for the TyG index. We performed mixed-effects Cox regression analyses to calculate hazard ratios (HR) and 95% CIs to test the association of various factors in predicting macrovascular complications in T2DM. We first established three models to evaluate the predictive value of the TyG index for macrovascular complications: (1) Model 1: unadjusted; (2) Model 2: adjusted for age, duration of diabetes, and aortic calcification; (3) Model 3: adjusted for age, duration of diabetes, aortic calcification, hypertension, history of ACEI/ARB medication, history of insulin medication, albumin, BUN, and SCr. Furthermore, two models were established to evaluate the predictive value of TyG index for all-cause deaths: (1) Model 1: adjusted for age, duration of diabetes, hypertension, and aortic calcification; (2) Model 2: adjusted for age, duration of diabetes, hypertension, aortic calcification, ACEI/ARB medication history, albumin, TG, and TC. The Kaplan-Meier method was used to calculate all-cause mortality by TyG index quartiles and macrovascular complications, and Log rank test was used to compare the differences among groups. All of the analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA) and software version 3.6.1 (R Core Team, Vienna, Austria). All the statistical tests were 2-sided, and $P < 0.05$ was considered statistical significance.

Results

Baseline Characteristics of Study Participants

A total of 858 eligible participants were included in this analysis, their mean age was 67.13 ± 11.07 years, and 56% were male. According to whether the included patients had macrovascular complications or not, 500 participants had macrovascular complications. The baseline characteristics of all participants are shown in Table 1. Participants with macrovascular complications of diabetes have a longer diabetes course, a higher prevalence of hypertension and aortic calcification, take more ACEI/ARB and insulin, have higher TyG index, BMI, WBC, neutrophils, Scr, BUN, FPG, and TG, have lower RBC, albumin, HDL-C levels compared with simple T2DM group. Patients were divided into quartiles according to the admission TyG index levels (Q1:n=216, TyG index ≤ 8.70 ; Q2:n=215, $8.70 \leq$ TyG index ≤ 9.20 ; Q3:n=212, $9.20 \leq$ TyG index ≤ 9.67 ; Q4:n=215, TyG index ≥ 9.67). The baseline characteristics of quartiles of the TyG index for all participants are shown in Table 2. Participants in the Q2-Q4 groups had a longer duration of diabetes, were more likely to suffer from aortic calcification and macrovascular complications compared with the Q1 group, took more metformin and insulin, and had higher levels of BMI, FPG, TG, TC, and HDL-C.

The Association Between TyG Index and Other Parameters

We compared the association between TyG index and macrovascular disease-related variables in T2DM. As shown in Table 3, TyG index was associated with duration of diabetes ($r=0.345$, $p<0.001$), hypertension ($r=0.069$, $p=0.044$), aortic calcification ($r=0.253$, $p<0.001$), history of ACEI/ARB medication ($r=0.022$, $p=0.527$), history of insulin medication ($r=0.134$, $p<0.001$), HDL-C ($r=0.152$, $p<0.001$), albumin ($r=0.072$, $p=0.035$) and macrovascular complications ($r=0.345$, $p<0.001$).

Association of Variables with T2DM Macrovascular Complications

Categorical variables (0 or 1) were assigned to all included studies. The LASSO regression model was used to screen the most significant factors of T2DM complicated with macrovascular complications, and λ is taken the minimum value.

Table I Basic Characteristics of Participants

Variables	Simple T2DM (N=358)	Macrovascular Complications of T2DM (N=500)	P
Age, years	68 (59,76)	70(61,75)	0.164
Male, n%	192 (53.6%)	286 (57.2%)	0.299
Duration of diabetes, years	5 (2,10)	8 (5,12)	<0.001
BMI, kg/m ²	23.58(21.40,25.63)	24.52(22.32,26.36)	<0.001
WBC, 10 ⁹ /L	6.30 (5.10,7.60)	6.80 (5.50,8.65)	<0.001
RBC, 10 ¹² /L	4.39 (3.88,4.78)	4.14 (3.63,4.54)	<0.001
Neutrophils, 10 ⁹ /L	3.80 (2.90,4.90)	4.50 (3.40,6.40)	<0.001
ALT, U/L	18.00 (12.50,29.53)	16.45 (12.00,26.30)	0.127
AST, U/L	18.00 (14.95,24.93)	19.00 (15.00,27.00)	0.180
Albumin, g/L	40.55 (37.3,43.3)	39.4 (36.60,42.50)	0.004
SCr, μmol/L	67.70 (55.70,83.70)	77.70 (64.20,109.40)	<0.001
BUN, mmol/L	5.65 (4.60,7.23)	6.63 (5.13,9.20)	<0.001
FPG, mmol/L	7.30 (6.11,9.23)	8.47 (6.77,10.32)	<0.001
TG mmol/L	1.27 (0.90,1.78)	1.79 (1.24,2.53)	<0.001
TC, mmol/L	4.58 (3.60,5.27)	4.50 (3.63,5.35)	0.818
HDL-C, mmol/L	2.64 (2.04,3.32)	2.46 (1.85,3.03)	0.001
INR	0.98 (0.91,1.12)	0.99 (0.92,1.13)	0.318
TyG Index	8.91±6.17	9.44±0.74	<0.001
Hypertension, n%	176 (49.2%)	376 (75.2%)	<0.001
Medication history			
ACEI/ARB, n%	212(59.2%)	217(43.4%)	<0.001
Statins, n%	276(77.1%)	374(74.8%)	0.439
Metformin, n%	70(19.6%)	124(24.8%)	0.07
Alpha-glucosidase inhibitor, n%	74(20.7%)	127(25.4%)	0.107
Sulfonylurea, n%	66(18.4%)	86(17.2%)	0.64
Dipeptidyl peptidase 4 inhibitor, n%	20(5.6%)	17(3.4%)	0.12
Insulin, n%	80(22.3%)	142(28.4%)	0.046
Aortic calcification, n%	123(14.3%)	325(37.9%)	<0.001

Note: Data are presented as median (IQR) [25th percentile, 75th percentile] or n (%).

Abbreviations: BMI, body mass index; WBC, white blood cell count; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, blood creatinine; BUN, blood urea nitrogen; FPG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; TyG Index, triglyceride glucose index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors.

When the AUC is the largest, the corresponding variable is 23 (Figure 2). By calculating the coefficients of the included variables, 7 variables were finally selected, namely diabetes duration, gender, hypertension, ACEI/ARB medication history, aortic calcification, RBC, and HDL-C. Univariate regression analysis showed that, without adjustment for other factors, the odds ratio for the TyG index was 3.12 (95% CI 2.48–3.93). In the multiple regression analysis, this relationship persisted, with the odds ratio of 2.72 (95% CI 1.76–4.21) for the TyG index, indicating a strong association between the TyG index and macrovascular complications in T2DM. However, it is worth noting that the relationship between TG and macrovascular complications is unclear and will be excluded from the nomogram model (Table 4).

Nomogram Risk Model Establishment

The nomogram model was based on hypertension, aortic calcification, ACEI/ARB medication history, RBC, HDL-C, and TyG index (Figure 3A). The prognostic value of the nomogram was assessed using Harrell's concordance index (C-index) of 0.75. The calibration plot of the nomogram shows that the predicted curve is highly consistent with the ideal curve, and the calibration plot shows the agreement between prediction and observation (Figure 3B).

Table 2 Baseline Characteristics of TyG Index Quartile Groups

Variables	Q1 (n=216) ≤8.70	Q2 (n=215) 8.70–9.20	Q3 (n=212) 9.20–9.67	Q4 (n=215) ≥9.67	P
Age, years	69(60,77)	69(61,75)	68.5(59,76)	69(60,74.5)	0.908
Male, n%	126(58.3%)	117(54.4%)	126(59.4%)	109(50.7%)	0.248
Duration of diabetes, years	6.5(2,10)	8(5,10)	7(3,10)	8(5,12)	<0.001
BMI, kg/m ²	22.30(21.30,24.19)	22.62(21.36,24.99)	24.85(23.62,26.58)	25.69(24.51,27.25)	<0.001
WBC, 10 ⁹ /L	6.40(5.20,8.20)	6.30(5.30,7.65)	6.50(5.40,8.00)	7.10(5.55,9.30)	<0.001
RBC, 10 ¹² /L	4.11(3.64,4.64)	4.23(3.8,4.58)	4.25(3.73,4.71)	4.27(3.89,4.63)	0.307
Neutrophils, 10 ⁹ /L	4.30(3.10,5.88)	3.90(3.00,5.20)	4.20(3.30,5.58)	4.60(3.30,6.50)	0.007
ALT, U/L	17.00(12.00,27.60)	16.00(11.60,25.40)	17.00(12.00,27.50)	18.50(13.00,29.90)	0.152
AST, U/L	19.60(15.63,28.00)	17.10(13.30,23.00)	19.00(15.00,24.48)	19.1(15.00,27.70)	0.005
Albumin, g/L	39.30(36.55,42.15)	39.80(37.20,42.35)	40.85(36.80,43.25)	40.00(37.00,43.60)	0.23
SCr, μmol/L	73.20(61.50,101.65)	70.70(58.25,86.7)	76.35(60.95,106.2)	71(59.4,102.95)	0.082
BUN, mmol/L	6.37(5.00,8.81)	5.79(4.79,7.28)	6.2(4.86,8.36)	6.4(5.04,8.67)	0.021
FPG, mmol/L	6.225(5.08,7.33)	7.32(6.21,9.08)	8.495(7.44,9.93)	10.24(8.62,13.04)	<0.001
TG mmol/L	0.855(0.68,1.05)	1.3(1.12,1.54)	1.86(1.58,2.11)	2.83(2.18,3.78)	<0.001
TC, mmol/L	4.03(3.35,4.8)	4.42(3.57,5.14)	4.695(3.75,5.4)	4.9(4.16,5.69)	<0.001
HDL-C, mmol/L	2.32(1.63,2.85)	2.56(1.94,3.07)	2.655(2.05,3.265)	2.67(2.02,3.32)	<0.001
INR	1.02(0.92,1.15)	0.98(0.91,1.08)	0.995(0.925,1.15)	0.97(0.91,1.11)	0.075
Hypertension, n%	136(63.0%)	126(58.6%)	140(66.0%)	150(69.8%)	0.098
Medication history					
ACEI/ARB, n%	104(48.1%)	107(49.8%)	105(49.5%)	113(52.6%)	0.83
Statins, n%	169(78.2%)	161(74.9%)	151(71.2%)	171(79.5%)	0.22
Metformin, n%	37(17.1%)	42(19.5%)	53(25%)	62(28.8%)	0.016
Alpha-glucosidase inhibitor, n%	44(20.4%)	43(20.0%)	54(25.5%)	60(27.9%)	0.143
Sulfonylurea, n%	48(22.2%)	38(17.7%)	36(17.0%)	30(14.0%)	0.159
Dipeptidyl peptidase 4 inhibitor, n%	14(6.5%)	10(4.7%)	7(3.3%)	6(2.8%)	0.235
Insulin, n%	41(19%)	50(23.3%)	57(26.9%)	74(34.4%)	0.002
Aortic calcification, n%	74(8.6%)	107(2.5%)	122(14.2%)	145(16.9%)	<0.001
Macrovascular complications, n%	86(39.8%)	98(45.6%)	145(68.4%)	171(79.5%)	<0.001

Note: Data are presented as median (IQR) [25th percentile, 75th percentile] or n (%).

Abbreviations: BMI, body mass index; WBC, white blood cell count; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, blood creatinine; BUN, blood urea nitrogen; FPG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; INR, International normalized ratio; TyG Index, triglyceride glucose index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors.

Table 3 Correlation Between TyG Index and Other Clinical Variables

Variables	r	P
Age, years	0.005	0.875
Duration of diabetes, years	0.136	<0.001
Male	−0.04	0.244
Hypertension	0.069	0.044
Aortic calcification	0.253	<0.001
Statins	0.005	0.894
ACEI/ARB	0.022	0.527
Insulin	0.134	<0.001
TC, mmol/L	0.292	<0.001
HDL-C, mmol/L	0.152	<0.001
Albumin, g/L	0.072	0.035
Macrovascular complications	0.345	<0.001

Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TyG Index, triglyceride glucose index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors.

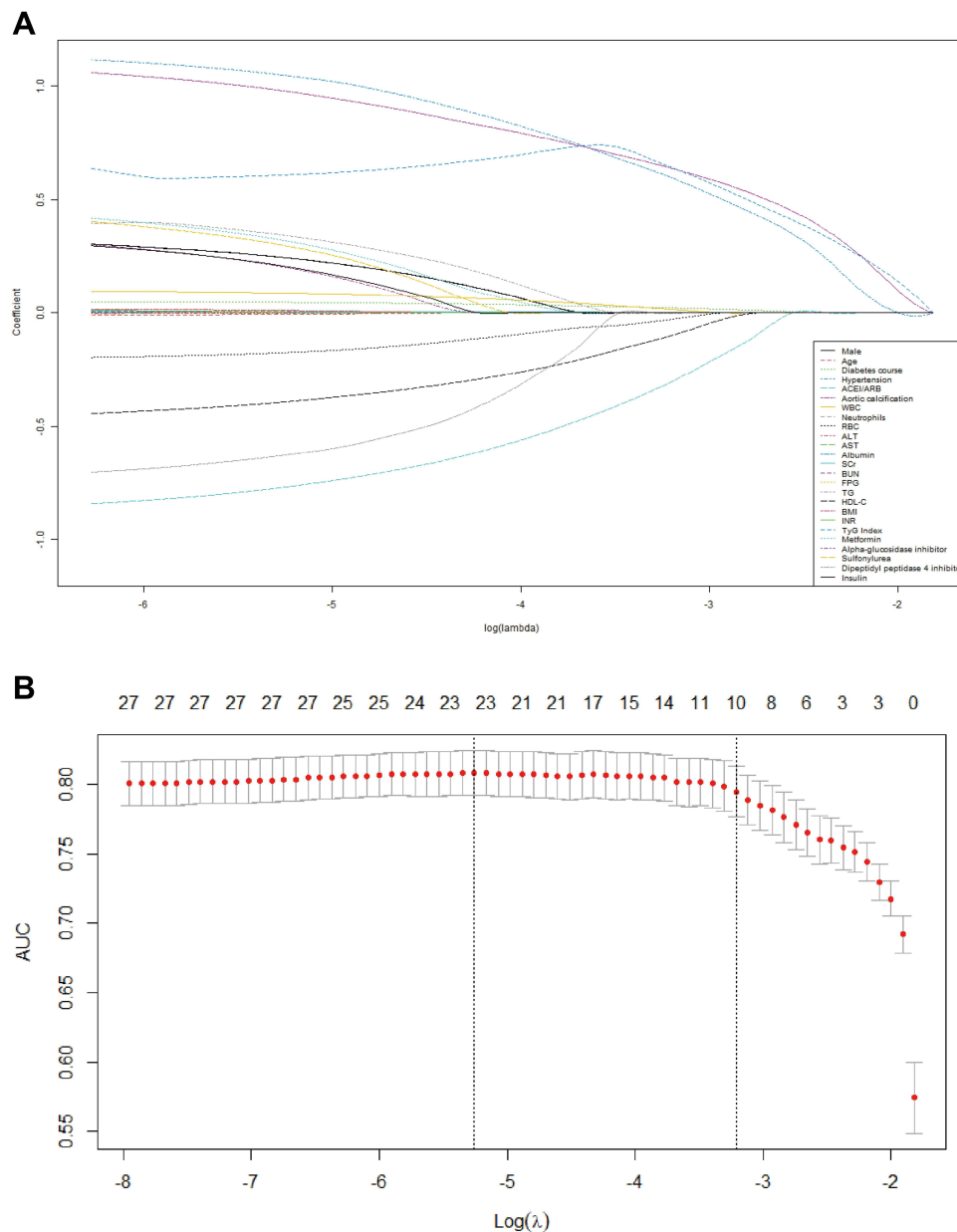


Figure 2 Selecting clinical features based on the least absolute shrinkage and selection operator (LASSO) logistic regression.

Notes: (A) Least Absolute Shrinkage and Selection Operator (LASSO) coefficient distribution for each variable. Variables with coefficients close to 0 are removed. Finally, 7 variables were included. (B) Cross-validation of tuning parameters in LASSO models.

Abbreviations: BMI, body mass index; WBC, white blood cell count; RBC, red blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, blood creatinine; BUN, blood urea nitrogen; FPG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; TyG Index, triglyceride glucose index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors.

ROC Curve of Type 2 Diabetes Mellitus Complicated with Macrovascular Complications

The ROC curves of the TyG index, HDL-C, and RBC in T2DM with macrovascular complications are shown in Figure 4. The area under the ROC curve for the TyG index was 0.702 (95% CI 0.67–0.74), the RBC was 0.396 (95% CI 0.36–0.43), and the TG was 0.432 (95% CI 0.39–0.47). The TyG index was a significant predictor of future macrovascular complications in T2DM. The results also found that the best cut-off value of the TyG index for predicting macrovascular complications was 9.31, with a sensitivity of 59% and a specificity of 74%. The Youden Index was 0.33. The area under

Table 4 Logistic Regression Analysis of Related Factors with T2DM Complicated with Macrovascular Disease

Variables	Univariate		Multivariate	
	OR 95% CI	p	OR 95% CI	p
TyG Index	3.12(2.48–3.93)	<0.001	2.72(1.76–4.21)	<0.001
Hypertension	3.14 (2.35–4.19)	<0.001	3.26(2.32–4.58)	<0.001
Aortic calcification	3.55 (2.667–4.72)	<0.001	2.48(1.77–3.45)	<0.001
ACEI/ARB	0.53 (0.40–0.70)	<0.001	0.40(0.29–0.56)	<0.001
RBC	0.57 (0.47–0.71)	<0.001	0.55(0.43–0.71)	<0.001
TG	2.10 (1.74–2.52)	<0.001	1.33(0.98–1.80)	0.07
HDL-C	0.80 (0.69–0.93)	0.003	0.63(0.52–0.76)	<0.001

Abbreviations: RBC, red blood cell count; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TyG Index, triglyceride glucose Index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors; OR, odds ratio; CI, confidence interval.

the curve of the TyG index was higher than that of RBC and HDL-C ($p < 0.001$). Therefore, the TyG index is better than the HDL-C and RBC in predicting the future macrovascular complications of diabetes mellitus.

Time Exposure Duration of TyG Index and Risk of All-Cause Mortality

During a median follow-up period of 41 months, 52 participants had all-cause deaths. In the Cox proportional hazard Model (Table 5), the HRs of TyG index were 1.87 (95% CI 1.32–2.64, $p < 0.001$) in Model 1, 1.99 (95% CI 1.38–2.86, $p < 0.001$) in Model 2, 1.89 (95% CI 1.29–2.76, $p = 0.001$) in Model 3. Furthermore, a proportional hazards regression model was established using the TyG index as a categorical variable. In the unadjusted variable model, quartile 2 was 0.96 (95% CI 0.39–2.37, $p = 0.933$), quartile 3 was 1.71 (95% CI 0.76–3.86, $p = 0.196$), quartile 4 was 2.66 (95% CI 1.23–5.77, $p = 0.013$). In Model 1, quartile 2 was 0.94 (95% CI 0.38–2.33, $p = 0.896$), quartile 3 was 1.60 (95% CI 0.69–3.74, $p = 0.276$), and quartile 4 was 3.61 (95% CI 1.57–8.30, $p = 0.003$). In Model 2, quartile 2 was 0.92 (95% CI 0.37–2.29, $p = 0.861$), quartile 3 was 1.55 (95% CI 0.66–3.65, $p = 0.311$), quartile 4 was 3.36 (95% CI 1.37–8.28, $p = 0.008$) (Figure 5).

As shown in Figure 6A, the Kaplan-Meier survival analysis showed that the cumulative incidence of all-cause mortality increased with higher TyG index quartiles (Log rank test, $P = 0.020$). We also looked at the changes in all-cause mortality with macrovascular complications. We found that the cumulative incidence of all-cause mortality in the macrovascular complications group increased compared with the T2DM group Figure 6B.

Discussion

Type 2 diabetes incidence is growing annually, with a younger age trend, due to changes in lifestyles and improved living standards in today's society. Type 2 diabetes causes many complications, damages vital organs of the human body, and seriously affects patients' quality of life. Type 2 diabetes is an independent risk factor for heart, brain, kidney, and other macrovascular complications.¹⁵ In diabetic patients, macrovascular problems are the leading cause of disability and mortality. Diabetic individuals' risk of macroangiopathy rose by 2–4 times compared to non-diabetic people.¹⁶ The pathophysiology of type 2 diabetic macroangiopathy is still unknown. Previous research has found that hyperglycemia, dyslipidemia, smoking, and hypertension are linked to the advancement of type 2 diabetic macroangiopathy. IR is an essential factor in this.

IR has been linked to mild chronic inflammation,^{17,18} and it is thought to have a role in the development of atherosclerotic cardiovascular diseases (ASCVDs).¹⁹ IR may alter the redox state of blood arteries and induce macrophage, endothelial, and vascular smooth muscle cell death, contributing to the advancement of atherosclerosis and vascular calcification.²⁰ This raises the possibility of severe vascular complications. Insulin, on the other hand, causes the vascular endothelium to generate nitric oxide (NO), which oxidizes lipoproteins, slowing intimal calcification and preventing the development of vascular smooth muscle cells (VSMCs).²¹ When IR develops, the likelihood of vascular calcification rises. At the same time, the higher the IR index, the higher the calcification score in the coronary arteries.²² IR is also linked to increased sympathetic nervous system activity and decreased cardiac autonomic nerve function, related to ASCVD pathogenesis.^{23,24}

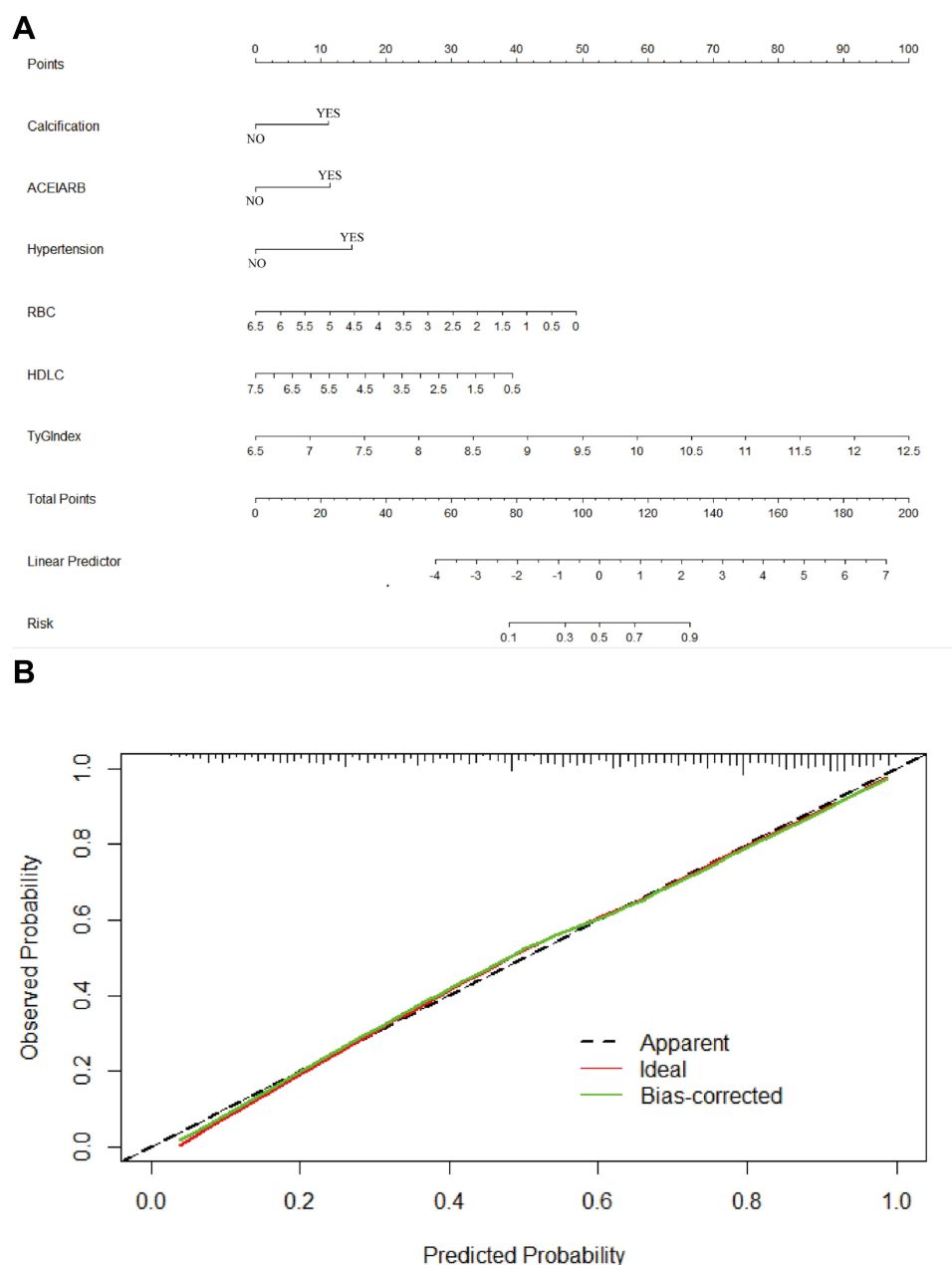


Figure 3 A nomogram was constructed to predict macrovascular complications in T2DM patients.

Notes: (A) A nomogram for predicting T2DM patients with macrovascular complications. (B) Calibration curve of nomogram risk model for T2DM with macrovascular complications.

In recent years, the TyG index has been used as an effective alternative index for assessing IR. Compared to standard IR markers, the TyG index is inexpensive, convenient, and has a high application value in clinical and epidemiological research.²⁰ Numerous studies have shown that the TyG index may accurately predict T2DM development. However, the results are not consistent. Tohidi et al found that FPG was a better predictor of T2D than the TyG index, TG/HDL-C, and HOMA-IR index. Separated by gender, the TyG index predicted diabetes with increased ability but was still no better than HOMI-IR.²⁵ A study of 4109 healthy Korean participants found that TyG index can assess coronary atherosclerosis with more independent associations than HOMA-IR, especially at the fourth point TyG index (adjusted HR:4.68,95% CI 2.19–10.01).²⁶ Metabolic process research supports the TyG index's significance in T2DM prediction. More free fatty acids enter the liver when this occurs, and the body compensates by increasing the liver's absorption of triglycerides and

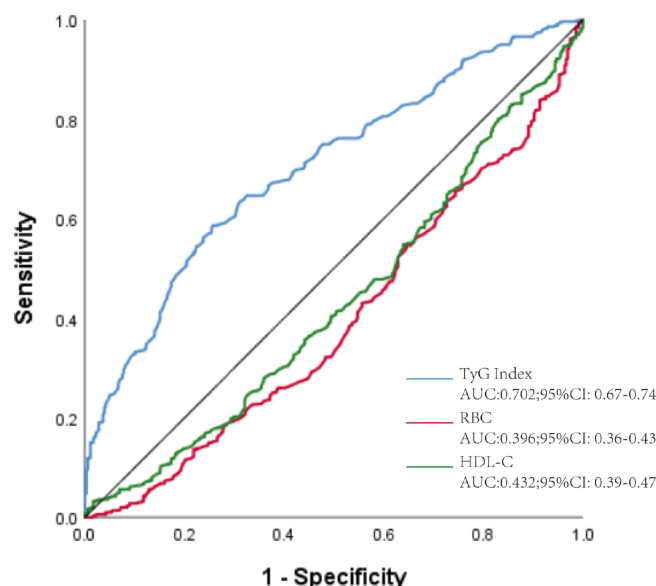


Figure 4 ROC curve of TyG index, RBC, and HDL-C in predicting T2DM complicated with macrovascular complications.

Notes: The ROC curve and AUC value of the nomogram. The area under the ROC curve for the TyG index was 0.702 (95% CI 0.67–0.74), the RBC was 0.396 (95% CI 0.36–0.43), and the TG was 0.432 (95% CI 0.39–0.47). The best cut-off value of the TyG index for predicting macrovascular complications was 9.31, with a sensitivity of 59% and a specificity of 74%. The Youden Index was 0.33.

the production and secretion of VLDL. Since the TyG index is used to react or even replace IR, IR increases the production of inflammatory factors and alters the body's coagulation function, which may lead to thrombosis.²⁷ Simultaneously, IR may promote atherosclerotic progression and induce plaque instability, mechanisms by which T2DM progression leads to macrovascular complications.^{28,29} However, the specific mechanism by which the TyG index predicts T2DM is unclear. Cells may be susceptible to glucotoxicity and lipotoxicity, and high glucose levels increase reactive oxygen species, leading to cellular damage. Increased triglyceride concentrations in pancreatic islets are also thought to alter glucose metabolism and damage cells, leading to poor glycemic control and macrovascular disease.

Many studies have also verified the TyG index's effectiveness in predicting and assessing the progression of ASCVDs progression.^{30,31} A South Korean study of 4319 adults showed an important link between the TyG index and coronary plaques in healthy people (OR:1.95, 95% CI 1.23–3.11).³² Another retrospective cohort study similarly found that the

Table 5 Cox Proportional Hazards for All-Cause Mortality in T2DM with or without Macrovascular Complications

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years	-	-	1.15(1.10–1.20)	<0.001	1.14(1.10–1.19)	<0.001
Duration of diabetes, years	-	-	1.01(0.97–1.05)	0.652	1.01(0.97–1.06)	0.636
Aortic calcification	-	-	0.93(0.51–1.71)	0.811	0.85(0.46–1.58)	0.603
Hypertension	-	-	-	-	0.79(0.44–1.42)	0.430
ACEI/ARB	-	-	-	-	0.52(0.29–0.94)	0.029
Insulin	-	-	-	-	1.47(0.83–2.61)	0.188
Albumin, g/L	-	-	-	-	0.97(0.92–1.02)	0.198
SCr, μmol/L	-	-	-	-	1.00(0.99–1.00)	0.188
BUN, mmol/L	-	-	-	-	1.05(0.99–1.10)	0.080
TyG index	1.87(1.32–2.64)	<0.001	1.99(1.38–2.86)	<0.001	1.89(1.29–2.76)	0.001

Notes: Model 1 was unadjusted; Model 2 was adjusted for age, duration of diabetes, and aortic calcification; Model 3 was adjusted for age, duration of diabetes, aortic calcification, hypertension, history of ACEI/ARB medication, history of insulin medication, albumin, BUN, and SCr.

Abbreviations: Scr, blood creatinine; TyG Index, triglyceride glucose index; BUN, blood urea nitrogen; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors; HR, hazard ratio; CI, confidence interval.

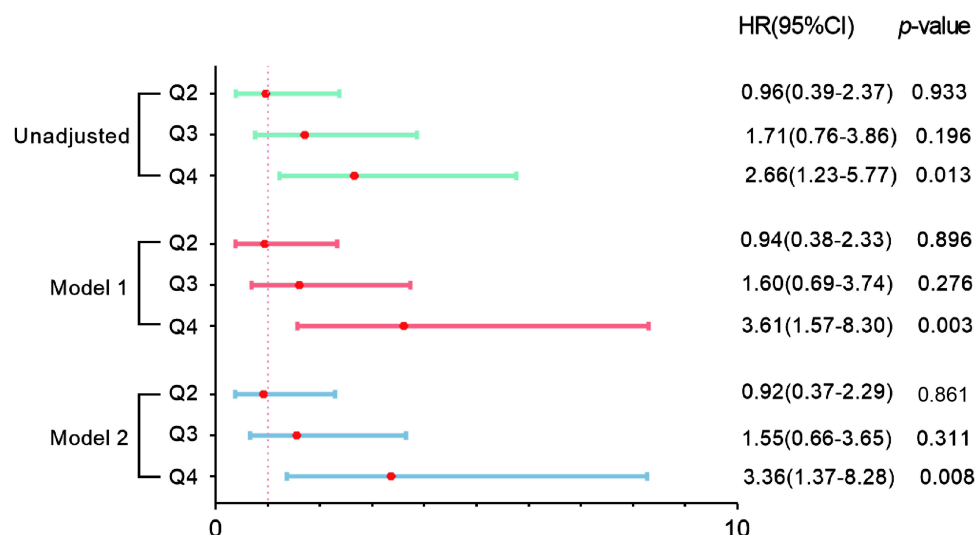


Figure 5 Association of TyG index quartiles with all-cause mortality in T2DM.

Notes: Quartile 1 is used as reference category. Model 1 was adjusted for age, duration of diabetes, hypertension, and aortic calcification; Model 2 was adjusted for age, duration of diabetes, hypertension, aortic calcification, ACEI/ARB medication history, albumin, TG, and TC.

Abbreviations: TyG Index, triglyceride glucose index; RBC, red blood cell count; HDL-C, high-density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-converting enzyme inhibitors; TG, triglyceride; TC, total cholesterol; HR, hazard ratio; CI, confidence interval.

risk of cardiovascular disease (CVD) in the highest quartile of the TyG index was 1.72 times higher than the risk of macrovascular disease in the lowest quartile (HR:1.72, 95% CI 1.37–2.16).³³

Although a large number of studies have confirmed that the TyG index can be used as a predictor of T2DM and an assessment of adverse cardiovascular events. But this conclusion is not entirely consistent. For example, Laura et al did not find an association between TyG index and CVD in patients who already had T2DM at baseline.³⁴ Cho et al also demonstrated that in subjects who already had T2DM at baseline, they failed to find an independent association between the TyG index and the presence of obstructive coronary artery disease.³⁵ The inconsistency of their conclusions can be explained by the following hypothesis: the control of indicators such as TG and FPG will vary greatly among different races and different regions. Compared with patients in developed countries, patients in developing countries may not have healthy habits and regular treatment regimens, so their analytical parameters may not be well controlled. Therefore, this study is more aimed at a single-center study in this region (China, Zhenjiang). The medical services they received differed less, and the findings of this study may be more applicable to the prognosis of these patients. Triglyceride and fasting blood glucose, test indicators that can fluctuate greatly in the short term, are considered important indicators for controlling T2DM in the short term. However, they are rarely used to predict the risk of macrovascular complications in the short term, because FPG and triglycerides can be adjusted in the short term, so we are concerned about the inaccuracy of predicting long-term macrovascular complications or all-cause mortality events.

The main findings are as follows: (1) the TyG index is closely related to macrovascular complications in T2DM; and (2) the TyG index is an independent predictor of macrovascular complications in T2DM and can predict the risk of all-cause mortality in T2DM; (3) a TyG index of 9.31 was the cutoff value for macrovascular complications. Regression analysis shows that TyG index, ACEI/ARB medication history, hypertension, RBC, high-density lipoprotein, and T2DM with macrovascular complications were strongly correlated, including these variables in the nomogram model. The total score was calculated by adding the specified number of points for each predictor in the nomogram. A higher total score indicates a higher risk of macrovascular complications for each patient. This model shows that the TyG index plays an important role in the occurrence and development of macrovascular complications. Therefore, Intervention strategies for high-risk patients can be developed quickly. The TyG index is a cost-effective and straightforward IR indicator. It can replace hyperinsulinemic-positive glucose clamp and HOMA-IR to evaluate IR better. The TyG index was included in the risk model even though triglycerides and fasting blood glucose were not the most predictive indicators in the risk model. This shows that patients who come to the clinic are less likely to have high levels of both than predicted and that

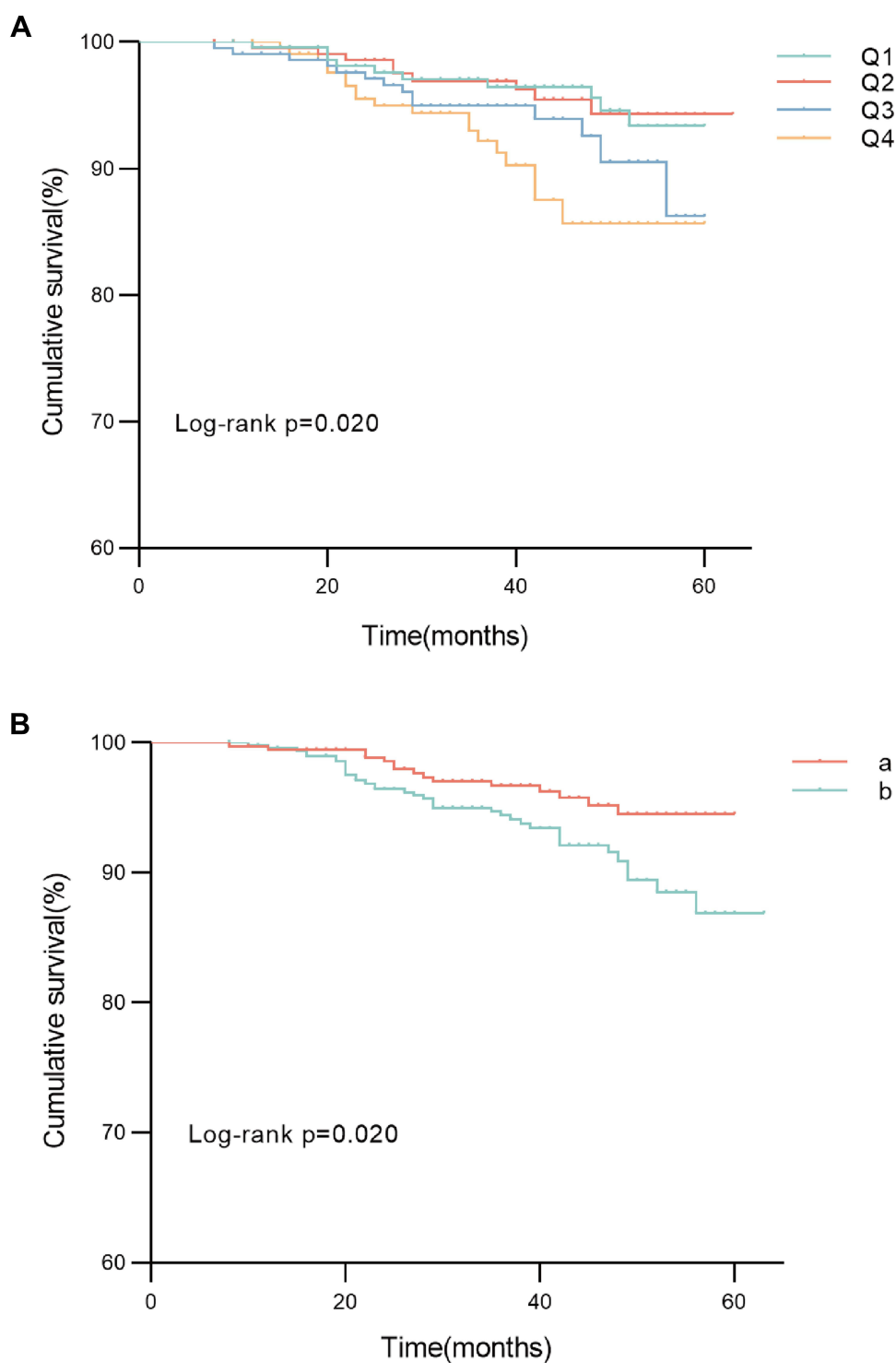


Figure 6 Prognostic analysis of patients with T2DM.

Notes: (A) Kaplan-Meier survival curves of all-cause mortality for TyG index quartiles. Q1 group (TyG ≤ 8.70), Q2 (TyG 8.70–9.20), Q3 (TyG 9.20–9.67), and Q4 (TyG ≥ 9.67). (B) Kaplan-Meier survival curves for all-cause mortality in T2DM with or without macrovascular complications. ^aWithout macrovascular complications; ^bWith macrovascular complications.

increased levels of one or both may increase the risk of macroangiopathy. It also compensates for a potentially problematic subset of diabetes patients with average or near-normal fasting blood glucose and triglycerides. Clinicians frequently overlook this population, resulting in diabetic macrovascular problems.

To our knowledge, few studies have included participants who have been diagnosed with macrovascular complications. We hope that by comparing the TyG index of patients with T2DM alone and T2DM with macrovascular complications, a convenient laboratory index can be obtained to evaluate the short-term prognosis of patients with T2DM and macrovascular complications. Therefore, we followed up with all patients to compare the short-term prognosis difference between T2DM and T2DM with macrovascular complications. As expected, all-cause mortality increased with higher TyG index quartiles. At the same time, T2DM patients with macrovascular complications have a higher risk of all-cause mortality.

This study also has some limitations. First, this is a single-center study with a small study sample size. Second, the changes in FBG and triglycerides are affected by many factors and may fluctuate significantly in a short time. We included baseline data at admission, ignoring the effect of dynamic changes in the TyG index on macrovascular complications and all-cause mortality in T2DM. Third, many variables were not included because the baseline characteristics of the participants were retrospectively included, such as glycosylated hemoglobin, past or current smoking history, systolic blood pressure, and diastolic blood pressure. For medication history, we included only ACEIs/ARBs and statins, but not insulin and other types of antihypertensive drugs. Fourth, the study is based on Chinese patients and needs to be further validated in a multi-ethnic study.

Conclusion

In summary, the TyG index, as a low-cost indicator of insulin resistance, can be used to identify the occurrence of macrovascular disease in T2DM patients. Our findings indicate that a high TyG index was independently associated with an increased risk of all-cause mortality in diabetic patients with macroangiopathy, independent of other traditional cardiovascular risk factors. These findings support the contribution of the TyG index to the risk of macrovascular complications and all-cause mortality, and suggest that patients with diabetes should minimize TG on the basis of glycemic control, which is crucial for the long-term prognosis of patients with diabetes.

Data Sharing Statement

The original data can be available by email at any time (Yao Haipeng: 1065968514@qq.com).

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Disclosure

The authors declare no conflicts of interest in relation to this work.

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