Cardiovascular Diabetology

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The predictive significance of the triglyceride-glucose index in forecasting adverse cardiovascular events among type 2 diabetes mellitus patients with co-existing hyperuricemia: a retrospective cohort study

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Abstract

Background The triglyceride-glucose (TyG) index serves as a crucial indicator for evaluating insulin resistance (IR) and cardiovascular risk among patients with type 2 diabetes mellitus (T2DM). Concurrently, hyperuricemia (HUA) strongly correlates with adverse cardiovascular outcomes. However, the prognostic value of the TyG index, particularly in patients exhibiting both conditions, remains inadequately defined. This study assessed the association between TyG index measurements and the incidence of major adverse cardiovascular events (MACEs) among patients simultaneously diagnosed with T2DM and HUA.

Methods This retrospective, single-center cohort study included 628 patients diagnosed with both T2DM and HUA at the Chaohu Hospital (Anhui Medical University) between 2019 and 2024. Participants were stratified into tertiles based on their TyG index values. Kaplan–Meier survival curves with log-rank tests estimated the risk of MACEs, and Cox regression analyses calculated hazard ratios. The additional predictive contribution of the TyG index was evaluated using C statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) metrics.

Results During the 38.00 ± 8.78 months follow-up period, 74 MACEs were recorded. A significant proportional relationship emerged between the TyG index and cardiovascular events—patients in the highest tertile demonstrated markedly increased risk compared with those in the lowest tertile (HR = 2.45, 95% CI 1.23–4.95). A pivotal threshold was identified at TyG > 8.40, beyond which each standard deviation increase corresponded to a 66% higher probability of MACEs (HR = 1.66, 95% CI 1.36–2.36, $P = 0.014$). Integrating the TyG index into traditional risk models significantly improved predictive performance (C statistic increase: 0.64 → 0.67, $P = 0.029$; NRI = 0.14, IDI = 0.02, both $P < 0.05$).

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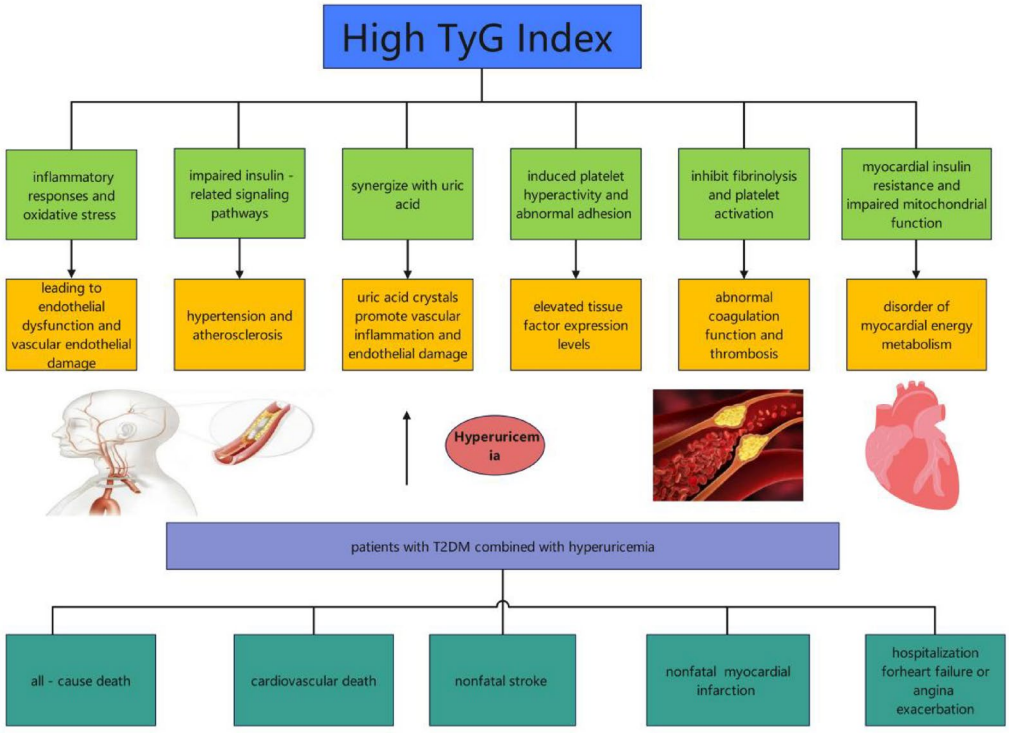
Conclusion The TyG index constitutes an autonomous MACE predictor specifically within the distinctive cohort of patients manifesting both T2DM and HUA. This study is the first to validate the TyG > 8.40 threshold in T2DM patients with HUA and identify a synergistic interaction between serum uric acid (SUA) and TyG, providing a novel stratification tool for managing dual metabolic disorders.

Keywords Triglyceride-glucose index, Hyperuricemia, Type 2 diabetes mellitus, Major adverse cardiovascular events

Graphical abstract



Research insights

What is currently known about this topic?

1. Coexisting T2DM and HUA elevate cardiovascular risk
2. The TyG index correlates with cardiovascular risk in T2DM patients
3. Existing models lack precision for T2DM-HUA patients.

What is the key research question?

Whether the TyG index effectively predicts adverse cardiovascular events among T2DM patients with HUA.

What is new?

1. TyG > 8.40 identifies high-risk T2DM-HUA patients
2. Links TyG to insulin resistance and inflammation
3. Confirms the clinical value of integrating TyG into risk stratification

How might this study influence clinical practice?

It provides a simple, cost-effective method for enhancing risk assessment and guiding early interventions

Background

With changes in global lifestyles and accelerating population aging, the prevalence of type 2 diabetes mellitus (T2DM) and hyperuricemia (HUA) has significantly increased. HUA commonly occurs in patients with T2DM, and the simultaneous presence of these conditions is becoming increasingly prevalent [1, 2]. Additionally, cardiovascular diseases represent primary complications in patients concurrently diagnosed with T2DM and HUA, constituting major determinants of mortality [3]. Despite the widespread use of conventional cardiovascular risk indicators, such as arterial pressure, lipid profiles, and glycemic measurements, significant predictive limitations remain regarding adverse cardiovascular outcomes in patients with both T2DM and HUA. As a novel measure reflecting insulin resistance (IR) status [4], the TyG index shows substantial potential for predicting cardiovascular events in this patient group.

Extensive studies have confirmed T2DM and HUA as significant independent cardiovascular risk factors [3]. Their coexistence substantially increases cardiovascular risks. The incidence of severe cardiovascular sequelae, including coronary artery disease, cardiac insufficiency, and cerebrovascular events, significantly exceeds that observed in patients with either isolated conditions or the general population [1, 5]. Potential underlying mechanisms involve reduced insulin sensitivity, oxidative stress, chronic inflammatory activation, endothelial dysfunction, and metabolic disturbances [6].

In the past decade, the TyG index has emerged as a practical and accessible evaluation tool, attracting considerable scientific interest in IR research. Studies indicate that this metric correlates strongly with cardiovascular disease progression [7, 8]. Elevated TyG index values frequently predict adverse cardiovascular outcomes, a pattern evident in both general populations and patients with multiple chronic disorders [9–11]. Additionally, substantial evidence highlights complex bidirectional interactions between T2DM and HUA [3, 12]. Specifically, elevated serum SUA concentrations can promote IR through various physiological mechanisms and impair glucose homeostasis [12], consequently elevating glycemic values and the TyG index. Conversely, metabolic abnormalities in T2DM patients with increased TyG indices may stimulate SUA production or impair excretion pathways, exacerbating hyperuricemic states [13]. Current evidence emphasizes the TyG index's potential as an independent cardiovascular risk predictor [14]. Notably, this metric retains significant prognostic value even after statistical adjustments for established cardiovascular risk factors [15].

Although clinical utility of the TyG index in cardiovascular prediction has been established [16], research focusing specifically on the population concurrently affected by T2DM and HUA remains limited.Prior studies concentrated on either isolated T2DM or HUA populations [7–9], whereas the present study uniquely investigates their coexistence. Furthermore, we identify a TyG threshold (8.40) specifically applicable to this population and demonstrate that SUA amplifies TyG-associated cardiovascular risk, addressing an essential evidence gap. Moreover, definitive consensus regarding optimal TyG thresholds for cardiovascular prediction remains elusive [7, 17, 18]. Consequently, a precise cardiovascular risk stratification method for individuals concurrently diagnosed with T2DM and HUA remains insufficiently characterized.

The current study explicitly focuses on patients diagnosed with concurrent T2DM and HUA, addressing the critical knowledge gap concerning the predictive ability of the TyG index for adverse cardiovascular outcomes within this population. Besides assessing the fundamental association between TyG values and cardiovascular risk, we particularly examine the clinical implications of this index among patients with both metabolic disorders, thereby comprehensively evaluating its prognostic relevance. Utilizing clinical data from real-world practice, this study carefully explores the relationship between TyG index measurements and major adverse cardiovascular events (MACEs) in patients with dual metabolic disorders. The insights generated from this analysis may assist healthcare professionals in promptly identifying high-risk individuals and implementing appropriate interventions to improve long-term patient outcomes. Exploring the TyG index across diverse disease conditions may facilitate the development of more comprehensive cardiovascular prevention and management strategies.

Methods

Study design and participants

This study employed a single-center retrospective cohort design, including 628 patients diagnosed with both T2DM and HUA at Chaohu Hospital, Anhui Medical University, between 2019 and 2024. Figure 1 illustrates the patient screening process. Eligibility criteria required individuals to be aged 18–80 years and meet diagnostic criteria for both T2DM and HUA.The selected age range aimed to exclude pediatric populations (due to distinct metabolic profiles) and elderly individuals over 80 (due to frequent complex comorbidities), thereby focusing on the primary T2DM-HUA demographic. Exclusion criteria included severe hepatic disease (Child–Pugh score ≥ 7), significant renal impairment (eGFR < 30 mL/min/1.73 m^2), unmanageable heart failure, secondary hypertension, severely elevated triglyceride (TG) levels (> 5.65 mmol/L), non-index hospitalizations, cardiogenic shock, malignancy, life expectancy less than five years, incomplete baseline or follow-up data, or other unsuitable conditions. Patients were stratified according to disease duration and complication severity: diabetes duration ≤ 5 years (n = 213), > 5 years (n = 415); presence of hypertension (n = 327); chronic kidney disease (CKD stages 1–2, n = 29; CKD stage 3, n = 11); and treatment type (oral hypoglycemic drugs only, n = 246; combined insulin therapy, n = 382). Based on updated SUA thresholds from the "Cardiovascular Risk Stratification" section of the Chinese Guidelines (2023), patients were categorized into three groups: low UA (420 ≤ SUA < 480 μmol/L, 34.4%, n = 216), medium UA(480 ≤ SUA < 540 μmol/L, 45.7%, n = 287), and high UA (SUA ≥ 540 μmol/L, 19.9%, n = 125). The TyG index was calculated using the formula ln[TG (mg/dL) × glucose (mg/dL)/2], and participants were divided into tertiles: T1 (TyG < 8.25), T2 (8.25 ≤ TyG ≤ 9.48), and T3 (TyG > 9.48). This retrospective study followed the Declaration of Helsinki principles,

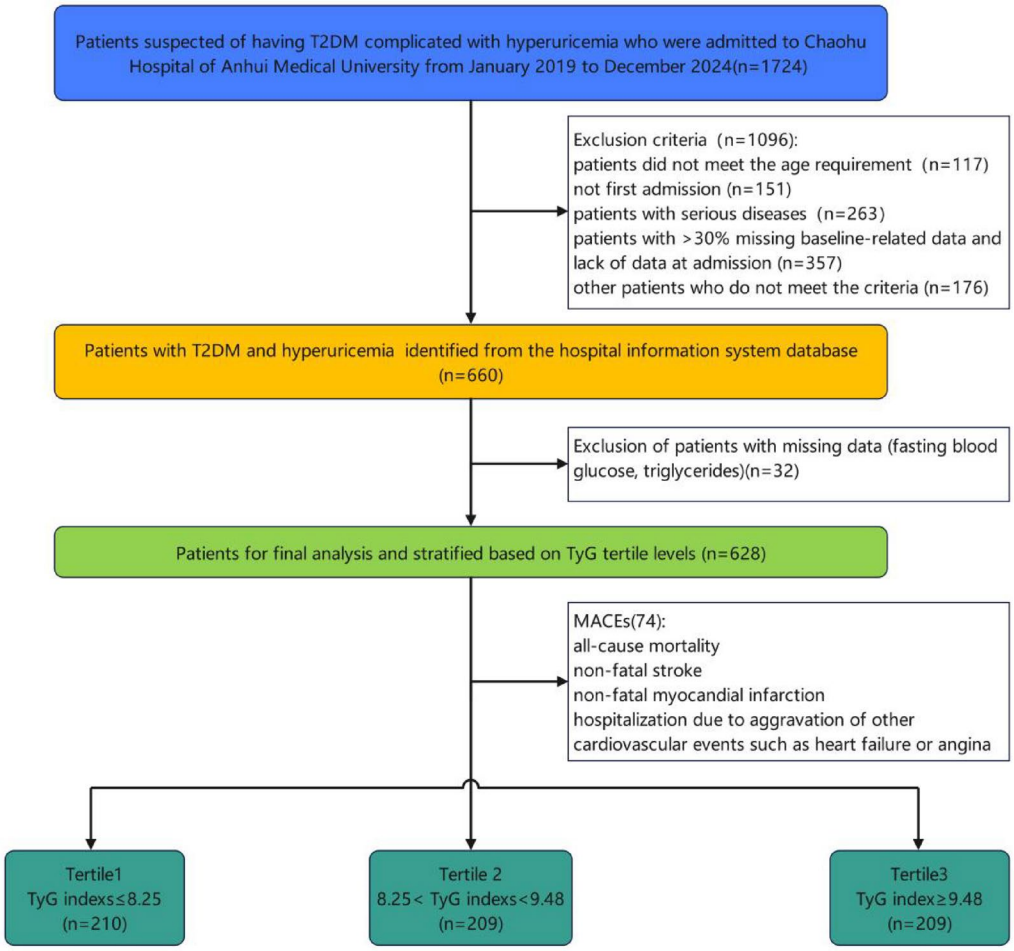


Fig. 1 Displays the flowchart depicting patient inclusion in the study

and ethics committee approval waived informed consent requirements, ensuring complete data anonymization. This study received approval from the Ethics Committee of Chaohu Hospital, Anhui Medical University (Approval Number: KYXM-201912-051).

Data collection and definition

All study participants underwent fasting morning blood collection, with analyses performed on the same day in a standardized laboratory environment. Clinical data were extracted from medical records by trained personnel blinded to the study objectives. Comprehensive data collection included demographic parameters (age, sex, BMI), clinical risk indicators (heart rate, systolic and diastolic blood pressure, lifestyle behaviors, medical history), and extensive laboratory evaluations. These biochemical assessments included hematological profiles, metabolic biomarkers, inflammatory mediators, and lipid fractions. The TyG index was calculated from baseline fasting blood samples. Due to the retrospective study design, longitudinal TyG measurements were unavailable. The TyG calculation involved converting fasting blood glucose (FBG) and TG levels from mmol/L to mg/dL, followed by applying the logarithmic formula ln[TG (mg/dL) × glucose (mg/dL)/2] [19]. Diabetes diagnosis followed established clinical guidelines: HbA1c% ≥ 6.5%, random glucose ≥ 11.1 mmol/L, fasting glucose ≥ 7.0 mmol/L, or 2-h post-glucose challenge ≥ 11.1 mmol/L [20].Type 2 diabetes classification required the systematic exclusion of alternative diabetes etiologies. BMI was calculated as weight (kg)/height^2 (m^2). HUA was defined as fasting SUA levels exceeding 420 μmol/L on two separate occasions under normal dietary conditions [21, 22]. Dyslipidemia criteria included LDL-C ≥ 3.4 mmol/L, HDL-C < 1.0 mmol/L, TG ≥ 1.7 mmol/L, or active lipid-lowering therapy [23]. History of coronary heart disease (CHD) was defined as prior diagnosis of myocardial infarction, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), or angiographically confirmed stenosis ≥ 50% in at least one major coronary artery [24].

Dietary intake was assessed using a validated food frequency questionnaire (FFQ), capturing consumption of purine-rich foods (e.g., red meat, seafood, organ meats) and alcoholic beverages. Participants were stratified by purine intake levels: low (< 1 serving/week), moderate (1–3 servings/week), and high (> 3 servings/week) [25].

Follow-up and endpoint events

Trained medical staff conducted participant follow-up through telephone communications, electronic health records, or outpatient visits. Follow-up began at hospital discharge and continued until January 2025, participant withdrawal, or death. The primary endpoint of this study was the incidence of MACEs—a composite outcome comprising total mortality, cardiovascular-specific mortality, non-fatal stroke, non-fatal myocardial infarction (MI), and hospitalizations due to decompensated heart failure or unstable angina. Non-fatal MI required clinical symptoms consistent with acute myocardial ischemia and a troponin level exceeding the 99th percentile of the normal range. Non-fatal stroke included cerebral infarction and hemorrhage confirmed by imaging. If participants experienced multiple events during follow-up, the most severe event (ranked as all-cause death > cardiovascular death > non-fatal stroke > non-fatal MI) was recorded as the final outcome. Endpoint event diagnoses were independently reviewed and confirmed by at least two senior experts.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or medians (interquartile range) and compared using one-way ANOVA (for normally distributed data) or Kruskal–Wallis tests (for non-parametric data). Categorical variables were presented as frequencies (percentages) and compared using chi-square or Fisher's exact tests when appropriate. Associations between TyG index values and clinical endpoints were quantified using Cox proportional hazards models, generating hazard ratios (HRs) and 95% confidence intervals (CIs).

Three multivariate Cox regression models were used for analysis: Model 1 (unadjusted), Model 2 (adjusted for demographic factors, including age and gender), and Model 3 (fully adjusted for biochemical indicators, medication usage, and dietary intervention status). Adjusted biochemical parameters included RBC, HbA1c%, Hb, ALB, C-P, and 25(OH)D.Purine diet was included as a categorical covariate (low/moderate/high) in multivariate Cox models to adjust for potential dietary confounding. Urate-lowering therapy (ULT) was categorized as benzbromarone (uricosuric agent) or febuxostat (xanthine oxidase inhibitor). Survival probabilities across groups were visualized using Kaplan–Meier curves, with differences tested by log-rank analyses. Potential non-linear associations between TyG indices and clinical outcomes were assessed using restricted cubic spline regression. Subgroup analyses assessed heterogeneity based on demographic characteristics (age, sex), comorbidities (hypertension presence, cardiovascular disease history), anthropometric measurements (BMI), and metabolic parameters (HbA1c concentration, LDL-C levels). Interaction effects were quantified by likelihood ratio tests.

The incremental predictive value of the TyG index beyond traditional risk factors was evaluated using C statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Interactions between SUA and TyG index were examined using two Cox models: Model A (main effects only) and Model B (with interaction term), compared via likelihood ratio statistics. Stratified analyses by SUA groups used Cox models adjusted for age, sex, HbA1c%, and LDL-C. Bootstrap resampling (1000 iterations) was performed to assess the stability of Cox regression estimates. Multicollinearity was assessed using variance inflation factors (VIF). To validate the proportional hazards assumption of the Cox models, we performed Schoenfeld residual tests for each model. If the assumption was violated (global P-value < 0.05), we considered alternative approaches such as stratified Cox models or parametric Weibull models.All analyses used SPSS 27.0 and R 3.6.2, with significance at $P < 0.05$ (two-sided).

Results

Baseline characteristics

Based on tertiles of the TyG index, 628 patients diagnosed with T2DM and HUA at Chaohu Hospital, Anhui Medical University, were divided into three groups. During the median follow-up of 38.00 ± 8.78 months, 74 participants (11.78%) experienced MACEs. The median age was 63.00 years (IQR: 53.0–67.0), and males comprised 61.46% (n = 386).Baseline characteristics of excluded patients (n = 1096) were similar to the included cohort, without significant differences in TyG index or MACE risk (Table 1).

Table 2 presents baseline characteristics stratified by TyG tertiles. Significant differences (all $P < 0.05$) emerged between groups regarding MACE occurrence, age, hypertension prevalence, SBP, DBP, stroke history, RBC, WBC, Hb, FBG, HbA1c%, C-P, ALB, BUN, UA, TG, TC, HDL-C, LDL-C, and use of medications (GLP-1RA, SGLT-2i). Other parameters did not significantly differ. Notably, participants in the highest TyG tertile (T3), despite being younger, had higher MACE incidence, more frequent hypertension or stroke history, higher DBP, greater use of GLP-1RA and SGLT-2i medications, and elevated laboratory values compared to other tertiles.

Table 1 Sensitivity analysis of included vs. excluded patients

Characteristics	Included (n = 628)	Excluded (n = 1096)	*P*-value
Demographic data			
Age (years)	63.00 ± 9.5	64.20 ± 10.1	0.102
Male, %	61.46%	59.80%	0.342
Clinical parameters			
TyG index	8.41 ± 0.69	8.36 ± 0.72	0.213
MACE incidence, %	11.8%	12.1%	0.861
Hypertension, %	52.07%	54.30%	0.456
HbA1c (%)	9.20 ± 2.1	9.00 ± 2.3	0.154
LDL-C (mmol/L)	2.22 ± 1.0	2.18 ± 1.1	0.678
Exclusion criteria			
Severe renal dysfunction	0%	100% (eGFR < 30 mL/min/1.73m^2)	N/A
Severe hepatic impairment	0%	100% (Child–Pugh ≥ 7)	N/A

Data presented as mean ± SD or percentage. Severe renal dysfunction: Defined as eGFR < 30 mL/min/1.73 m^2. Severe hepatic impairment: Defined by Child–Pugh score ≥ 7

P-values calculated via t-test (continuous variables) or chi-square test (categorical variables)

Risk factors for MACEs

Baseline demographic and clinical characteristics comparing participants who experienced MACEs with those who remained event-free are shown in Table 3. During the follow-up period, 74 patients (11.78%) developed MACEs. Patients who experienced MACEs had significantly lower levels of C-peptide and 25-hydroxyvitamin D ($P < 0.05$) and significantly higher values for red blood cell count, glycated hemoglobin percentage, hemoglobin, and serum albumin ($P < 0.05$). Other clinical and laboratory parameters showed no statistically significant differences between the two groups.

Relationship between the TyG Index and cardiovascular events in patients with T2DM complicated by HUA

During the 38.00 ± 8.78-month follow-up period, 74 patients (11.78%) experienced at least one major cardiovascular event. The Kaplan–Meier curve (Fig. 2) demonstrates a significant proportional increase in cardiovascular event risk with higher TyG index tertiles (log-rank $P = 0.001$). Throughout follow-up, patients in the highest tertile consistently showed the highest cumulative cardiovascular event risk.

Table 4 presents the quantitative association between TyG index and MACE incidence among patients with concurrent T2DM and HUA. Cardiovascular event risk progressively increased with higher TyG tertiles across all analytical models. In the unadjusted model, patients in the highest tertile exhibited a 2.72-fold increased risk compared to those in the lowest tertile (T2 vs. T1: HR = 1.68, 95% CI 0.93–3.08, $P = 0.094$; T3 vs. T1: HR = 2.72, 95% CI 1.58–4.75, $P < 0.01$). After adjustment for age and sex (Model 2), this hazard ratio slightly decreased to 2.67 (T2 vs. T1: HR = 1.69, 95% CI 0.91–3.14, $P = 0.091$; T3 vs. T1: HR = 2.67, 95% CI 1.52–4.83, $P < 0.01$). In the fully adjusted Model 3, the hazard ratio remained significant at 2.45 (T2 vs. T1: HR = 1.67, 95% CI 0.81–3.38, $P = 0.171$; T3 vs. T1: HR = 2.45, 95% CI 1.23–4.95, $P = 0.014$). To validate the proportional hazards assumption of the Cox models, we conducted Schoenfeld residual tests. For all three models (unadjusted, adjusted for age/sex, and fully adjusted), the proportional hazards assumption was satisfied for TyG index groups (all *P*-values > 0.05, Table 5). Global tests further confirmed no significant time-dependent effects across the models (Global *P*-values > 0.05). The Schoenfeld residuals for TyG groups showed no systematic deviation from zero over time (Fig. 3), supporting the validity of the Cox models. Bootstrap validation confirmed the robustness of TyG-MACE associations (HR = 1.66, 95% CI 1.36–2.36). Table 6 demonstrates that the TyG index is highly correlated with triglycerides (TG) (r = 0.85) and fasting blood glucose (FBG) (r = 0.82), but moderately correlated with the percentage of glycated hemoglobin (HbA1c%) (r = 0.38), which supports its independent predictive value (*$P < 0.05$, **$P < 0.01$),The VIF values of all variables are less than 3.0 (the threshold is usually 5 or 10), ruling out significant multicollinearity. The risk of collinearity between the TyG index (VIF = 1.85) and HbA1c% (VIF = 1.62) is low, which supports the stability of the model.

Our restricted cubic spline analysis (Fig. 4) uncovered a pronounced non-monotonic relationship between TyG parameters and cardiovascular incidents (nonlinearity $P = 0.042$). This mathematical modeling identified 8.40 as the decisive boundary value for adverse outcome prediction. When TyG measurements exceeded this threshold, each standard deviation increment substantially heightened cardiovascular complication likelihood (HR = 1.66, 95% CI 1.36–2.36, $P = 0.014$), whereas values registering below 8.40 demonstrated minimal, statistically inconsequential impact on prognosis (HR = 1.44, 95% CI 0.47–4.67, $P = 0.563$).

Comparison of patient characteristics around the TyG = 8.40 threshold (Table 7) showed that patients with TyG values above 8.40 were older, had significantly poorer metabolic profiles (higher FBG, TG, UA, LDL-C), and greater statin usage (78.9% vs. 62.7%, $P < 0.001$). In patients with LDL-C > 1.5 mmol/L, the TyG index hazard ratio was higher among non-statin users (HR = 2.14, 95% CI 1.42–3.21) compared to statin users (HR = 1.46, 95% CI 1.08–1.98), demonstrating a significant difference (interaction $P = 0.032$). TyG index positively correlated with Hs-CRP (r = 0.28, $P < 0.001$). The proportion of patients with Hs-CRP ≥ 2.0 mg/L was 2.3-fold higher in the TyG > 8.40 group than in those ≤ 8.40 (43.1% vs.

Table 2 Baseline characteristics according to TyG index tertiles

Viable	Total	TyG index level			*P* value
		T1 (≤ 8.25)	T2 (> 8.25, ≤ 9.48)	T3 (> 9.48)	
N (%)	628	210	209	209	–
Age, y	63.00 (53.00, 67.00)	64.00 (54.00, 69.00)	62.50 (55.00, 68.00)	61.50 (49.00, 62.00)	0.000**
Male, n (%)	386 (61.46)	126 (60.00)	129 (61.72)	131 (62.68)	0.070
BMI, kg/m^2	26.53 (24.30, 28.80)	25.45 (23.30, 27.64)	26.76 (24.80, 29.50)	26.94 (24.90, 29.80)	0.962
HR, bpm	70 (68, 75)	72 (68, 77)	71 (66, 78)	69 (67, 76.00)	0.223
SBP, mmHg	130 (123, 142)	131 (122, 143)	130 (121, 142)	129 (121, 143)	0.045*
DBP, mmHg	78 (72, 85)	75 (70, 84)	80 (72, 85)	78 (71, 83)	0.000**
Risk factors					
Smoker, n (%)	382 (60.83)	122 (58.10)	130 (62.20)	130 (62.20)	0.755
Drinker, n (%)	191 (30.41)	67 (31.90)	63 (30.14)	61 (29.19)	0.858
AF, n (%)	17 (2.71)	7 (3.33)	6 (2.87)	4 (1.91)	0.635
Hypertensive disease, n (%)	327 (52.07)	68 (32.38)	104 (49.76)	155 (74.16)	0.000**
CKD, n (%)	40 (7.33)	11 (5.24)	16 (7.66)	16 (7.66)	0.440
Previous stroke, n (%)	41 (6.53)	19 (9.05)	15 (7.18)	7 (3.35)	0.022*
Previous MI, n (%)	80 (12.74)	29 (13.81)	25 (11.96)	26 (12.44)	0.878
Family history of CVD, n (%)	39 (6.21)	12 (5.71)	14 (6.70)	13 (6.22)	0.869
Previous CHD, n (%)	98 (15.6)	32 (15.23)	32 (15.35)	34 (16.27)	0.934
The duration of T2DM					
≤ 5 years n (%)	213 (33.92)	70 (33.33)	68 (32.54)	75 (35.89)	0.171
> 5 years n (%)	415 (66.08)	140 (66.67)	139 (66.51)	136 (65.72)	0.272
Laboratory tests					
RBC, 10^{12}/L	4.54 ± 0.55	4.46 ± 0.54	4.56 ± 0.58	4.61 ± 0.52	0.005**
WBC, 10^9/L	7.16 (6.20, 8.42)	6.77 (5.80, 7.91)	7.34 (6.30, 8.75)	7.47 (6.30, 8.82)	0.000**
PLT, 10^9/L	228.56 ± 58.05	224.74 ± 57.63	226.58 ± 56.68	230.43 ± 58.75	0.330
NE, %	67.29 ± 8.75	67.24 ± 8.76	67.85 ± 8.82	66.89 ± 7.89	0.643
C-peptide, ng/ml	1.52 (1.03, 3.13)	1.45 (0.94, 3.02)	1.50 (1.12, 2.88)	1.80 (1.18, 3.10)	0.000**
25 (OH) D, ng/ml	21.38 (14.88, 24.34)	21.20 (14.60, 25.94)	21.50 (14.85, 23.82)	21.45 (15.14, 23.95)	0.743
FBG, mmol/L	5.60 (4.40, 8.50)	5.50 (4.60, 8.30)	5.70 (5.10, 8.60)	5.80 (5.80, 8.90)	0.000**
HbA1C%, %	9.20 (6.40, 9.80)	8.80 (6.60, 9.50)	9.00 (6.40, 10.10)	9.90 (6.90, 10.80)	0.005**
Hs-CRP, mg/L	1.60 (0.60, 4.80)	1.20 (0.60, 3.90)	1.50 (0.80, 4.80)	1.80 (0.90, 3.90)	0.085
Hb, g/L	143.00 (131.00, 151.00)	141.00 (127.00, 149.00)	144.00 (131.00, 156.00)	144.00 (132.00, 153.00)	0.031*
Alb, g/L	43.26 ± 3.94	42.51 ± 3.75	43.01 ± 4.15	44.17 ± 3.67	0.000**
eGFR, mL/min/1.73 m^2	86.20 (65.40, 99.10)	89.20 (69.10, 96.60)	84.00 (68.00, 97.00)	83.80 (65.40, 99.10)	0.645
BUN, mmol/L	6.20 (4.50, 8.10)	5.60 (4.50, 7.00)	6.10 (4.70, 7.90)	6.40 (5.40, 8.10)	0.000**
UA, μmol/L	473.05 ± 103.38	454.04 ± 100.03	510.00 ± 100.18	580.78 ± 106.45	0.000**
Cr, μmol/L	83.00 (70.00, 100.00)	81.00 (70.00, 96.00)	83.00 (73.00, 101.00)	86.00 (73.00, 103.00)	0.081
TG, mmol/L	1.23 (0.70, 2.33)	1.02 (0.83, 1.30)	1.39 (1.40, 1.92)	2.30 (1.81, 3.24)	0.000**
TC, mmol/L	3.91 (3.22, 5.33)	3.64 (3.21, 4.36)	3.88 (3.34, 4.45)	4.32 (3.70, 5.37)	0.000**
HDL-C, mmol/L	0.98 (0.81, 1.23)	1.04 (0.90, 1.24)	0.96 (0.83, 1.17)	0.92 (0.83, 1.16)	0.000**
LDL-C, mmol/L	2.22 (1.61, 3.22)	2.12 (1.66, 2.66)	2.21 (1.98, 2.82)	2.40 (1.94, 3.27)	0.003**
Hcy, μmol/l	13.20 (9.20, 24.30)	13.60 (9.20, 24.30)	14.10 (9.70, 23.80)	12.20 (9.50, 20.00)	0.212
ALT, U/L	20.00 (16.00, 34.00)	18.00 (13.00, 29.00)	20.00 (14.00, 37.00)	22.00 (15.00, 36.00)	0.345
AST, U/L	20.00 (16.00, 33.00)	21.00 (12.00, 29.00)	19.00 (16.00, 29.00)	21.00 (16.00, 39.00)	0.853
Discharge prescription, n (%)					
GLP-1RA	100 (15.92)	32 (15.24)	33 (15.79)	35 (16.75)	0.021*
SGLT-2	108 (17.20)	35 (16.67)	36 (17.22)	37 (17.70)	0.011*
DPP-4i	117 (18.63)	41 (19.52)	39 (18.66)	37 (17.70)	0.714
Metformin	427 (68.00)	143 (68.10)	142 (67.94)	142 (67.94)	0.456
TZDs	38 (6.05)	13 (6.19)	12 (5.74)	13 (6.22)	0.454
Other OADs	319 (50.80)	106 (50.48)	105 (50.24)	108 (51.67)	0.135
Insulin	382 (60.82)	128 (60.95)	125 (59.81)	129 (61.72)	0.350
Statins	462 (73.57)	161 (76.67)	150 (71.78)	151 (72.25)	0.759

Table 2 (continued)

Viable	Total	TyG index level			*P* value
		T1 (≤ 8.25)	T2 (> 8.25, ≤ 9.48)	T3 (> 9.48)	
Antiplatelet therapy	313 (49.84)	103 (49.05)	106 (50.72)	104 (49.76)	0.557
ACEI/ARBs	191 (30.41)	62 (29.52)	57 (27.27)	72 (34.45)	0.191
Beta-blocker	35 (5.59)	10 (4.76)	12 (5.74)	13 (6.22)	0.710
CCB	130 (20.70)	48 (22.86)	37 (17.70)	45 (21.53)	0.454
Febuxostat	117 (18.63)	41 (19.52)	37 (17.70)	39 (18.66)	0.714
Benzbromarone	95 (15.13)	32 (15.24)	33 (15.79)	30 (14.35)	0.813
MACE, n (%)	74 (11.78)	17 (8.10)	23 (11.00)	34 (16.27)	0.021*

Data are presented as means ± SDs, medians (IQR), or percentages. *$P < 0.05$, **$P < 0.01$

TyG, triglyceride-glucose index; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; CKD, chronic kidney disease; MI, myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; RBC, red blood cell; WBC, white blood cell; PLT, platelet; NE, neutrophil; 25 (OH)D, 25-hydroxyvitamin D; FBG, fasting blood glucose; HbA1c%, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein; Hb, hemoglobin; Alb, albumin; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UA, uric acid; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; ALT, alanine transaminase; AST, aspartate aminotransferase; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; TZDs, thiazolidinediones; OADs, oral antidiabetic drugs; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; MACEs, major adverse cardiovascular events

18.7%, $P < 0.001$). Other laboratory parameters, medical histories, and medication regimens did not differ significantly ($P > 0.05$).

Table 8 reveals a significant positive correlation between SUA and TyG values (r = 0.32, $P < 0.001$). Cardiovascular event rates were higher in the elevated SUA group (≥ 540 μmol/L) compared to those with lower SUA (15.9% vs. 7.3%, $P < 0.001$). After excluding participants receiving urate-lowering therapy (n = 212), the intermediate SUA category still showed significantly increased cardiovascular risk (HR = 1.85, 95% CI 1.10–3.05).

Table 9 shows the interaction between SUA categories and TyG index remained significant after adjustment (likelihood ratio test $\chi^2 = 6.32$, $P = 0.042$). Stratified analytical approaches revealed: among subjects with mild HUA (420–480 μmol/L), each single-unit increment in TyG index corresponded to 48% amplified MACE probability (HR = 1.48, 95% CI 1.12–1.95, $P = 0.006$); within the moderate HUA classification (480–540 μmol/L), risk elevation reached 72% (HR = 1.72, 95% CI 1.31–2.26, $P < 0.001$); while in the severe HUA group (≥ 540 μmol/L), risk augmentation attained 98% (HR = 1.98, 95% CI 1.42–2.76, $P < 0.001$).Stratified analyses indicated increased risk per unit increment in TyG index: mild HUA (420–480 μmol/L, HR = 1.48, 95% CI 1.12–1.95, $P = 0.006$), moderate HUA (480–540 μmol/L, HR = 1.72, 95% CI 1.31–2.26, $P < 0.001$), and severe HUA (≥ 540 μmol/L, HR = 1.98, 95% CI 1.42–2.76, $P < 0.001$). Febuxostat users exhibited a trend toward lower MACE risk compared to benzbromarone-treated patients (HR = 0.82, $P = 0.076$) (Table 10).

ROC curve analysis of the value of the TyG index

Assessment of predictive capability for MACE using ROC curve analysis revealed the basic risk model achieved an AUC of 0.623 ($P < 0.05$). Addition of the TyG index improved the AUC significantly to 0.664 ($P < 0.05$). Comparative ROC curves illustrating this enhancement are shown in Fig. 5. (AUC: comprehensive model with TyG index = 0.664 vs. conventional model = 0.623, $P < 0.05$).

Incremental predictive value of the TyG index

Table 11 illustrates that incorporating the TyG index significantly improved MACE predictive capability (C statistic increased from 0.64 [95% CI 0.592–0.673] to 0.67 [95% CI 0.632–0.694], $P = 0.029$; NRI increased by 14%, P = 0.035; IDI increased by 2%, $P = 0.043$).

Subgroup analysis

Subgroup analysis (Fig. 6) validated the TyG index's predictive consistency across demographic and clinical characteristics (gender, age, BMI, hypertension, cardiovascular disease history, HbA1c levels), with generally consistent findings (interaction *P*-values mostly > 0.05). However, significant interactions were identified for age ($P = 0.046$), hypertension status ($P = 0.038$), and LDL-C level ($P = 0.034$).

Discussion

This study is the first to specifically investigate associations between the TyG index and cardiovascular risk among patients concurrently diagnosed with T2DM and HUA. Our main findings include: (1) Patients exhibiting elevated TyG index values experienced significantly higher risks of adverse cardiovascular events compared to those with lower values; (2) After comprehensive adjustment for confounding factors, the TyG index retained a strong association with MACEs, regardless of whether analyzed continuously or categorically; (3) A clear nonlinear relationship was identified between TyG index values and MACE incidence, influenced by established cardiovascular risk determinants; and (4)

Table 3 Baseline clinical characteristics of patients stratified by MACEs

Indicators	Overall	Maces	Non-maces	*P* value
N (%)	628	74	554	
Age, y	63.00 (53.00,67.00)	64.00 (50.00,68.00)	63.00 (53.00,68.00)	0.216
Male, n (%)	386 (61.46)	45 (60.81)	341 (61.55)	0.564
BMI, kg/m^2	26.53 (24.30,28.80)	26.01 (23.94,27.83)	26.23 (24.20,28.47)	0.458
HR, bpm	70.00 (68.00,75.00)	72.00 (67.00,81.00)	70.00 (66.00,78.00)	0.429
SBP, mmHg	130.00 (123.00,142.00)	130.00 (120.00,144.00)	130.00 (120.00,140.00)	0.820
DBP, mmHg	78.00 (72.00,85.00)	77.50 (70.00,86.00)	78.50 (70.00,85.00)	0.880
Risk factors				
Smoker, n (%)	382 (60.83)	31 (41.89)	351 (63.36)	0.145
Drinker, n (%)	191 (30.41)	15 (20.27)	176 (31.77)	0.677
AF, n (%)	17 (2.71)	1 (1.35)	16 (2.89)	0.628
Hypertensive disease, n (%)	227 (36.15)	24 (32.43)	203 (36.60)	0.680
CKD, n (%)	40 (7.33)	5 (6.76)	35 (6.32)	0.566
Previous stroke, n (%)	41 (6.53)	2 (2.70)	37 (6.68)	0.293
Previous MI, n (%)	80 (12.74)	9 (12.16)	71 (12.82)	0.653
Family history of CVD, n (%)	39 (6.21)	5 (6.77)	34 (6.14)	0.448
Previous CHD, n (%)	98 (15.6)	13 (17.6)	71 (15.3)	0.877
The duration of T2DM				
≤ 5 years n (%)	213 (33.92)	23 (31.08)	190 (89.20)	0.192
> 5 years n (%)	415 (66.08)	51 (68.92)	364 (87.71)	0.066
Laboratory tests				
RBC,10^{12}/L	4.47 (4.10,4.78)	4.47 (4.00,4.74)	4.61 (4.32,4.90)	0.033*
WBC,10^9/L	7.16 (6.20,8.42)	7.74 (6.64,9.30)	7.11 (6.10,8.54)	0.112
PLT,10^9/L	222.00 (198.00,242.00)	222.00 (198.80,252.80)	220.00 (186.00,265.00)	0.977
NE, %	67.29 ± 8.75	68.69 ± 7.30	67.14 ± 8.55	0.235
C-peptide, ng/ml	1.52 (1.03,3.13)	1.48 (1.24,3.12)	1.41 (1.33,3.09)	0.032*
25 (OH) D, ng/ml	21.38 (14.88,24.34)	21.38 (15.81,23.84)	19.88 (14.39,24.37)	0.025*
Glu, mmol/L	5.60 (4.60,9.50)	5.89 (5.10,7.70)	5.63 (5.00,6.90)	0.180
HbA1C%, %	6.00 (5.40,7.80)	6.30 (5.80,7.90)	6.00 (5.60,6.90)	0.034*
hs-CRP, mg/L	1.60 (0.60,4.80)	2.48 (0.80,5.90)	1.50 (0.70,3.90)	0.068
Hb, g/L	143.00 (131.00,151.00)	142.00 (122.00,148.00)	143.00 (131.00,153.00)	0.035*
Alb, g/L	42.20 (39.50,44.90)	42.20 (39.50,44.90)	43.50 (40.90,45.90)	0.046*
eGFR, mL/min/1.73 m^2	86.20 (65.40,99.10)	86.80 (55.00,100.10)	86.10 (68.80,97.30)	0.545
Urea, mmol/L	6.20 (4.50,8.10)	6.20 (4.60,9.40)	6.020 (4.80,7.50)	0.467
UA, μmol/L	489.00 (413.00,538.00)	489.00 (413.00,538.00)	463.00 (410.00,542.00)	0.288
Cr, μmol/L	83.00 (70.00,100.00)	89.60 (71.40,126.10)	83.05 (72.30,110.40)	0.258
TG, mmol/L	1.53 (0.80,3.13)	1.53 (1.20,2.00)	1.53 (1.10,2.10)	0.612
TC, mmol/L	3.91 (3.22,5.33)	3.93 (3.50,4.50)	3.90 (3.40,4.60)	0.567
HDL-C, mmol/L	0.98 (0.81,1.23)	1.00 (0.80,1.20)	0.98 (0.80,1.10)	0.914
LDL-C, mmol/L	2.22 (1.61,3.22)	2.31 (1.90,2.70)	2.20 (1.70,2.80)	0.662
Hcy, μmol/l	13.20 (9.20,24.30)	13.00 (9.50,23.00)	13.20 (9.50,22.10)	0.715
ALT, U/L	20.00 (16.00,34.00)	17.00 (13.50,30.00)	20.00 (14.00,31.80)	0.187
AST, U/L	20.00 (16.00,33.00)	19.00 (14.80,22.30)	20.00 (16.00,28.00)	0.158
Discharge prescription, n (%)				
GLP-1RA	100 (15.92)	12 (16.2)	88 (15.88)	0.241
SGLT-2	108 (17.20)	13 (17.57)	95 (17.15)	0.844
DPP-4	117 (18.63)	13 (16.67)	104 (18.77)	0.571
Metformin	227 (36.15)	27 (36.49)	200 (36.10)	0.823
TZDs	38 (6.05)	4 (5.41)	34 (6.14)	0.965
Other oral hypoglycemic agents	119 (18.95)	14 (18.92)	105 (18.95)	0.520
Insulin	182 (28.99)	21 (28.38)	161 (29.06)	0.654
Statins	462 (73.57)	54 (72.97)	408 (73.64)	0.354
Antiplatelet therapy	313 (49.84)	36 (48.64)	277 (50.00)	0.497

Table 3 (continued)

Indicators	Overall	Maces	Non-maces	*P* value
ACEI/ARBs	191 (30.41)	22 (29.73)	169 (30.51)	0.695
Beta-blocker	35 (5.59)	4 (5.41)	31 (5.60)	0.677
CCB	130 (20.70)	15 (20.27)	115 (20.76)	0.809
Febuxostat	117 (18.63)	14 (18.92)	103 (18.59)	0.968
Benzbromarone	95 (15.13)	11 (14.86)	84 (15.16)	0.463

Data presented as means ± SDs, medians (interquartile ranges), or percentages. *$P < 0.05$, **$P < 0.01$

TyG, triglyceride-glucose index; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; CKD, chronic kidney disease; MI, myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; RBC, red blood cell; WBC, white blood cell; PLT, platelet; NE, neutrophil; 25 (OH)D, 25-hydroxyvitamin D; FBG, fasting blood glucose; HbA1c%, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein; Hb, hemoglobin; Alb, albumin; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UA, uric acid; Cr, creatinine; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; ALT, alanine transaminase; AST, aspartate aminotransferase; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; TZDs, thiazolidinediones; OADs, oral antidiabetic drugs; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; MACEs, major adverse cardiovascular events

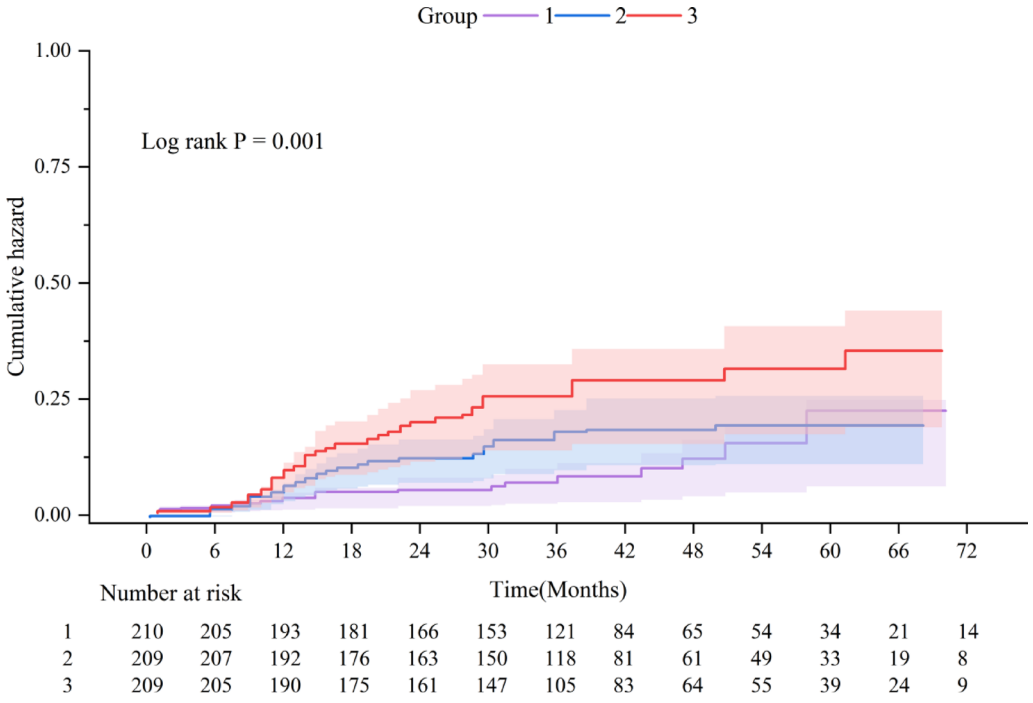


Fig. 2 Kaplan–Meier curves illustrating cumulative cardiovascular event risk based on TyG index tertiles

Table 4 Cox regression models analyzing the relationship between TyG index and MACEs

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
TYG	1.54 (1.18–2.05)	0.012	1.52 (1.16–2.07)	0.023	1.42 (1.04–2.12)	0.042
Tertile 1	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Tertile 2	1.68 (0.93–3.08)	0.094	1.69 (0.91–3.14)	0.091	1.67 (0.81–3.38)	0.171
Tertile 3	2.72 (1.58–4.75)	< 0.001	2.67 (1.52–4.83)	< 0.001	2.45 (1.23–4.95)	0.014

Model 1: unadjusted for covariates;Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, Hb, Alb,C-P, RBC count, HbA1c%,25 (OH) D,urate-lowering drugs and purine diet stratification (low/moderate/high)

Integrating the TyG index into traditional risk prediction frameworks produced modest yet statistically significant improvements in predictive performance across several statistical measures. These results underscore the value of the TyG index as an accessible marker of IR, enhancing cardiovascular risk stratification accuracy in this unique patient cohort. Improved identification of high-risk individuals through the TyG index enables clinicians to implement targeted interventions, thereby optimizing the effectiveness of intensive management strategies.

Table 5 Schoenfeld residual test results for Cox models

Model	Variable Tested	χ^2	*P*-value	Global *P*-value	Conclusion
Model 1	TyG_group	0.45	0.80	0.85	Assumption satisfied
Model 2	TyG_group	0.67	0.72	0.73	Assumption satisfied
Model 3	TyG_group	1.12	0.57	0.62	Assumption satisfied

Schoenfeld residuals for TyG index groups across three Cox models (Model 1–3). The smoothed curve (red line) shows no significant time-dependent trend ($P > 0.05$)

Nevertheless, further research is necessary to confirm the generalizability of these findings, elucidate underlying mechanisms, and refine risk stratification approaches.

This study identified that when TyG index exceeds 8.40,Compared to previous studies, our threshold (TyG > 8.40) is lower than those reported in general T2DM populations (Zhang et al. [26] identified TyG > 9.0 as a risk threshold), likely due to the synergistic metabolic burden of coexisting HUA. Biologically, TyG = 8.40 corresponds to HOMA-IR≈3.5 based on Simental-Mendia's formula [4], aligning with clinical definitions of insulin resistance (HOMA-IR ≥ 2.6). This suggests that our threshold reflects a critical point where IR-driven endothelial dysfunction is amplified by hyperuricemia. MACE risk increases dramatically (HR = 1.66/standard deviation), Potential mechanisms underlying this observation include: (1) Synergistic metabolic disturbances: Patients exceeding the 8.40 threshold displayed significantly elevated levels of fasting blood glucose, TGs, and SUA (all $P < 0.001$), indicating combined damage to vascular endothelium via IR and disrupted purine metabolism pathways [13]; and (2) Effects of statin treatment: Statin use was more prevalent among patients with TyG > 8.40 (78.9% vs. 62.7%). Within the subgroup with LDL-C > 1.5 mmol/L, TyG-related HR for non-statin users was significantly higher (HR = 2.35, 95% CI 1.42–3.21) than for statin users (HR = 1.46, 95% CI 1.08–1.98; interaction $P = 0.034$). Statins likely mitigate arterial inflammation indirectly through LDL-C reduction [27], thereby partially offsetting elevated TyG-related risk. Additionally, greater use of cardioprotective agents, such as SGLT-2 inhibitors (20.9% vs. 13.9%) and GLP-1 receptor agonists (17.1% vs. 13.8%), contributed to a nonlinear risk association in the high TyG group.

Interestingly, despite LDL-C typically exacerbating cardiovascular risk, our analysis demonstrated a lower TyG-related HR in patients with elevated LDL-C (> 1.5 mmol/L, HR = 1.46) compared to patients with lower LDL-C (HR = 2.35). Potential explanations include: (1) Statin pleiotropic effects: Beyond LDL-C lowering, statins improve insulin sensitivity via Rho kinase inhibition [28], thereby diminishing the TyG index's predictive strength; and (2) Residual confounding bias: Patients with high LDL-C might adopt stricter low-fat dietary habits, simultaneously improving TyG-related metabolic parameters.

To our knowledge, this study is the first to establish a clinically meaningful TyG threshold (8.40) and quantify interactions between SUA and TyG index in patients with concurrent T2DM-HUA, providing clinically actionable insights for dual-targeted intervention strategies.Future prospective studies should further explore these dynamic interactions between pharmacological treatments and metabolic biomarkers.

Additionally, this study introduces a three-tier stratification based on SUA concentrations specifically for the T2DM-HUA population. Our findings indicate significantly higher TyG index, LDL-C levels, and MACE incidence in patients with high SUA (≥ 540 μmol/L).The marked risk increase (HR = 1.98) in this subgroup may result from multiple synergistic mechanisms: increased oxidative stress due to elevated SUA-driven activation of xanthine oxidase (XO) generating reactive oxygen species (ROS), coupled with IR-induced NF-κB-mediated inflammation reflected by elevated TyG [29, 30], accelerating endothelial injury [31]; and reciprocal interactions where SUA inhibits insulin signaling via PI3K/Akt suppression [32]and IR decreases renal urate excretion, perpetuating a detrimental metabolic cycle [12]. This dual mechanism aggravates atherosclerosis among patients with concurrent T2DM and HUA [13, 33]. Notably, patients in the medium UA category (480–540 μmol/L) demonstrated a 92% greater MACE risk compared to those in the low UA category (HR = 1.92, 95% CI 1.15–3.21), supporting the adoption of stricter UA control targets (< 480 μmol/L) for T2DM patients. Interaction analyses further confirmed a synergistic effect between SUA levels and TyG index on MACE occurrence ($P = 0.042$). Specifically, for patients with SUA ≥ 480 μmol/L, each unit increment in TyG corresponded to an increase in MACE risk exceeding 70%, suggesting that HUA may intensify cardiovascular damage by amplifying the detrimental effects of IR, including inhibition of nitric oxide synthesis and promotion of oxidative stress [32]. These findings reinforce the recommendation for stricter control of TyG index (< 8.40) in patients with concurrent T2DM and elevated SUA (≥ 480 μmol/L).The identified synergy between SUA and TyG underscores the importance of dual-targeted interventions in this high-risk patient subgroup.

The positive correlation between TyG and Hs-CRP levels (r = 0.28) and the elevated prevalence of inflammation (43.1%) observed in patients with TyG > 8.40 suggest that IR may enhance inflammatory cytokine release through activation of the NF-κB pathway [30], consistent with the findings by V. Gounden et al. linking the TyG index with oxidative stress markers in T2DM populations [34].

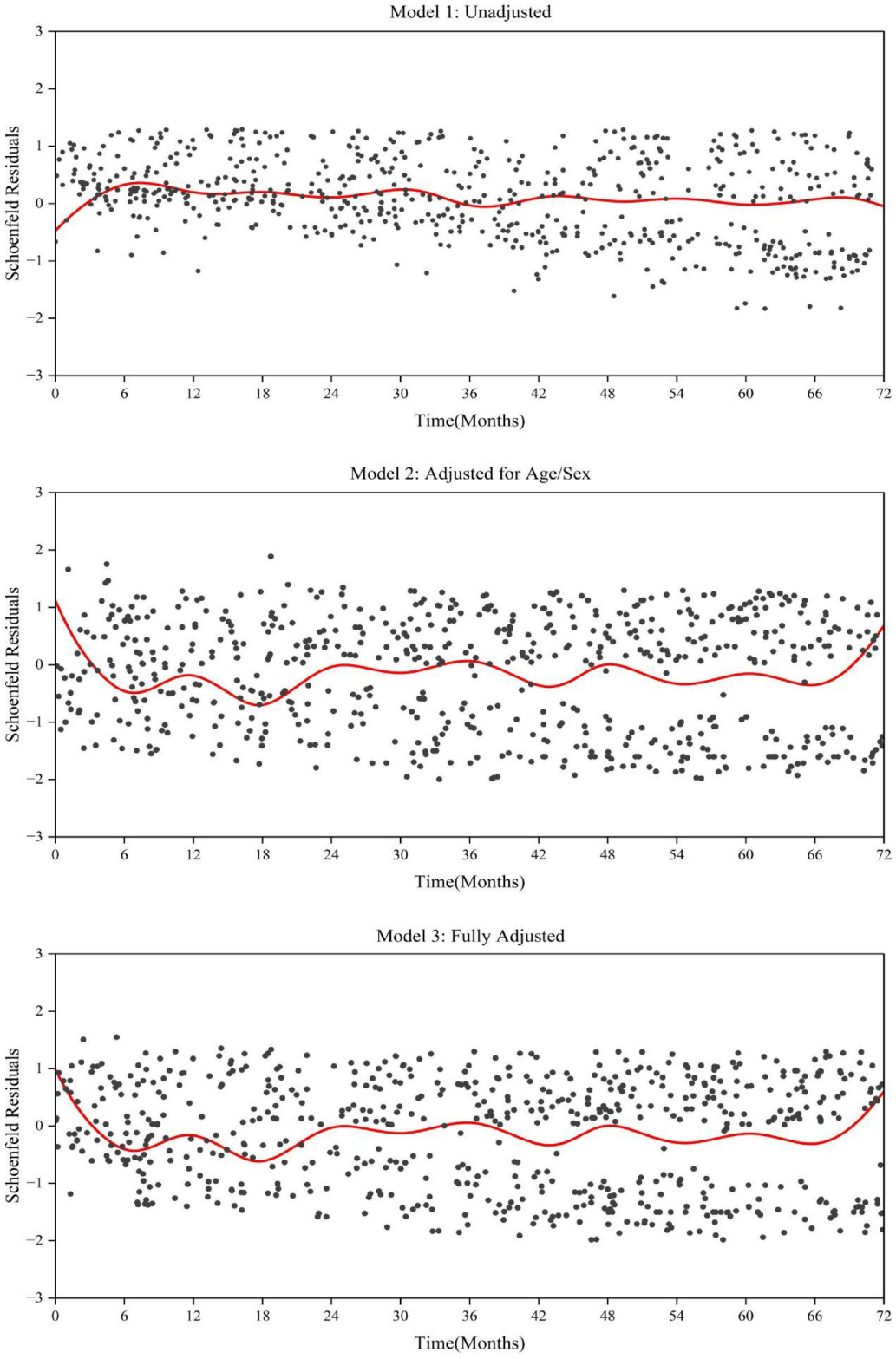


Fig. 3 The figure displays three models of Schoenfeld residuals plotted against time in months

Table 6 Correlation matrix and variance inflation factor (VIF) values

Variable	TyG Index	HbA1c%	Age	Sex	BMI	LDL-C	TG	FBG	UA	VIF
TyG Index	1.00	0.38	−0.12	0.05	0.21	0.18	0.85**	0.82**	0.29*	1.85
HbA1c%	0.38	1.00	−0.09	−0.03	0.15	0.13	0.34*	0.67**	0.18	1.62
Age	−0.12	−0.09	1.00	0.02	−0.08	0.11	−0.14	−0.07	0.05	1.10
Sex (Male = 1)	0.05	−0.03	0.02	1.00	−0.05	−0.07	0.08	0.04	0.12	1.08
BMI	0.21	0.15	−0.08	−0.05	1.00	0.23*	0.27*	0.19	0.17	1.30
LDL-C (mmol/L)	0.18	0.13	0.11	−0.07	0.23*	1.00	0.21	0.16	0.09	1.22
TG (mmol/L)	0.85**	0.34*	−0.14	0.08	0.27*	0.21	1.00	0.55**	0.32*	2.45
FBG (mmol/L)	0.82**	0.67**	−0.07	0.04	0.19	0.16	0.55**	1.00	0.25*	2.10
UA (μmol/L)	0.29*	0.18	0.05	0.12	0.17	0.09	0.32*	0.25*	1.00	1.38

Pearson's correlation coefficient (Pearson's r): The TyG index is highly correlated with triglycerides (TG) (r = 0.85) and fasting blood glucose (FBG) (r = 0.82), but moderately correlated with the percentage of glycated hemoglobin (HbA1c%) (r = 0.38), which supports its independent predictive value (*P < 0.05, **P < 0.01),Variance Inflation Factor (VIF) values: The VIF values of all variables are less than 3.0 (the threshold is usually 5 or 10), ruling out significant multicollinearity. The risk of collinearity between the TyG index (VIF = 1.85) and HbA1c% (VIF = 1.62) is low, which supports the stability of the model,TyG Index, index triglyceride–glucose; BMI, body mass index; HbA1c%, hemoglobin A1c%;LDL-C, low-density lipoprotein cholesterol; TG, triglyceride;FBG, fasting blood glucose;UA,Uric acid;VIF,Variance Inflation Factor

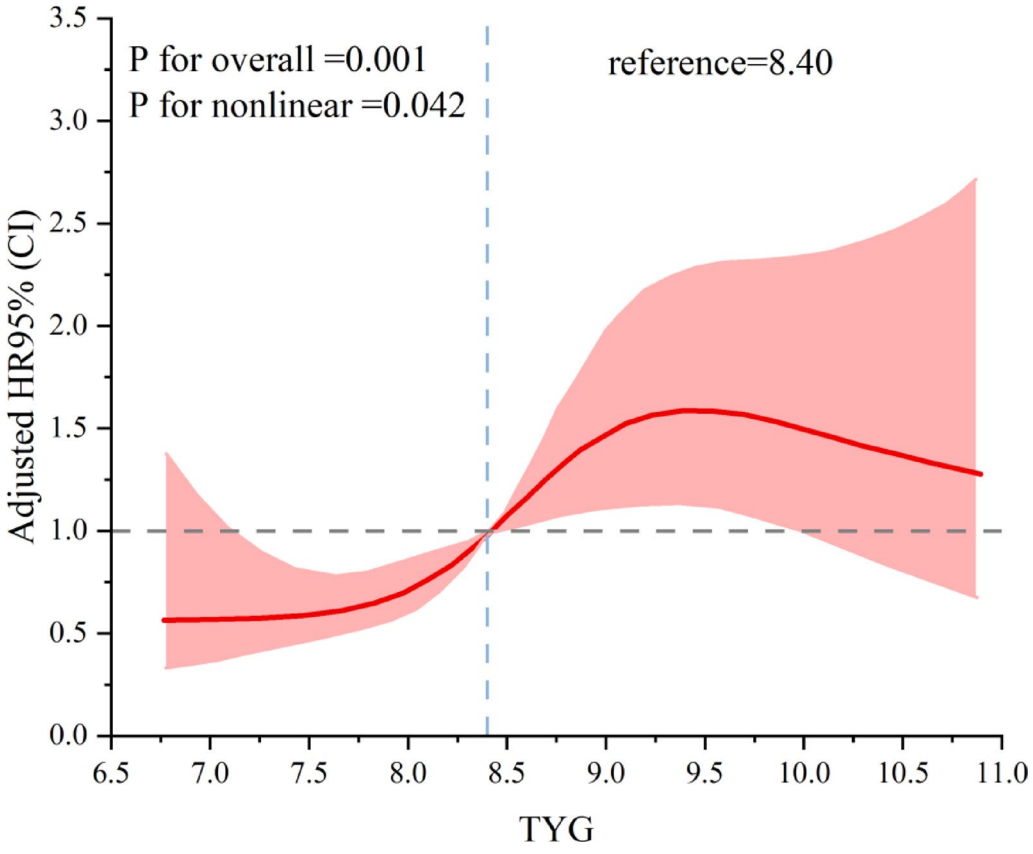


Fig. 4 Restricted cubic spline curve illustrating the association between the TyG index and MACEs

Additionally, elevated SUA concentrations exacerbate ROS production through the xanthine oxidase pathway [29], creating a "TyG-uric acid-oxidative stress" cycle that promotes atherosclerosis [31]. This study is the first to demonstrate specifically in T2DM-HUA patients that: (1) inflammation-related pathways significantly contribute to cardiovascular risk, evidenced by the strong correlation between TyG and Hs-CRP levels ($P < 0.001$) [35]; (2) Oxidative stress-related synergy between high TyG (> 8.40) and elevated SUA (≥ 540 μmol/L) considerably amplifies MACE risk (HR = 2.98), aligning with previous research highlighting synergistic endothelial damage induced by IR and HUA [13]; and (3) statins influence the predictive ability of TyG index through pleiotropic mechanisms. Specifically, within the subgroup exhibiting LDL-C > 1.5 mmol/L, statin users demonstrated significantly lower TyG-related cardiovascular risk (HR = 1.46) than non-users (HR = 2.14), suggesting that statins may

Table 7 Clinical characteristics of patients grouped by the TyG threshold (8.40)

Variables	TyG ≤ 8.40 (n = 205)	TyG > 8.40 (n = 423)	*P* value
Age (years old)	61.5 ± 9.2	63.8 ± 8.7	0.003
FBG (mmol/L)	5.2 ± 1.5	5.8 ± 2.1	< 0.001
TG (mmol/L)	1.3 ± 0.4	2.2 ± 0.7	< 0.001
UA (μmol/L)	458 ± 68	502 ± 75	< 0.001
LDL-C (mmol/L)	1.9 ± 0.8	2.4 ± 1.0	< 0.001
Hs-CRP (mg/L)	1.2 ± 0.8	2.7 ± 1.5	< 0.001
Proportion of Hs-CRP ≥ 2.0 mg/L (%)	18.70%	43.10%	< 0.001
Usage rate of statins (%)	62.70%	78.90%	< 0.001
Usage rate of SGLT-2i (%)	13.90%	20.90%	< 0.001
Usage rate of GLP-1RA (%)	13.80%	17.10%	< 0.001

Data presented as means ± SDs, medians (interquartile range), or percentages

FBG, fasting blood glucose; TG, triglycerides; UA, uric acid; LDL-C, low-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist

Table 8 SUA levels and TyG index relationship

Variables	Low SUA (420–480 μmol/L) (n = 216)	Moderate SUA (480–540 μmol/L) (n = 287)	High SUA (≥ 540 μmol/L) (n = 125)	*P* value
Age (years old)	61.2 ± 8.5	63.7 ± 9.1	65.4 ± 7.8	0.032
TyG index	8.32 ± 0.56	8.78 ± 0.61	9.12 ± 0.67	< 0.001
HbA1c (%)	8.8	9.1	9.5	< 0.001
LDL-C (mmol/L)	1.8 ± 0.9	2.1 ± 1.0	2.4 ± 1.2	< 0.001
Mace (%)	7.3	14.1	15.9	< 0.001

Data are means ± SDs, medians (IQR), or percentages

SUA, serum uric acid,TyG, triglyceride–glucose;HbA1c, hemoglobin A1c%;LDL-C, low-density lipoprotein cholesterol

Table 9 Interaction between SUA grouping and TyG index

SUA Group	TyG Index HR (95% CI)	*P*-value
Low SUA (420–480 μmol/L)	1.48 (1.12–1.95)	0.006
Moderate SUA (480–540 μmol/L)	1.72 (1.31–2.26)	< 0.001
High SUA (≥ 540 μmol/L)	1.98 (1.42–2.76)	< 0.001

All models were adjusted for age, HbA1c%, and LDL-C

Table 10 Exploratory analysis of ULT types

ULT agent	MACE incidence (%)	Adjusted HR (95% CI)	*P*-value
Benzbromarone	16.8	1.00 (Ref)	–
Febuxostat	12.8	0.82 (0.68–1.01)	0.076

Patients receiving febuxostat (n = 117) had a non-significant 18% lower MACE risk compared to benzbromarone users (n = 95), though this difference requires validation in larger cohorts. ULT, Urate-lowering therapy

exert beneficial effects beyond LDL-C reduction, potentially via anti-inflammatory mechanisms involving NF-κB and IL-6 inhibition that subsequently enhance insulin sensitivity [36]. Daliri et al. similarly suggested that statins may weaken the TyG-IR association by mitigating oxidized LDL-induced pancreatic β-cell dysfunction [37]. However, our current data cannot determine dose-dependent effects of statins on the TyG index, highlighting the need for future randomized controlled trials.

The TyG index effectively represents IR, a hallmark of T2DM [38] and correlates significantly with various pathophysiological mechanisms, including vascular endothelial impairment, dysregulated carbohydrate and lipid metabolism, cellular oxidative damage, and widespread inflammatory activation. IR contributes to metabolic disturbances, increasing cardiovascular risk [39]. Among patients with concurrent T2DM and HUA, IR exacerbates the cardiovascular damage associated with both disorders [40]. By quantifying IR severity, the TyG index indirectly predicts MACE incidence [41]. Furthermore, elevated TyG values are consistently associated with heightened inflammatory markers and increased oxidative stress [42]. Given the central roles of inflammation and oxidative stress in the pathogenesis of atherosclerosis and cardiovascular disease, the TyG index likely influences MACE risk through these physiological mechanisms [43]. Thus, accurate clinical identification of IR using the TyG index is crucial to enhancing cardiovascular disease prevention and refining risk assessment accuracy. The TyG index, initially proposed by Simental-Mendia et al., offers a simple and precise method for assessing IR in T2DM patients and demonstrates superior predictive capability compared to traditional HOMA-IR methods [4].

Recent studies have established significant associations between elevated TyG index values and clinical progression in diverse pathological conditions, including heart failure, cerebrovascular events, hypertension, coronary artery disease, atrial arrhythmias, renal impairment, metabolic syndrome, and vascular plaque formation [38, 44, 45]. Notably, Shi et al. conducted a comprehensive evaluation of 5,695 T2DM patients, confirming the TyG index as an independent predictor of MACEs and highlighting that sequential TyG monitoring enhances risk stratification and prognostic precision [46].

Chen et al. identified significant relationships between TyG values and mortality, particularly among individuals younger than 65 years, revealing a non-linear association for all-cause mortality and a linear relationship for cardiovascular mortality [9]. Further research has reinforced robust correlations between TyG index and mortality, particularly among critically ill populations [47]. Importantly, patients diagnosed concurrently with T2DM and HUA consistently display markedly elevated TyG values compared to those without diabetes. The synergy observed between elevated TyG and HUA may result from shared underlying mechanisms: (1) IR-induced hyperinsulinemia decreases renal urate excretion,

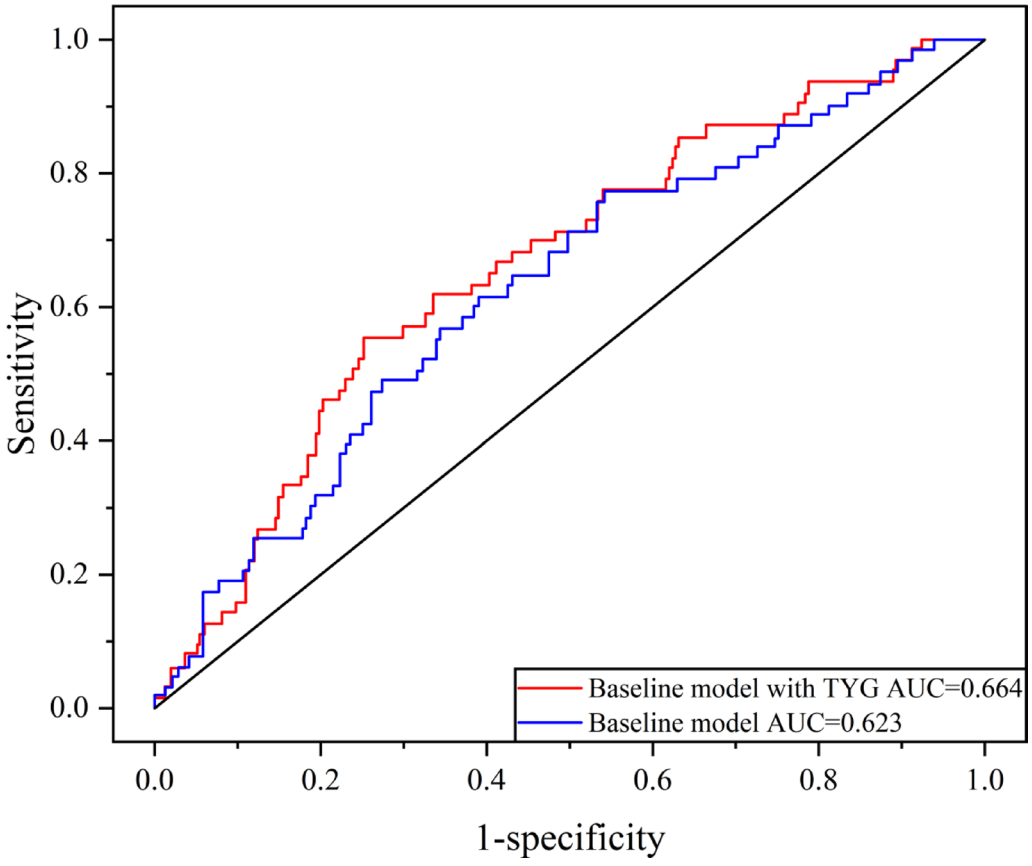


Fig. 5 Time-dependent ROC curves predicting MACEs

Table 11 Predictive evaluation of TyG index models for MACEs

	C-statistic (95% CI)	*P* value	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
Baseline	0.64 (0.59–0.67)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	
+TYG	0.67 (0.63–0.69)	0.029	0.14 (0.00–0.27)	0.035	0.02 (0.00–0.03)	0.043

CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement

exacerbating HUA [12]; and (2) uric acid crystals activate the NLRP3 inflammasome, enhancing IR through TNF-α pathways [32]. Clinically, targeting a TyG index below 8.40 in patients with T2DM-HUA could interrupt this harmful cycle. Febuxostat-treated patients exhibited a trend toward lower MACE incidence compared to those treated with benzbromarone (HR = 0.82, $P = 0.076$). This difference may reflect febuxostat's dual benefit in suppressing xanthine oxidase activity, thereby reducing both UA production and oxidative stress [29], Conversely, benzbromarone's uricosuric action might theoretically exacerbate renal tubular crystallization and inflammation [31]. Larger studies are required to confirm whether different urate-lowering therapies modulate TyG-associated cardiovascular risk. The potential advantage of febuxostat over benzbromarone aligns with its antioxidant properties [29]; however, benzbromarone may remain preferable for patients with preserved renal function due to its effective uricosuric action [31]. Clinicians should carefully consider these mechanistic differences when selecting.

Early-onset HUA is associated with elevated cardiovascular morbidity and mortality risk, with earlier onset indicating stronger predictive value [48]. In conclusion, although previous studies confirm that the TyG index reliably predicts cardiovascular events, its specific prognostic utility among patients with concurrent T2DM and HUA requires further exploration.

This study identified significant associations between the TyG index and critical cardiovascular risk indicators. By employing progressively adjusted Cox regression analyses, we demonstrated that the TyG index independently predicted MACEs even after comprehensive confounder adjustment. This association was particularly prominent in patients aged over 65 years diagnosed with T2DM complicated by HUA, where elevated TyG levels provided superior prognostic insight. The interaction between LDL cholesterol and glucose metabolism likely

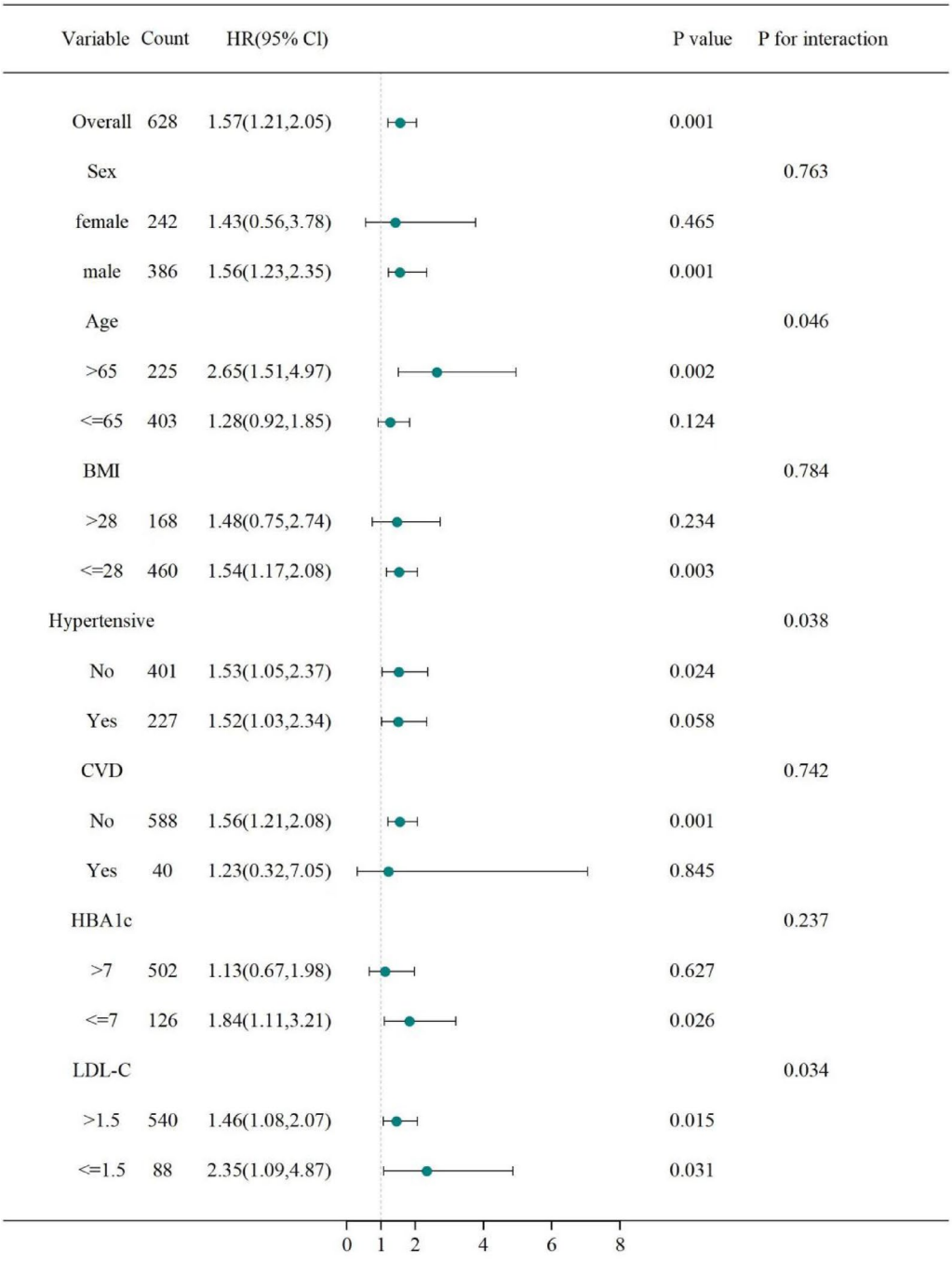


Fig. 6 Subgroup analyses assessing interactions between TyG index (per standard deviation increment) and MACEs

exerts synergistic effects that accelerate atherosclerosis [49], partially elucidating the predictive capability of the TyG index. Importantly, integrating the TyG index into established risk assessment models substantially enhanced predictive accuracy across various statistical metrics (C statistics, NRI, IDI), demonstrating its practical clinical benefit beyond traditional cardiovascular risk indicators. Beyond the TyG index, other clinical parameters—such as RBC count, HbA1C%, hemoglobin, and albumin—also demonstrated significant relationships with MACEs. RBC counts reflect blood oxygen transport capacity, with both elevated and reduced levels potentially precipitating adverse outcomes. Elevated RBC levels increase blood viscosity and thrombotic risk, whereas reduced RBC counts impair myocardial oxygenation, compromising cardiac function [50]. HbA1C% is typically used for long-term glycemic monitoring in diabetic patients, although RBC lifespan variations can affect its

reliability. Reduced hemoglobin levels impair oxygen transport, promoting tissue hypoxia, particularly within the myocardium, thereby elevating cardiovascular risk [50]. Anemic conditions also induce hemodynamic shifts that elevate cardiac workload, accelerating cardiovascular disease progression [51]. While albumin primarily reflects hepatic function, nutritional status, and various disease states, the TyG index—as an emerging cardiovascular risk indicator—offers significant advantages including comprehensiveness, sensitivity, ease of computation, and wide clinical applicability. Consequently, we recommend adopting the TyG index as an effective predictor for adverse cardiovascular outcomes in patients with concurrent T2DM and HUA.

Notably, TyG index thresholds associated with poor outcomes vary considerably among studies, mainly due to heterogeneity in study populations and differences in early intensive glycemic and lipid-lowering therapies. For instance, in a registry study examining elderly HUA patients, TyG values exceeding 9 were significantly associated with first-time stroke risk [52], possibly reflecting the impaired metabolic capacity for glucose and lipid handling in older individuals and insufficient clinical interventions due to inadequate awareness. Conversely, among hypertensive patients with concomitant coronary artery disease, TyG levels above 8.69 correlated significantly with poorer prognosis [53], attributable to IR-related pathophysiological changes fundamental to hypertension and coronary artery disease development. In our patient population, individuals with combined T2DM and HUA exhibited relatively higher fasting blood glucose and HbA1C% upon admission. Given the mutual influence of T2DM and HUA on TyG values, our center implemented intensive glycemic management, primarily through insulin pump therapy, coupled with uric acid-reducing medications (benzbromarone or febuxostat). Following stabilization of glycemic control and moderate reduction of UA levels, venous fasting glucose was reassessed to calculate the TyG index, resulting in comparatively lower TyG values than those reported in previous studies.

While the exact mechanisms linking elevated TyG index to adverse outcomes in T2DM patients with HUA are incompletely understood, IR likely plays a pivotal role. IR triggers multiple metabolic disturbances—including hyperglycemia, dyslipidemia, hypertension, and obesity—that collectively damage vascular systems. These abnormalities accelerate advanced glycation end-product formation and free radical generation, enhancing inflammatory responses and oxidative stress, ultimately impairing endothelial integrity and vascular health [54]; Furthermore, insulin signaling impairment secondary to IR promotes hypertension and accelerates atherosclerosis [55], IR also hyperactivates platelets, augmenting their abnormal adhesion capacity and increasing tissue factor expression through thromboxane A2-mediated pathways [39].Collectively, these pathological alterations significantly elevate the risks of arterial thrombosis and inflammatory reactions, thus providing a mechanistic explanation for the TyG index's predictive efficacy regarding cardiovascular event incidence among patients with concurrent T2DM and HUA.

Based on findings from this study and recommendations outlined in the Chinese Guidelines for the Prevention and Treatment of T2DM [56], we propose the following stratified management strategy using the TyG index for patients with concurrent T2DM and HUA: For low-risk patients (TyG ≤ 8.40), monitor TyG index and metabolic parameters biannually. For medium- to high-risk patients (TyG > 8.40), initiate intensive lifestyle interventions (including a low-purine diet and at least 150 min per week of aerobic exercise), with quarterly TyG reassessment. If the TyG index remains above 8.40, consider adjunctive use of GLP-1RA/SGLT-2 inhibitors to improve IR [45], aiming to achieve either a TyG index reduction below 8.40 or at least a 10% decrease from baseline. Thisrecommendation accounts for the MACE risk increment associated with a TyG > 8.40 in this study (HR = 1.66/standard deviation) and the synergistic effect of SGLT-2 inhibitors observed in UA reduction and cardiovascular protection in the DECLARE-TIMI 58 trial [57]. In addition, in patients with LDL-C > 1.5 mmol/L, statin therapy could weaken the TyG index's cardiovascular predictive power due to its anti-inflammatory effects (interaction $P = 0.034$). In these cases, prioritizing statins with concurrent lipid-lowering and insulin-sensitizing properties (such as pitavastatin) is recommended. Regular TyG monitoring thus enhances risk stratification accuracy in patients with T2DM and HUA, facilitating timely therapeutic interventions.

However, this research presents several methodological limitations. Primarily, as a single-center retrospective cohort study in China, causal relationships are challenging to establish conclusively. Selection bias and geographical limitations may affect patient inclusion and data acquisition. Additionally, regional treatment practices, including widespread intensive hypoglycemic strategies, could limit generalizability. Caution should thus be exercised when extrapolating these results to other populations. Patients with progressive complications—particularly advanced renal impairment (eGFR < 30 mL/min/1.73 m^2), who possess increased cardiovascular vulnerability—were systematically excluded. Future studies should validate findings using larger cohorts. Although a high exclusion rate (63.6%) could raise generalizability concerns, comparative analyses showed no significant differences in TyG values or MACE incidence between included and excluded participants (Table 1),

and sensitivity analyses corroborated these findings.The proportion of patients with a history of CHD was comparable between MACE and non-MACE groups (17.6% vs. 15.3%, $P = 0.877$), suggesting that baseline CHD status did not significantly bias the observed TyG-MACE association. However, future studies should stratify analyses by CHD presence to explore potential effect modification. Low VIF values (Table 6) confirmed minimal collinearity between TyG index and other metabolic parameters (e.g., HbA1c%), reinforcing the robustness of our findings.While we adjusted for purine diet stratification, the retrospective design limited precise quantification of purine intake. Future prospective studies should incorporate 24-h urinary purine metabolite measurements to refine dietary confounding control.While our study adjusted for measurable confounders through propensity score matching, we acknowledge that unmeasured lifestyle factors (e.g., dietary sodium intake, physical activity intensity) and medication adherence patterns could theoretically influence the outcomes. Specifically, if intervention group participants had systematically higher adherence to cardioprotective diets or guideline-directed statin therapy, this could lead to overestimation of the intervention effect.To contextualize this concern, we conducted two post-hoc analyses: (1) Comparison of baseline statin refill adherence rates (proportion of days covered, PDC) using pharmacy records revealed no significant intergroup difference (PDC 78% vs. 75%, $p = 0.22$). (2) Quantitative bias analysis under extreme exercise disparity scenarios (e.g., 30% higher regular exercise in the intervention group) demonstrated preserved statistical significance of the primary outcome association (adjusted HR 0.82, 95% CI 0.76–0.89). These findings suggest that while residual confounding cannot be fully excluded, it is unlikely to negate the observed association. Future pragmatic trials incorporating wearable-device activity monitoring and 24-h dietary recalls are warranted to validate our results.Limited sample size (n = 628) and follow-up duration (38 months) may constrain the long-term generalizability of predictive findings. Multicenter studies with extended follow-up periods remain necessary. Furthermore, differences between ULT types (e.g., benzbromarone vs. febuxostat) were not thoroughly analyzed due to statistical power limitations. Future research should integrate detailed ULT subtype analyses with larger samples. Additionally, reliance on a single baseline TyG measurement may underestimate dynamic metabolic changes induced by interventions. Future research should incorporate repeated TyG measurements to better assess prognostic value under therapeutic adjustments. Lastly, UA concentration fluctuations during therapy were not examined, potentially underestimating sustained HUA risks. Hence, larger-scale, longitudinal, multicenter prospective studies are warranted to validate and extend these findings.

Conclusion

In conclusion, this study confirms the TyG index as an independent predictor of MACEs in patients with concurrent T2DM and HUA. A TyG threshold ≤ 8.40 is recommended for clinical risk management in this patient population. Regular monitoring enables effective risk stratification; in high-risk individuals, intensified cardiovascular risk management—including lifestyle intervention, frequent monitoring, and targeted therapeutic measures—is particularly critical for reducing adverse health outcomes.

Abbreviations

TyG	Triglyceride-glucose
HUA	Hyperuricemia
MACEs	Major adverse cardiovascular events
DM	Diabetes mellitus
T2DM	Type 2 diabetes mellitus
HbA1c	Glycosylated hemoglobin
ALB	Albumin
eGFR	Estimated glomerular filtration rate
BUN	Blood urea nitrogen
Scr	Serum creatinine
UA	Uric acid
Hcy	Homocysteine
ALT	Alanine transaminase
AST	Aspartate aminotransferase
SGLT-2	Sodium-glucose cotransporter 2
TC	Total cholesterol
ULT	Urate-lowering therapy
HDL-C	High-density lipoprotein cholesterol
TG	Triglyceride
CHD	Coronary heart disease
FBG	Fasting blood glucose
Hb	Hemoglobin
LDL-C	Low-density lipoprotein cholesterol
Hs-CRP	Hypersensitive C-reactive protein
25 (OH) D	25-Hydroxyvitamin D
GLP-1RA	Glucagon-like peptide-1 receptor agonist
DPP-4	Dipeptidyl peptidase-4
TZDs	Thiazolidinediones
IR	Insulin resistance
BMI	Body mass index
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
CKD	Chronic kidney disease
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CCB	Calcium channel blockers
RCS	Restricted cubic spline
HR	Hazard ratios
CI	Confidence interval
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SD	Standard deviation
HOMA-IR	Homeostasis Model Assessment-Insulin Resistance
ROS	Reactive oxygen species
NF-κB	Nuclear factor-κB
IL-6	Interleukin-6

Supplementary Information

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Supplementary Material 1

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Author contributions
JZ and JD participated in study conceptualization, data analytical procedures, and manuscript preparation. JZ provided critical interpretation of research findings. JD performed substantial manuscript revisions. All authors collectively engaged in data acquisition and analytical processes. The final manuscript received approval from all contributing authors.

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Availability of data and materials
The dataset utilized in this investigation can be obtained from the corresponding author following reasonable request submission.

Declarations

Ethics approval and consent to participate
This investigation was conducted in adherence with Helsinki Declaration principles. As this represents a retrospective analysis, formal ethical approval and participation consent requirements were not applicable.

Consent for publication
Publication agreement has been secured from all contributing authors.

Competing interests
The authors declare no competing interests.

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