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The prognostic value of triglyceride-glucose index to adverse renal outcomes in patients with type 2 diabetes mellitus: results from the cohort study of ACCORD

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Abstract

Background The triglyceride-glucose (TyG) index is a new and good biomarker of insulin resistance (IR). The prognostic utility of the TyG index for patients with type 2 diabetes mellitus (T2DM) remains uncertain. Our study seeks to elucidate the connection between the TyG index and adverse renal outcomes within a T2DM population, while also examining if these relationships are influenced by subgroup variations.

Methods We analyzed data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, involving 10,196 T2DM participants, to assess the link between triglyceride-glucose levels and adverse renal outcomes. This evaluation included Restricted Cubic Spline (RCS) analysis, Kaplan–Meier survival analysis, and Multivariate Cox proportional regression. Additionally, we examined the interaction between subgroups concerning adverse renal outcomes.

Results During a 7-year follow-up, 5824 patients (57.1%) experienced worsening renal function, 2309 patients (23.2%) developed albuminuria, and 280 patients (2.7%) advanced to renal failure. After adjusting for a range of confounding variables, triglyceride-glucose levels were significantly linked to both worsening renal function ($p < 0.001$) and the onset of albuminuria ($p = 0.020$). Nonetheless, no significant association was observed between triglyceride-glucose levels and renal failure ($p = 0.247$). Furthermore, there was no significant subgroups interaction to the associations between TyG levels and adverse renal outcomes.

Conclusion Our study underscores the significant relationship between the triglyceride-glucose index and the risk of adverse renal outcomes in patients with T2DM. The TyG index, as a readily calculable measure, offers clinicians a valuable tool for anticipating the risk of adverse renal outcomes in this patient population.

Keywords Type 2 diabetes Mellitus, Triglyceride-glucose, Insulin resistance, Adverse renal outcomes

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Introduction

The global prevalence of diabetes among adults aged 20 to 79 years is projected to rise from 6.4%, affecting 285 million individuals in 2010, to 7.7%, impacting 439 million adults by 2030. This period is expected to witness a 69% surge in the number of adults with diabetes in developing countries and a 20% increase in developed countries [1]. The kidney represents a critical site of microvascular damage in diabetes, with approximately 50% of individuals with type 2 diabetes mellitus (T2DM) developing diabetic kidney disease (DKD), characterized by impaired renal function, elevated urinary albumin excretion, or both [2]. DKD has emerged as the leading cause of end-stage renal disease (ESRD) in the United States and many developed nations, accounting for 30–50% of new ESRD cases [3]. Among the long-term complications of diabetes, DKD places the most substantial burden on patients, manifesting in significant financial costs and adverse impacts on daily life. Notably, individuals with DKD face a heightened risk of adverse health outcomes, such as frailty, reduced quality of life, ESRD, progressive damage to other organs, and premature death. The majority of excess mortality associated with T2DM is notably concentrated among those suffering from DKD [4], underscoring the imperative to mitigate the incidence of adverse renal outcomes and alleviate the associated prognosis through early diagnosis and intervention.

Insulin resistance (IR), a state wherein physiological concentrations of insulin elicit a diminished biological response, has been implicated in the pathogenesis of various metabolic disorders [5]. The triglyceride-glucose (TyG) index has been developed as a biochemical surrogate for the identification of IR in both diabetic and nondiabetic individuals [6]. While the hyper-insulinemic-euglycemic clamp test remains the gold standard for assessing IR, this method is time-consuming and laborious which renders it impractical for widespread clinical application [7]. Consequently, the TyG index, derived from fasting triglyceride and glucose levels, has gained recognition as a straightforward, accessible, and cost-effective surrogate marker for IR [8]. Previous research has established the TyG index as an independent predictor of future stroke, myocardial infarction, cardiovascular mortality, and all-cause/non-cardiovascular mortality in the general population, highlighting its role in forecasting cardiovascular and metabolic diseases [9–11]. Moreover, the TyG index has demonstrated clinical utility in predicting adverse cardiovascular events in patients with or without diabetes who have pre-existing cardiovascular disease [12–14]. However, the association between TyG and the risk of adverse renal outcomes remains less well-defined. While several studies have reported a correlation between elevated TyG levels and an increased risk of chronic kidney disease (CKD) [15–18], others, such as Pan et al., have not identified a significant association between TyG levels and CKD in patients with T2DM [19]. The inconsistency in these findings can be attributed to limitations in sample sizes, differences in study populations, and varying degrees of adjustment for confounding factors. As such, further research with specific populations, larger sample sizes and adjusting for a range of confounding variables is warranted to clarify the relationship between TyG and CKD.

Therefore, this study aims to assess the associations between the TyG index and adverse renal outcomes in patients with T2DM utilizing data from the ACCORD trial and to explore potential modifications of these associations within subgroups.

Methods

Study design and participants

Our study engaged in a retrospective analysis utilizing data derived from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, funded by the National Heart, Lung, and Blood Institute. The ACCORD trial was characterized by a multicenter, randomized, double 2×2 factorial design, aimed at exploring the effects of three distinct medical treatment strategies on the morbidity and mortality among individuals with T2DM. These strategies included the glycemia, lipid, and blood pressure trials, each designed to evaluate their respective impacts on cardiovascular disease (CVD) outcomes. The trial enrolled 10,251 middle-aged and elderly participants, diagnosed with T2DM, featuring an average glycated hemoglobin level of 8.3% and a median diabetes duration of 10 years. Recruitment spanned from June 2001 to October 2005, across 77 research sites in the United States and Canada. Inclusion criteria targeted individuals at high risk for CVD events, attributable to either existing clinical CVD, a pronounced likelihood of CVD, or the presence of two or more CVD high-risk factors. The specific criteria for inclusion and exclusion were detailed in the foundational ACCORD study documentation [20]. Our analysis excluded participants who lacked baseline TyG values. Notably, the employment of the ACCORD dataset in our investigation received approval from the National Heart, Lung, and Blood Institute, thus upholding the required ethical and regulatory standards.

Data collection and outcomes

The dataset for this analysis comprised a comprehensive array of variables, including demographic details (age, sex, race, educational attainment, body mass index, smoking status, and alcohol use). Clinical indicators common to the cohort were also meticulously recorded, encompassing blood pressure, glycated hemoglobin (HbA1c) levels, the duration of diabetes, cardiovascular disease history, lipid profiles, heart rate, and details

of treatment regimens. Additionally, established kidney risk factors, such as estimated glomerular filtration rate (eGFR), serum creatinine (SCr) levels, and urinary albumin levels, were evaluated. The TyG index, serving as a key variable, was calculated using the formula: TyG index = Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2].

Initially, the cohort consisted of 10,251 individuals diagnosed with type 2 diabetes mellitus, from which those lacking baseline TyG values were excluded, narrowing the focus to 10,196 patients for our study.

The study specifically aimed to explore three adverse renal outcomes based on ACCORD trial definitions: the doubling of serum creatinine levels or a significant decrease in estimated glomerular filtration rate by more than 20 mL/min corresponding to worsening renal function, the onset of albuminuria, and the occurrence of renal failure including end-stage renal disease or serum creatinine levels exceeding 3.3 mg/dL corresponding.

Statistical analysis

In our analysis, continuous variables were summarized using either the mean and standard deviation or the median and interquartile range, while categorical variables were expressed as proportions. To compare groups, we applied the unpaired Student's t test or the Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. The cutoff point for TyG levels was determined through maximally selected log-rank statistics. Kaplan–Meier Survival analysis and Cox proportional hazards models, adjusted for potential confounders, were utilized to calculate the prevalence of events and estimate survival times across TyG categories, and to analyze the time-to-event outcomes, respectively. To explore the relationship between TyG levels and various adverse renal outcomes, we employed restricted cubic spline analysis, allowing for the investigation of both linear and nonlinear associations. Model adjustments were made in three stages, based on established potential confounders of TyG's association with renal outcomes. The model 1 adjusted for demographics and clinical measures including age, sex, education attainment, race, smoking status, alcohol use, blood pressures, and body mass index (BMI). The model 2 added metabolic factors such as glycated hemoglobin (HbA1c), duration of diabetes, serum creatinine, and urinary albumin to the adjustments. Finally, model 3 further adjusted for the use of angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) treatment, glycemia trial, blood pressure trial, and lipid trial. All analyses were conducted using R version 4.3.0. A two-sided p value<0.05 was considered statistically significant in our analysis.

Results

Baseline characteristics of the patients

The baseline characteristics of the study cohort were comprehensively outlined in Table 1. With an average age of 62.77 years, the demographic distribution included 61.5% males and 62.5% identifying as White. The median TyG index was established at 9.10. Notably, a critical threshold for serum TyG levels linked to adverse renal outcomes was identified as 10.27, determined through maximally selected log-rank statistics, depicted in Fig. 1. A detailed analysis of baseline demographic and biochemical measurements, categorized by TyG levels, was presented in Table 1. This analysis underscored the association of elevated baseline TyG levels with several demographic and clinical parameters, including age, sex, race, educational attainment, BMI, duration of diabetes, SBP, DBP, heart rate, the use of insulin, HbA1c, FPG, and lipid profiles (TC, TG, HDL-C, VLDL-C), as well as serum potassium, estimated glomerular filtration rate, serum creatinine, urinary creatinine, urinary albumin and urinary albumin to creatinine ratio (UACR) levels. Higher TyG levels correlated with increased triglycerides, BMI, HbA1c, and fasting plasma glucose, indicating more severe insulin resistance. Moreover, patients with elevated TyG levels demonstrated a significantly higher risk of developing adverse renal outcomes, as statistically substantiated by the p value for worsening renal function ($p<0.001$), albuminuria ($p=0.003$) and renal failure ($p=0.045$), as shown in Table 1.

The linear or nonlinear relationship between TyG and adverse renal outcomes

In our investigation, we explored the nature of the relationship—whether linear or nonlinear—between the TyG index and various adverse renal outcomes. Through the application of restricted cubic spline analysis, we sought to thoroughly examine this association. The analysis yielded evidence of a linear relationship between TyG levels and the adverse renal outcomes, namely worsening renal function (p for nonlinearity = 0.1239), albuminuria (p for nonlinearity = 0.5465), and renal failure (p for nonlinearity = 0.7337). Consequently, these results suggested collectively that the risk associated with adverse renal outcomes increases in a linear manner in relation to TyG levels.

The risk of adverse renal outcomes were related with TyG levels

The association between TyG levels and the risks of adverse renal outcomes was elucidated through Kaplan-Meier survival analysis, with the findings presented in Fig. 3. This analysis revealed that individuals with lower TyG levels exhibited a higher survival probability, implying a more favorable renal prognosis. The log-rank test

Table 1 Baseline demographic characteristics of participants of ACCORD Study according to TyG

Variable	Overall (*n* = 10196)	TyG < 10.27 (*n* = 8871)	TyG ≥ 10.27 (*n* = 1325)	*p* value
TyG	9.49(0.73)	9.30(0.57)	10.71(0.41)	< 0.001
Age, years	62.77(6.63)	63.44(6.86)	62.98(6.73)	< 0.001
Sex,%				0.025
Male	6268(61.5)	5416(61.1)	852(64.3)	
Female	3928(38.5)	3455(38.9)	473(35.7)	
Race,%				< 0.001
Non-white	3825(37.5)	3518(39.7)	307(23.2)	
White	6371(62.5)	5353(60.3)	1018(76.8)	
Education levels,%				0.01
Less than high school	1502(14.7)	1347(15.2)	155(11.7)	
High school graduate or GED	2692(26.4)	2328(26.3)	364(27.5)	
Some college	3343(32.8)	2889(32.6)	454(34.3)	
College degree or higher	2652(26.0)	2300(25.9)	352(26.6)	
BMI, kg/m^2	32.23(5.40)	32.11(5.43)	32.98(5.13)	< 0.001
Duration of diabetes, years	10.80(7.59)	10.98(7.69)	9.61(6.80)	< 0.001
Smoking,%	4281(48.3)	3770(48.6)	511(45.8)	0.088
Alcohol consumption, drinks / weekly	0.96(2.68)	0.95(2.66)	0.98(2.79)	0.68
Blood pressure, mmHg				
Systolic	136.35(17.11)	136.22(17.14)	137.22(16.86)	0.047
Diastolic	74.88(10.66)	74.61(10.60)	76.71(10.89)	< 0.001
Heart rate, bpm	72.68(11.75)	72.22(11.66)	75.71(11.91)	< 0.001
History of CVD,%	3586(35.2)	3096(34.9)	490(37.0)	0.147
Medication use,%				
ARB	1705(16.8)	1488(16.8)	217(16.5)	0.803
ACEI	5538(54.5)	4853(54.8)	685(52.1)	0.064
Insulin	3717(37.7)	3272(38.2)	445(34.5)	0.013
HbA1c, %	8.30(1.06)	8.23(1.01)	8.78(1.19)	< 0.001
Plasma concentration				
Total cholesterol, mg/dL	183.31(41.85)	178.43 (37.85)	215.99 (51.57)	< 0.001
TG, mg/dL	190.1(148.39)	153.18 (69.90)	437.52 (257.75)	< 0.001
VLDL-C, mg/dL	36.54(24.35)	30.58 (13.83)	76.45 (38.11)	< 0.001
LDL-C, mg/dL	104.90(33.91)	104.85 (32.94)	105.20 (39.83)	0.726
HDL-C, mg/dL	41.87(11.62)	42.99 (11.63)	34.33 (8.30)	< 0.001
Fasting plasma glucose (mg/dL)	175.20(56.18)	166.48 (49.63)	233.56 (62.31)	< 0.001
Serum potassium (mmol/L)	4.47(0.47)	4.47 (0.48)	4.50 (0.43)	0.013
Serum creatinine (mg/dL)	0.91(0.23)	0.92 (0.23)	0.88 (0.25)	< 0.001
eGFR (ml/min/1.73 m2)	91.05(27.15)	90.29 (24.68)	96.12 (39.57)	< 0.001
Urinary albumin (mg/dL)	10.21(36.35)	9.55 (34.66)	14.68 (45.83)	< 0.001
Urinary creatinine (mg/dL)	124.37(66.18)	125.10 (66.38)	119.52 (64.62)	0.004
Urinary albumin to creatinine ratio (mg/g)	98.47(357.62)	89.80 (316.81)	156.05 (554.05)	< 0.001
Glycemia trial,%				0.384
Standard glucose control	5092(49.9)	4415(49.8)	677(51.1)	
Intensive glucose control	5104(50.1)	4456(50.2)	648(48.9)	
Blood pressure trial,%				0.096
None	5482(53.8)	4971(54.0)	691(52.2)	
Standard blood pressure control	2359(23.1)	2062(23.2)	297(22.4)	
Intensive blood pressure control	2355(23.1)	2018(22.7)	337(25.4)	
Lipid trial,%				0.085
None	4714(46.2)	4080(46.0)	634(47.8)	
Standard lipid control	2735(26.8)	2413(27.2)	322(24.3)	
Intensive lipid control	2747(26.9)	2378(26.8)	369(27.8)	
Adverse renal outcomes,%				

Table 1 (continued)

Variable	Overall (*n* = 10196)	TyG < 10.27 (*n* = 8871)	TyG ≥ 10.27 (*n* = 1325)	*p* value
Worsening renal function	5824 (57.1)	4949 (55.8)	875 (66.0)	< 0.001
Albuminuria	2039 (23.2)	1741 (22.7)	298 (26.7)	0.003
Renal failure	280 (2.7)	232 (2.6)	48 (3.6)	0.045

Data are presented as mean (SD) or as n (%). *p* value for the test of the difference across dichotomy of TyG were obtained by using the χ2 test (categorical variables), ANOVA (continuous variables). GED, General Education Development.

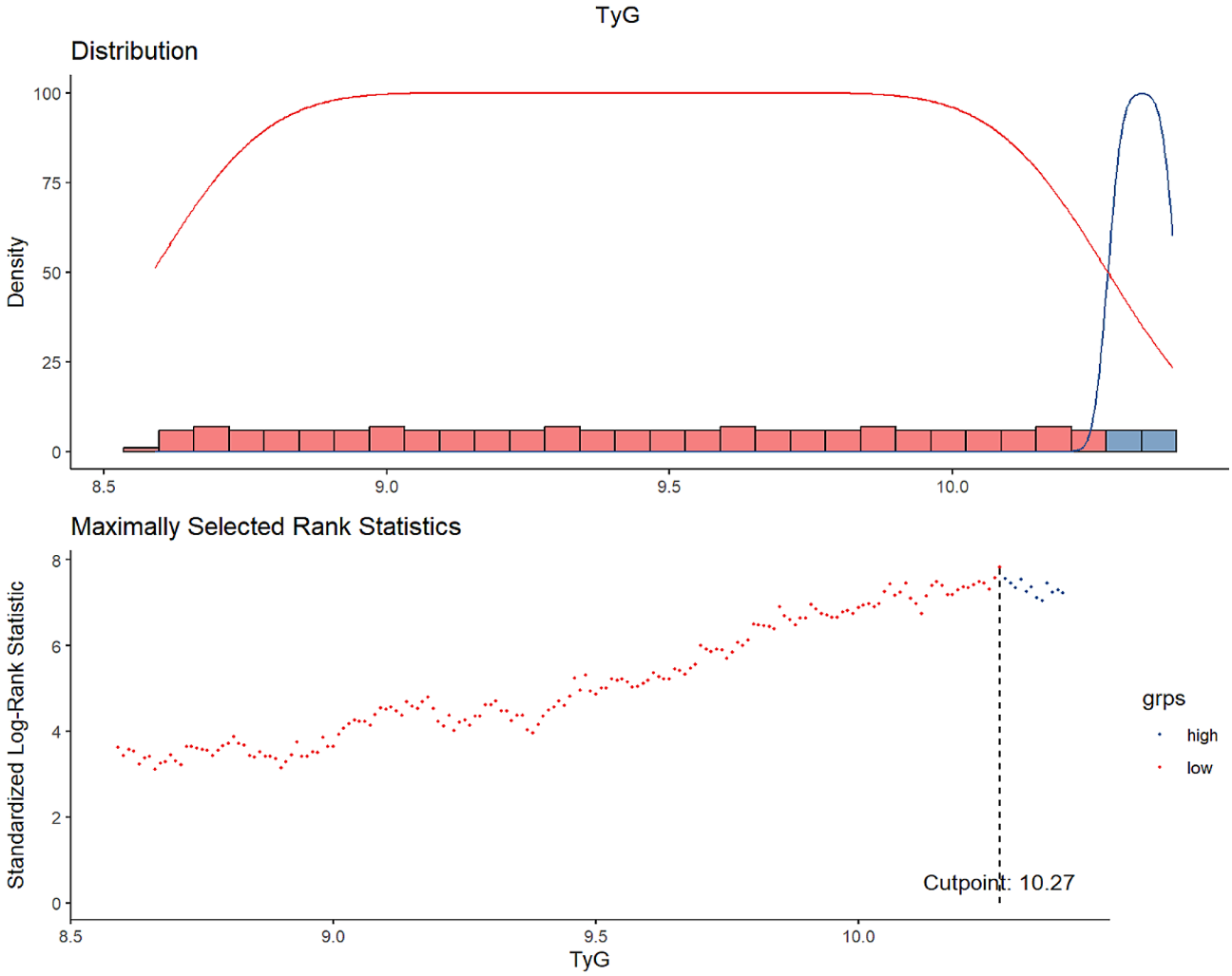

Fig. 1 Maximally selected log-rank statistics for cutoff point of TyG

was utilized to evaluate the statistical significance of the observed differences, indicating that higher TyG levels were significantly associated with an increased risk of adverse renal outcomes. Specifically, the disparities for worsening renal function, albuminuria, and renal failure were statistically significant, with *p* value of less than 0.0001 for worsening renal function, 0.00032 for albuminuria, and 0.025 for renal failure, underscoring the critical impact of TyG levels on renal health.

Baseline TyG levels and adverse renal outcomes

In evaluating the relationship between baseline TyG levels and adverse renal outcomes, our study implemented Cox proportional regression analysis across three progressively adjusted models. Model 1 accounted for age, sex, education attainment, race, BMI, smoking status, alcohol use, DBP, and SBP. Model 2 expanded upon Model 1 by including HbA1c, diabetes duration, SCr and UACR. Model 3 further incorporated treatments with ACEI, ARB, glycemia trial, blood pressure trial, and lipid trial, building on the covariates of Model 2. The

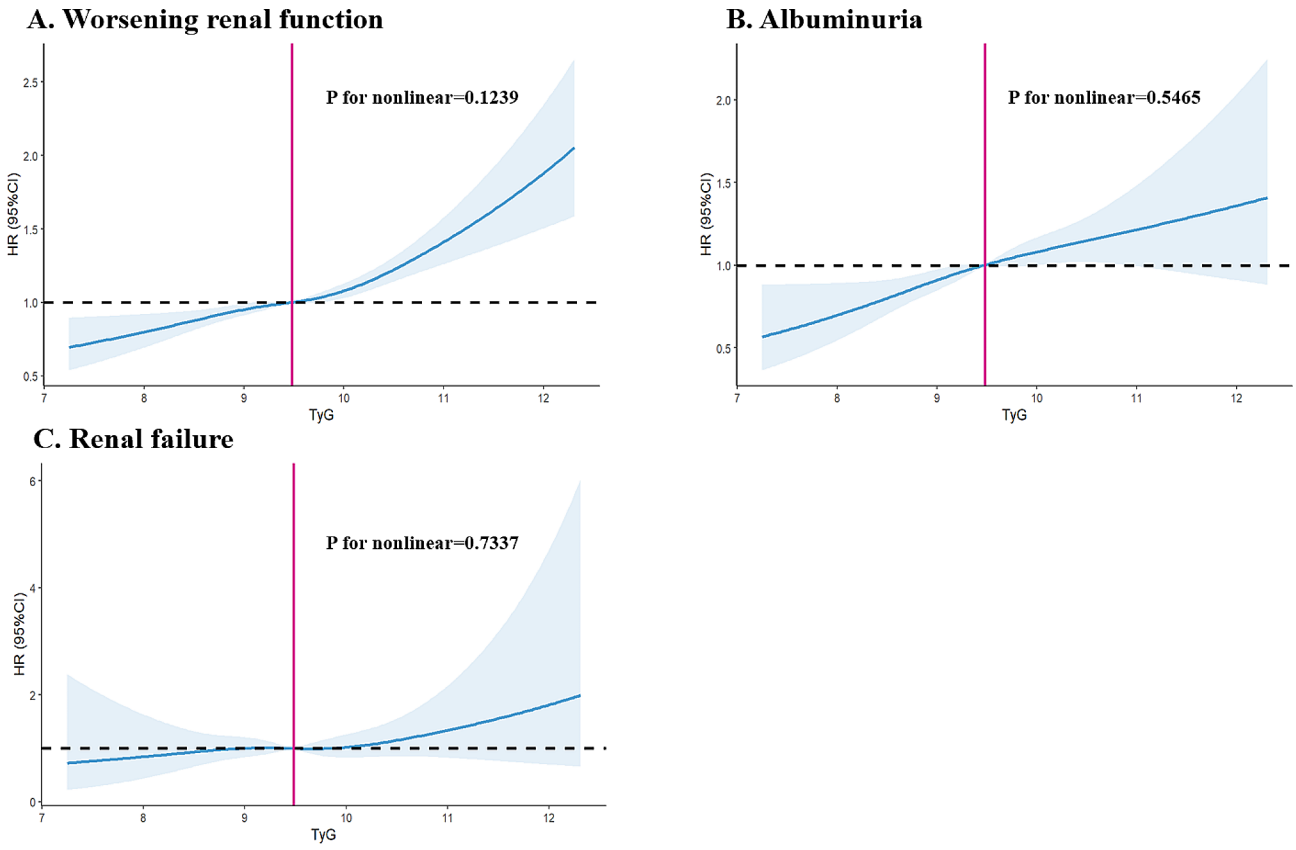

Fig. 2 The linear relationship between TyG and adverse renal outcomes by performing Restricted cubic spline analysis

analyses demonstrated that, following adjustments for both demographic and conventional renal risk factors in Model 3, baseline TyG levels were independently associated with the incidence of adverse renal outcomes in patients with T2DM. Specifically, the hazard ratios (HRs) for the adverse renal outcomes in comparison to lower TyG levels were as follows: For worsening renal function, HR was 1.24 (95% CI 1.14–1.35, $p<0.001$); for albuminuria, HR was 1.19 (95% CI 1.03–1.37, $p=0.020$); and for renal failure, HR was 1.24 (95% CI 0.86–1.79, $p=0.247$), as detailed in Table 2.

Interaction between subgroups to adverse renal outcomes

To explore the relationship between the TyG levels and adverse renal outcomes across various subgroups, interaction between subgroups to adverse renal outcomes was also evaluated. Analysis indicated that the p value for interaction among subgroups concerning worsening renal function was not statistically significant (p for interaction >0.05), as depicted in Fig. 4. Further examination of the interactions relating to albuminuria and renal failure can be found in Supplemental Fig. 1 and Fig. 2, respectively. These findings suggested that the relationship between TyG levels and adverse renal outcomes remains consistent and significant across different subgroups of patients with T2DM, indicating a uniform impact of TyG levels on renal health irrespective of subgroup distinctions.

Discussion

Our investigation focused on the relationship between TyG index levels and adverse renal outcomes within a cohort of individuals with T2DM from the ACCORD study, also examining the consistency of these associations across different subgroups. We discovered a significant link between baseline TyG levels and the incidence of adverse renal outcomes, a relationship that persisted across various subgroups. Remarkably, this association remained evident even when accounting for established risk factors like serum creatinine levels, urinary protein content, and the use of ARB or ACEI. These findings highlighted the TyG index as a reliable predictor for early adverse renal outcomes among T2DM patients. Nonetheless, it's critical to emphasize that the effectiveness of TyG in predicting late-stage renal adverse outcomes warrants further exploration. This study firstly utilized the ACCORD trial and underscored the TyG index's potential as a tool in the early identification of T2DM patients in the United States at risk for renal complications,

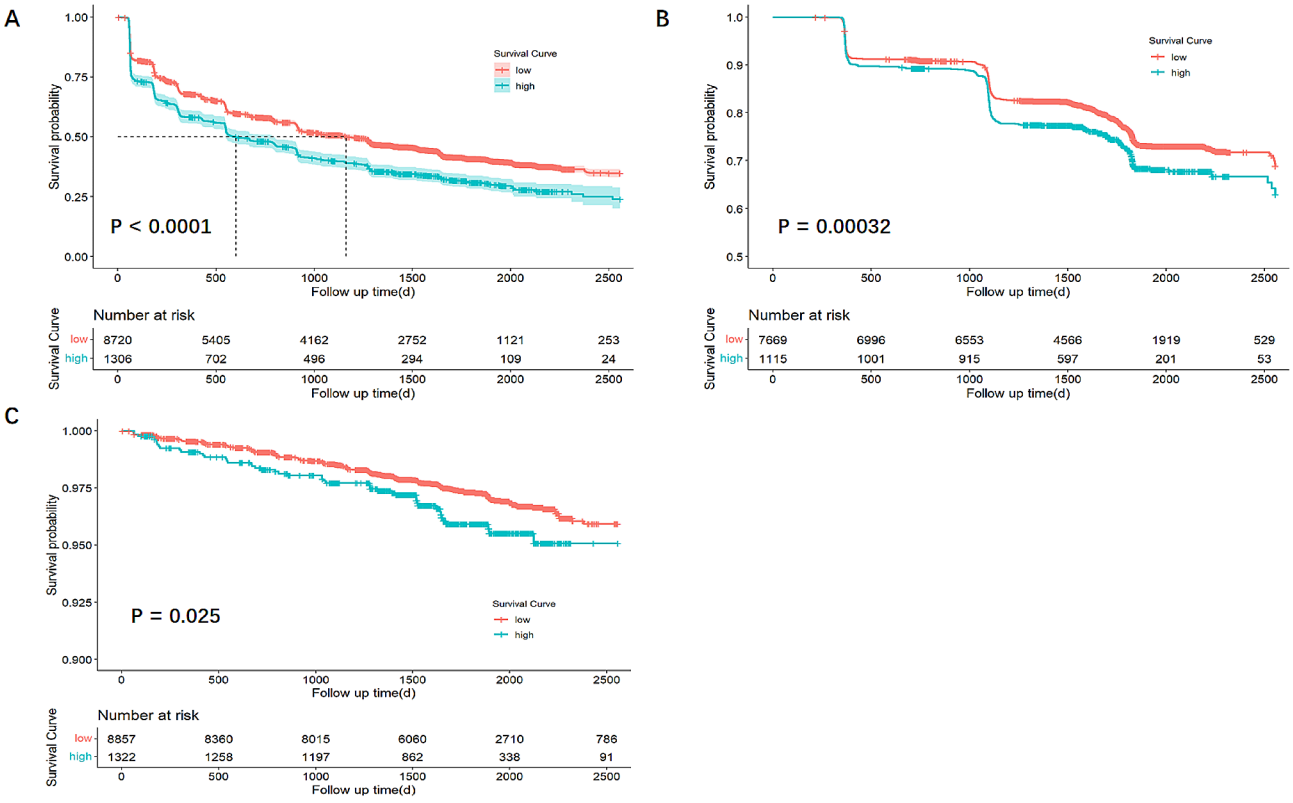

Fig. 3 Kaplan - Meier survival analysis for adverse renal outcomes according to binary of TyG levels. (**A**) Worsening renal function; (**B**) Albuminuria; (**C**) Renal failure

Table 2 Association of TyG with adverse renal outcomes in T2DM

TyG	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Worsening renal function			
TyG < 10.27 (*n* = 8871)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
TyG ≥ 10.27 (*n* = 1325)	1.32 (1.22–1.43)	1.20 (1.10–1.31)	1.24 (1.14–1.35)
p for trend	*p* < 0.001	*p* < 0.001	*p* < 0.001
Per 1 SD	1.11 (1.08–1.14)	1.07 (1.04–1.11)	1.07 (1.03–1.10)
p for 1 SD	*p* < 0.001	*p* < 0.001	*p* < 0.001
Albuminuria			
TyG < 10.27 (*n* = 8871)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
TyG ≥ 10.27 (*n* = 1325)	1.32 (1.15–1.52)	1.20 (1.04–1.38)	1.19 (1.03–1.37)
p for trend	*p* < 0.001	*p* = 0.014	*p* = 0.020
Per for 1 SD	1.15 (1.09–1.21)	1.10 (1.04–1.16)	1.09 (1.04–1.15)
p for 1 SD	*p* < 0.001	*p* < 0.001	*p* = 0.001
Renal failure			
TyG < 10.27 (*n* = 8871)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
TyG ≥ 10.27 (*n* = 1325)	1.48 (1.05–2.07)	1.25 (0.87–1.79)	1.24 (0.86–1.79)
p for trend	*p* = 0.024	*p* = 0.237	*p* = 0.247
Per for 1 SD	1.14 (0.99–1.30)	1.08 (0.94–1.25)	1.08 (0.94–1.25)
p for 1 SD	*p* = 0.058	*p* = 0.279	*p* = 0.283

Model 1: adjusted for age, sex, race, education levels, BMI, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure.

Model 2: adjusted for model 1 covariables plus Hba1c, duration of diabetes, serum creatinine, urinary albumin.

Model 3: adjusted for model 2 covariables plus treatment with angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, glycemia trial, blood pressure trial, and lipid trial.

Variable	Count	Percent	HR (95% CI)	P value	P for interaction
Overall	8212	100	1.26 (1.16 to 1.37)	<0.001	
Age					0.967
>= 60	5214	63.5	1.27 (1.14 to 1.43)	<0.001	
< 60	2998	36.5	1.23 (1.08 to 1.39)	0.001	
Sex					0.948
Male	5025	61.2	1.30 (1.17 to 1.44)	<0.001	
Female	3187	38.8	1.21 (1.06 to 1.39)	0.006	
Education.levels					0.255
Less than high school	1187	14.5	1.43 (1.12 to 1.82)	0.004	
High school graduate or GED	2151	26.2	1.15 (0.97 to 1.35)	0.099	
Some college	2658	32.4	1.36 (1.18 to 1.57)	<0.001	
College degree or higher	2216	27	1.20 (1.02 to 1.40)	0.026	
Race					0.158
Non-white	3016	36.7	1.09 (0.92 to 1.30)	0.315	
White	5196	63.3	1.32 (1.20 to 1.45)	<0.001	
BMI					0.921
>= 28	6373	77.6	1.26 (1.15 to 1.38)	<0.001	
< 28	1839	22.4	1.25 (1.03 to 1.52)	0.026	
Smoking					0.106
No	4270	52	1.38 (1.23 to 1.54)	<0.001	
Yes	3942	48	1.14 (1.01 to 1.29)	0.036	
The.history.of.CVD					0.658
No	5353	65.2	1.22 (1.10 to 1.36)	<0.001	
Yes	2859	34.8	1.34 (1.17 to 1.54)	<0.001	
Duration.of.diabetes					0.486
>= 10	4184	50.9	1.22 (1.08 to 1.38)	0.001	
< 10	4028	49.1	1.29 (1.15 to 1.44)	<0.001	
SBP					0.809
>= 140	3307	40.3	1.25 (1.10 to 1.42)	<0.001	
< 140	4905	59.7	1.26 (1.13 to 1.41)	<0.001	
HbA1c					0.866
>= 8	4280	52.1	1.28 (1.15 to 1.41)	<0.001	
< 8	3932	47.9	1.23 (1.06 to 1.42)	0.005	
eGFR					0.699
>= 90	3844	46.8	1.26 (1.13 to 1.40)	<0.001	
< 90	4368	53.2	1.22 (1.07 to 1.40)	0.004	
The.use.of.ARB					0.741
No	6783	82.6	1.28 (1.17 to 1.40)	<0.001	
Yes	1429	17.4	1.17 (0.95 to 1.45)	0.148	
The.use.of.ACEI					0.145
No	3698	45	1.17 (1.04 to 1.33)	0.012	
Yes	4514	55	1.34 (1.20 to 1.50)	<0.001	
Insulin					0.461
No	4889	61.7	1.27 (1.14 to 1.40)	<0.001	
Yes	3040	38.3	1.21 (1.04 to 1.40)	0.012	

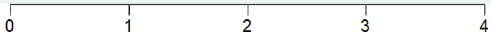

Fig. 4 Interaction between subgroups to worsening renal function

independent of traditional risk factors, suggesting its utility in clinical practice and future research directions.

Our study delved into the TyG index, it is very clear that the TyG index is an indicator composed of two risk factors, namely lipid-related and glucose-related factors, which reflect insulin resistance in the human body [21]. Previous research has described that fasting plasma glucose primarily reflects insulin resistance in the liver, while fasting triglycerides mainly reflect insulin resistance in adipocytes [9]. In fact, it was documented that the TyG index was the best index to identify individuals with insulin resistance, even superior to visceral

adiposity indicators and other lipid parameters [7, 8, 22]. This index, first proposed in 2008, was shown to outperform the homeostasis model assessment-insulin resistance (HOMA-IR) index in identifying IR, demonstrating a sensitivity of 84.0% and specificity of 45.0% in a significant cross-sectional study of apparently healthy individuals [23]. Further research by Guerrero-Romero et al. in 2010 involving 99 participants with varying body weights and glucose tolerance highlighted the TyG index's optimal performance for IR assessment, exhibiting high specificity (85.0%) and sensitivity (96.5%) compared to the gold standard, the Euglycemic-Hyperinsulinemia Clamp Test [22]. Since its inception, the TyG index has been established as a reliable and accessible tool for evaluating IR in individuals at high risk through extensive clinical studies. Previous research primarily focused on cardiovascular diseases (CVDs) such as coronary artery calcification (CAC), acute coronary syndrome (ACS), heart failure (HF), arterial stiffness (AS), stent restenosis, and stable coronary artery disease (CAD) [21]. Laura et al. utilized a large sample from the Vascular Metabolic CUN cohort (VMCUN cohort) over a median follow-up of 10 years to first suggest a positive association between the TyG index and CVD events, including, peripheral arterial disease (PAD), cerebrovascular disease and coronary heart disease (CHD), independent of confounding factors [24]. Despite the extensive application of the TyG index in cardiovascular research, limited studies have explored its relationship with adverse renal outcomes. Our current investigation assesses the TyG index as a potential risk factor for incident adverse renal outcomes in the T2DM population, with a focus on evaluating whether this significant association is consistent across different subgroups.

The relationship between triglyceride-glucose (TyG) index levels and chronic kidney disease (CKD) has been explored in some studies, revealing inconsistent results. Despite these discrepancies, a growing body of evidence suggested a strong link between TyG levels and adverse renal outcomes. A community-based cross-sectional study identified a significant association between higher TyG index levels and increased micro-albuminuria [25], while a cohort study in China reported that elevated TyG index levels were significantly correlated with a higher risk of developing albuminuria, particularly among individuals with metabolic dysfunction [26]. Further research has shown associations of TyG levels with acute kidney injury (AKI) [27], end-stage renal disease [28], hyperuricemia [29] and worsening renal function [30, 31]. These findings underscore the necessity for additional studies to clarify the relationship between the TyG index and CKD, especially in patients with T2DM who are at risk of insulin resistance. This area remains pivotal for ongoing research and clinical investigation.

This investigation aimed to assess the TyG index as a predictor for adverse renal outcomes among individuals with T2DM. Our findings robustly supported the TyG index as a valuable predictor for early renal adverse outcomes. After adjusting for confounding factors, the study revealed a significant association between TyG levels and key adverse renal outcomes, including worsening renal function and the onset of albuminuria. The UACR and eGFR, well-established markers for chronic kidney disease risk assessment, underscore the importance of regular monitoring to manage renal function in diabetic patients effectively. The potential lag in these markers becoming abnormal, indicating already present advanced kidney damage, highlights the urgent need for innovative biomarkers for early detection. Our results demonstrated TyG's capability to effectively predict early renal adverse outcomes, addressing a critical gap in current biomarkers and facilitating timely interventions for individuals with elevated TyG levels. Notably, our study did not observe a significant link between TyG levels and the progression to renal failure, likely due to the constrained follow-up period which limited observing these specific outcome events. This absence of statistical significance underlines the necessity for extended research to further elucidate TyG's relationship with late-stage renal adverse outcomes. Despite these considerations, our research offers compelling evidence of the TyG index as a reliable early indicator of adverse renal outcomes, presenting significant clinical utility.

The TyG index's predictive capacity for cardiovascular diseases has been linked to several molecular mechanisms, including smooth muscle cell dysfunction, coagulation, endothelial dysfunction, metabolic flexibility [21]. However, the specific mechanisms connecting the TyG index to incident adverse renal outcomes are less defined, though several plausible explanations exist. Firstly, insulin resistance is known to correlate with elevated levels of inflammatory markers [32] and inflammation has been recognized as an independent risk factor for incident adverse renal outcomes. Secondly, IR may activate the mitochondrial electron transport chain, leading to the production of reactive oxidative stress (ROS), which in turn can cause kidney tissue fibrosis [15]. Thirdly, hyperinsulinemia, often associated with IR, can detrimentally impact renal function by promoting glomerular hyperfiltration, endothelial dysfunction, and increased vascular permeability [33]. Therefore, individuals with higher TyG index values are likely to experience more severe kidney function impairment and are at a higher risk for adverse renal outcomes.

The utilization of a large sample size, access to high-quality subject information, and the application of various statistical methods enable our study to identify independent associations between the TyG index and

adverse renal outcomes, leading to robust conclusions. Nonetheless, it's essential to recognize our study's limitations. Even though we incorporate most recognized risk factors for adverse renal outcomes into our multivariable regression models, we cannot completely exclude the possibility of residual confounding factors. Moreover, it's important to highlight that our findings are observational. Although they strongly indicate a correlation between TyG levels and adverse renal outcomes, future prospective intervention studies are crucial to definitively determine TyG levels' causal effects on these outcomes. Additionally, due to a lack of fasting insulin levels in the ACCORD trial, we cannot compare whether TyG is better than HOMA-IR in predicting the occurrence of adverse renal outcomes. Finally, the population of the ACCORD trial included only high-risk patients with type 2 diabetes and additional studies are necessary to increase the generalizability of the results.

Conclusion

Our investigation focused on elucidating the relationship between the TyG index and adverse renal outcomes in individuals with T2DM. The outcomes of this study are significant, demonstrating a clear association between baseline TyG levels and adverse renal outcomes. Furthermore, our findings indicate that the TyG index could be a useful tool for risk stratification in predicting adverse renal outcomes among patients with T2DM. However, to enhance our understanding and validate these associations, further research is necessary. Future studies should aim to corroborate our results and explore whether interventions aimed at reducing TyG levels could offer benefits to patients with T2DM exhibiting elevated TyG levels. Such research has the potential to inform clinical practices, thereby improving the management and care of diabetic individuals at risk of developing adverse renal outcomes.

Supplementary Information

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Supplementary Material 1: Figure S1: Interaction between subgroups to albuminuria

Supplementary Material 2: Figure S2: Interaction between subgroups to renal failure

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Author contributions
ZZP, JXP and PY contributed to study design. JXP, ZZP and PY contributed to data acquisition. PY, JXP and ZZP contributed to data analysis. PY, LH, JXP and ZZP contributed to drafting of the manuscript. LJT contributed to supervision and mentorship. The final version of the manuscript was read and approved by all authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
The use of the ACCORD dataset in this study has been approved by the National Heart, Lung, and Blood Institute.

Competing interests
The authors declare no competing interests.

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