Cardiovascular Diabetology

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Association of triglyceride-glucose related indices with mortality among individuals with MASLD combined with prediabetes or diabetes

Yiheng Zhang[1†], Juanli Wu[1†], Tao Li[1], Yundong Qu[1] and Yan Wang[1*]

Abstract

Background The prognostic significance of triglyceride-glucose (TyG)-related indices in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) combined with prediabetes or diabetes is not yet fully understood. In this study, we explored their predictive value for mortality in this specific population.

Methods Patients with MASLD were identified from the National Health and Nutrition Examination Survey (NHANES III) database. TyG and its related parameters [TyG-waist circumference (TyG-WC), TyG-waist-to-height ratio (TyG-WHtR), TyG-weight-adjusted waist index (TyG-WWI), and TyG-body mass index (TyG-BMI),] were calculated. To examine the association between TyG-related indices and mortality risk, Cox regression models were utilized. Furthermore, we employed restricted cubic spline (RCS) analysis to investigate potential dose-response relationships. The predictive ability of the TyG indices for mortality was assessed by analyzing the time-dependent area under the curve (AUC).

Results In the cohort of patients with prediabetes or diabetes, 46.5% were diagnosed with MASLD. Over a median follow-up of 25.4 years, 1,163 individuals (53.9%) died, with 329 (15.3%) deaths attributed to cardiovascular causes and 78 (3.6%) to diabetes. Multivariate Cox regression models showed that TyG, TyG-BMI, TyG-WHtR, TyG-WWI, and TyG-WC were associated with all-cause and cardiovascular/diabetes-specific mortality. Furthermore, RCS analysis revealed a positive linear relationship between the TyG and TyG-WWI indices and all-cause mortality (p for nonlinear = 0.920; $p = 0.525$, respectively). In contrast, the TyG-WC, TyG-BMI, and TyG-WHtR indices exhibited a positive nonlinear association with all-cause mortality (p for nonlinear = 0.001; = 0.003; = 0.007, respectively). Time-dependent AUC curves demonstrated that the TyG-WWI index was the most robust predictor of both all-cause and cardiovascular mortality.

Conclusions Elevated levels of TyG, TyG-BMI, TyG-WHtR, TyG-WWI, and TyG-WC indices were associated with a poorer prognosis in MASLD patients with prediabetes or diabetes, with TyG-WWI being the strongest predictor.

Keywords MASLD, Triglyceride-glucose related indices, Diabetes, Mortality

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Introduction

A recent consensus, using a modified Delphi process and spearheaded by three major international liver organizations, proposed renaming non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) [1] to metabolic dysfunction-associated steatotic liver disease (MASLD), highlighting the significance of cardiometabolic risk factors (CMRFs) in predicting outcomes [2]. Furthermore, approximately half of individuals diagnosed with type 2 diabetes mellitus are also affected by NAFLD [3]. Insulin resistance (IR) plays an important role in the occurrence and development of these two diseases. The coexistence of steatosis in these patients often results in a poorer prognosis, underscoring the complexity and interplay between these metabolic disorders [4, 5].

The triglyceride-glucose index (TyG) is widely recognized as a surrogate marker for IR and has been shown to be closely associated with the occurrence and prognosis of various diseases [6, 7]. Its derivatives, which incorporate anthropometric measurements like body mass index (BMI), waist-height ratio (WHtR), waist circumference (WC), or weight-adjusted waist index (WWI), provide a more accurate reflection of body fat distribution and IR [8–11]. These measures may serve as predictive tools for adverse outcomes, guiding clinical decision-making and personalized treatment approaches.

Previous studies have found that the TyG index and its derivative indicators are associated with all-cause and cardiovascular mortality in various populations, including those with NAFLD, diabetes, and patients undergoing peritoneal dialysis [12–16]. Despite its potential, the specific impact of TyG-related indices on the prognosis of MASLD in patients with prediabetes or diabetes remains poorly understood. This knowledge gap underscores the need for further research to clarify their role and utility in clinical practice. This study combined data from the National Health and Nutrition Examination Survey (NHANES) and the National Death Index (NDI) to evaluate the association between TyG-related indices and MASLD in patients with prediabetes or diabetes.

Methods

Study population

This study is based on an analysis of the NHANES III, a cross-sectional study evaluating the health and nutritional status of individuals in the United States (Available online: https://www.cdc.gov/nchs/nhanes/, accessed on 1 September 2024). NHANES III received ethical approval from the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided informed consent.

Inclusion and exclusion criteria

In NHANES III, we initially included 13,856 individuals from the adult data who had available ultrasound data. Then, we excluded 1,269 participants who were missing data for BMI, WC, height, weight, triglycerides (TG), fasting blood glucose (FBG), and glycated hemoglobin (HbA1c). Additionally, we excluded individuals without prediabetes or diabetes ($n = 6,865$). Finally, we eliminated 1,088 participants with hepatitis C virus (HCV) and/or hepatitis B virus (HBV) infection, excessive alcohol consumption, or no follow-up, resulting in a final study sample of 4,634 participants (Fig. 1).

To evaluate the correlations between TyG-related indices and all-cause and cause-specific mortality in adults with MASLD and prediabetes or diabetes, only participants diagnosed with MASLD and prediabetes or diabetes were analyzed.

Definition

In NHANES III, hepatic steatosis was categorized using gallbladder/hepatic ultrasound as normal, mild, moderate, or severe. Mild to severe cases were classified as steatotic liver disease (SLD). MASLD was defined by the presence of SLD and at least one CMRF, excluding other causes of steatosis or heavy alcohol use (≥ 20/30 g per day for women/men). CMRFs were defined as follows: (a) Overweight or obesity: BMI ≥ 25 kg/m² or WC ≥ 94 cm for men and ≥ 80 cm for women; (b) diabetes or prediabetes: diabetes was defined as having a medical diagnosis, with HbA1c levels ≥ 6.5%, FPG levels ≥ 126 mg/dL, or a 2-hour blood glucose level ≥ 200 mg/dL. Prediabetes was identified by having FPG levels between 100 and 125 mg/dL, or HbA1c levels between 5.7% and 6.4%; (c) High blood pressure: blood pressure ≥ 130/85mmHg or antihypertensive treatment; (d) Hypertriglyceridemia: plasma triglycerides ≥ 1.70 mmol/L or lipid-lowering treatment; and (e) Low high-density lipoprotein cholesterol (HDL-c): plasma HDL-cholesterol ≤ 1.0 mmol/L for men and ≤ 1.3 mmol/L for women or lipid-lowering treatment [2].

The TyG, TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI indices were calculated using the following formulas: TyG index = Ln [TG (mg/dL) × FBG (mg/dL)/2]; TyG-BMI index = TyG index × BMI; TyG-WHtR index = TyG index × WC/height; TyG-WWI index = TyG index × WC/√weight; TyG-WC index = TyG index × WC. The Fibrosis-4 index (FIB-4) was calculated to assess hepatic fibrosis using the published formulas [17]. Pregnancy, breastfeeding, or having had a period in the past 12 months was defined as pre-menopausal.

Covariates

Socioeconomic characteristics such as sex, age, ethnicity, marital status, educational level, and family income ratio were collected. Additionally, data on smoking status,

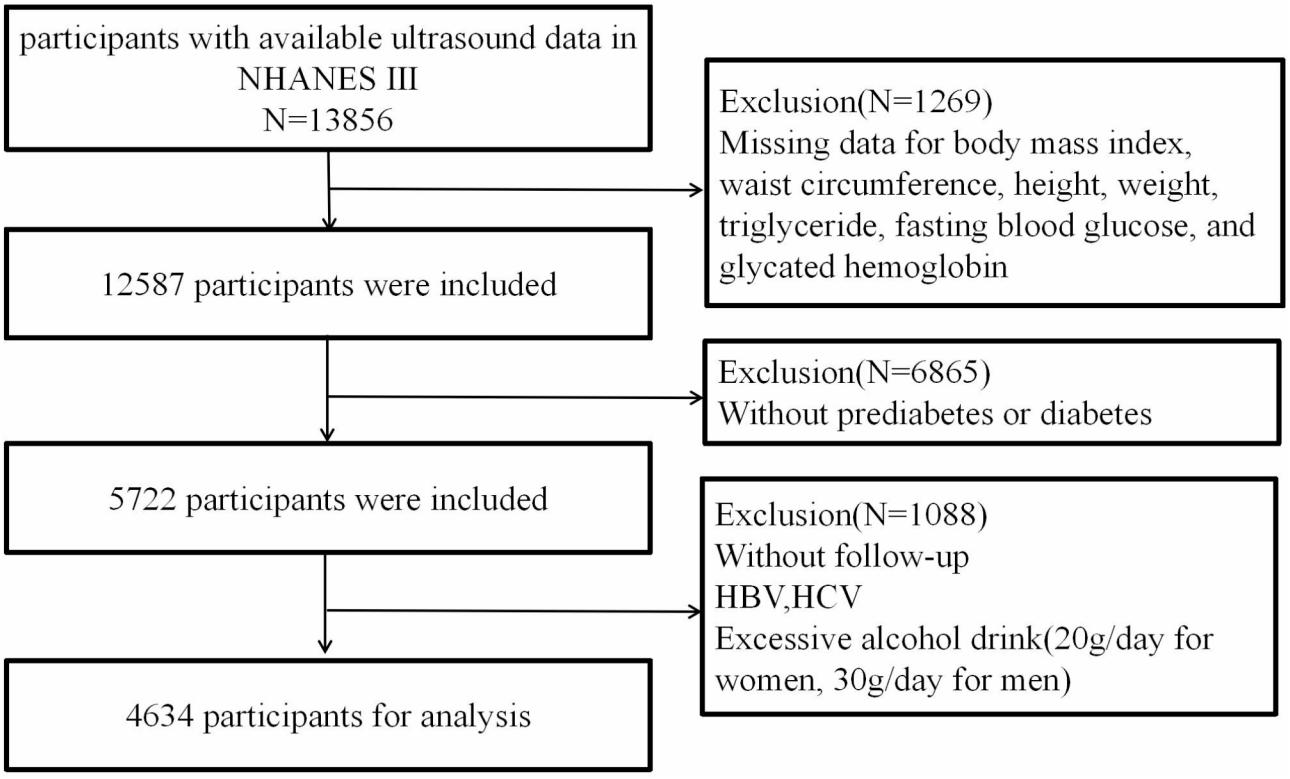

Fig. 1 Flowchart for selection of study population

history of heart attack, and the use of antihypertensive, lipid-lowering, and glucose-lowering medications were gathered. Furthermore, laboratory tests including creatinine, alanine aminotransferase (ALT), aspartate transaminase (AST), and platelet (PLT) counts were selected as potential confounders.

Ascertainment of mortality

Mortality data for participants in NHANES was obtained through record linkage with the NDI. Survival time was determined from the date of survey completion to the date of death or until December 31, 2019. All-cause mortality encompassed deaths from any cause, while cause-specific mortality was categorized as deaths due to heart disease or diabetes (codes 054–064 or 046 in NCHS).

Statistical analysis

The analysis followed NHANES guidelines, utilizing sampling weights to accurately represent the U.S. population. Continuous variables were presented as medians with interquartile ranges and compared using the Mann-Whitney test. Categorical variables were expressed as unweighted frequency counts with weighted percentages and compared using Chi-squared tests. Cox regression models were employed to determine hazard ratios (HR) and 95% confidence intervals (CI) linking TyG-related indices to mortality risk. To explore dose-response relationships, restricted cubic spline (RCS) regression models were used. The time-dependent area under the curve (AUC) of TyG-related indices was used to assess their predictive ability for mortality. Stratified analyses were performed by sex, age, smoking status, diabetes status, and FIB-4.

Analyses were conducted using R Software (Version 4.3.2) and the Free Statistics platform (Version 2.0). To rigorously interpret the associations between TyG, TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI with the survival of individuals with MASLD and prediabetes or diabetes, this study applied a Bonferroni correction [18]. The standard significance level of $p = 0.05$ was divided by five, resulting in a corrected significance level of $p = 0.01$ to account for multiple testing.

Results

Clinical baseline characteristics

A total of 4,634 patients with prediabetes or diabetes who had completed ultrasonography data were identified from the NHANES III database. Among these participants, 50.1% were men, 75.6% were Non-Hispanic White, and 46.5% were diagnosed with MASLD. Compared to non-MASLD participants, those with MASLD showed higher levels of BMI, WC, FBG, HbA1c, ALT, AST, systolic blood pressure (SBP), diastolic blood pressure (DBP), and TG. They were more likely to have a history of

using antihypertensive, lipid-lowering, and glucose-lowering medications, as well as a history of heart attacks. Additionally, they had higher incidences of hypertriglyceridemia, diabetes, high blood pressure, low HDL-c, and were more often overweight or obesity. Notably, all TyG-related indices were elevated in MASLD patients. However, there was no significant difference between the MASLD and Non-MASLD groups regarding the prevalence of significant liver fibrosis (FIB-4 > 1.3), platelet count, or creatinine levels (Table 1).

We then compared the baseline characteristics between the alive and deceased groups among MASLD patients

Table 1 Baseline characteristics among individuals with prediabetes or diabetes

Variables	Total *N* = 4634	non-MASLD *N* = 2477	MASLD *N* = 2157	*p*
Age, years	52.0 (41.0, 63.0)	51.0 (40.0, 63.0)	53.0 (42.0, 63.0)	0.001
Men, n (%)	2199 (50.1)	1173 (49.4)	1026 (50.9)	0.526
Ethnicity, n (%)				< 0.001
Non-Hispanic White	1744 (75.6)	959 (75.5)	785 (75.8)	
Non-Hispanic Black	1324 (11.9)	829 (13.5)	495 (9.8)	
Mexican American	1405 (5.6)	601 (4.3)	804 (7.2)	
Other ethnicities	161 (6.9)	88 (6.7)	73 (7.1)	
Family income ratio, n (%)				0.018
< 1.3	1363 (15.8)	692 (15.0)	671 (16.7)	
1.3–3.5	2302(48.3)	1220 (46.2)	1082 (50.9)	
> 3.5	969 (35.9)	565 (38.7)	404 (32.3)	
Married, n (%)	3148 (72.5)	1631 (71.1)	1517 (74.2)	0.089
Education level, n (%)				0.016
<= 12	3423 (62.5)	1763 (59.4)	1660 (66.4)	
> 12	1211 (37.5)	714 (40.6)	497 (33.6)	
Current smoker, n (%)	1082 (25.2)	663 (28.9)	419 (20.5)	< 0.001
SBP, mmHg	126.0 (115.0, 138.0)	124.0 (114.0, 136.0)	128.0 (118.0, 141.0)	< 0.001
DBP, mmHg	76.0 (70.0, 83.0)	75.0 (69.0, 82.0)	78.0 (71.0, 84.0)	< 0.001
BMI, kg/m^2	27.5 (24.3, 31.3)	25.8 (22.9, 29.2)	29.8 (26.4, 33.8)	< 0.001
WC, cm	97.5 (87.7, 106.5)	92.7 (84.1, 100.9)	103.2 (94.8, 111.9)	< 0.001
FBG, mmol/L	5.6 (5.0, 6.0)	5.6 (5.0, 5.9)	5.7 (5.2, 6.4)	< 0.001
HbA1c, %	5.6 (5.2, 5.9)	5.6 (5.2, 5.8)	5.7 (5.3, 6.1)	< 0.001
TG, mmol/L	1.6 (1.1, 2.3)	1.3 (0.9, 1.9)	1.9 (1.3, 2.8)	< 0.001
HDL-C, mmol/L	1.2 (1.0, 1.4)	1.3 (1.0, 1.5)	1.1 (0.9, 1.3)	< 0.001
Creatinine, umol/L	97.2 (88.4,106.1)	97.2 (88.4,106.1)	97.2 (79.6,106.1)	0.813
PLT, 10^9/L	264.0 (225.0, 308.0)	264.0 (226.0, 303.5)	264.0 (223.0, 313.0)	0.718
ALT, U/L	15.0 (11.0,22.0)	14.0 (10.0,19.0)	19.0 (13.0,26.0)	< 0.001
AST, U/L	19.0 (17.0,24.0)	19.0 (16.0,22.0)	20.0 (17.0,25.0)	< 0.001
FIB-4 > 1.3, n (%)	1301 (25.0)	705 (24.3)	596 (25.7)	0.461
TyG index	8.9 (8.4, 9.3)	8.7 (8.3, 9.1)	9.1 (8.7, 9.6)	< 0.001
TyG-BMI index	246.4 (209.5, 288.2)	226.5 (196.8, 259.0)	275.4 (240.1, 320.6)	< 0.001
TyG-WHtR index	5.1 (4.5, 5.9)	4.7 (4.3, 5.3)	5.7 (5.1, 6.4)	< 0.001
TyG-WWI index	97.6 (89.4, 105.7)	93.1 (86.6, 100.6)	102.7 (95.6, 110.0)	< 0.001
TyG-WC index	869.8 (755.5,981.5)	803.1 (719.3,903.9)	948.7 (855.3,1068.6)	< 0.001
Overweight or obesity, n(%)	3866 (80.3)	1889 (72.1)	1977 (90.4)	< 0.001
Hypertriglyceridemia, n (%)	2108 (46.4)	883 (34.9)	1225 (60.6)	< 0.001
High blood pressure, n (%)	2553 (51.2)	1259 (46.5)	1294 (57.0)	< 0.001
Low HDL-c, n (%)	2176 (47.0)	965 (37.3)	1211 (59.0)	< 0.001
diabetes, n(%)	1518 (27.9)	493 (19.4)	1025 (37.2)	< 0.001
Heart attack, n (%)	250 (4.9)	113 (3.7)	137 (6.5)	0.001
Antihypertensive medications, n (%)	1060 (20.1)	499 (16.4)	561 (25.4)	< 0.001
lipid-lowering medications, n (%)	235 (5.2)	119 (4.2)	116 (6.4)	0.004
Glucose-lowering medications, n (%)	323 (5.2)	101 (2.2)	222 (8.9)	< 0.001

Data are displayed as the median (interquartile range) or unweighted frequency counts (weighted percentage) as appropriate. The Mann-Whitney test for continuous variables and the chi-square test for categorical variables were used in this analysis

with prediabetes or diabetes. The deceased group was predominantly composed of Non-Hispanic Whites and characterized by older age. They also exhibited higher levels of SBP, WC, HbA1c, TG, creatinine, PLT, ALT, and FIB-4, along with lower education levels. Moreover, the TyG, TyG-WHtR, TyG-WC, and TyG-WWI indices were significantly elevated in the deceased group, which was also associated with higher rates of comorbidities, such as high blood pressure, diabetes, and a history of heart attacks, as well as greater use of antihypertensive and glucose-lowering medications compared to non-MASLD patients (Table 2).

Table 2 Baseline characteristics among MASLD individuals with prediabetes or diabetes by mortality status

Variables	Alive *N* = 994	Deceased *N* = 1163	*p*
Age, years	44.0 (36.0, 51.0)	62.0 (53.0, 68.0)	< 0.001
Men, n (%)	452 (51.3)	574 (50.6)	0.837
Ethnicity, n (%)			< 0.001
Non-Hispanic White	254 (66.9)	531 (83.9)	
Non-Hispanic Black	252 (11.4)	243 (8.4)	
Mexican American	440 (10.2)	364 (4.5)	
Other ethnicities	48 (11.6)	25 (3.1)	
Family income ratio, n (%)			0.992
< 1.3	327 (16.6)	344 (16.9)	
1.3–3.5	487 (51.0)	595 (50.9)	
> 3.5	180 (32.4)	224 (32.2)	
Married, n (%)	736 (78.7)	781(71.1)	0.042
Education level, n (%)			< 0.001
<=12	726 (59.8)	934 (72.3)	
> 12	268 (40.2)	229 (27.7)	
Current smoker, n (%)	172 (19.3)	247 (21.6)	0.504
SBP, mmHg	123.0 (113.0, 132.0)	134.0 (124.0, 148.0)	< 0.001
DBP, mmHg	78.0 (72.0, 85.0)	77.0 (71.0, 84.0)	0.345
BMI, kg/m^2	29.8 (26.5, 34.4)	29.8 (26.4, 33.7)	0.794
WC, cm	102.2 (93.0, 110.5)	104.5 (97.0, 113.0)	0.001
FBG, mmol/L	5.7 (5.2, 6.2)	5.7 (5.2, 6.9)	0.079
HbA1c, %	5.6 (5.2, 5.9)	5.8 (5.4, 6.3)	< 0.001
TG, mmol/L	1.8 (1.2, 2.7)	2.0 (1.4, 2.9)	0.006
HDL-C, mmol/L	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	0.404
Creatinine, umol/L	97.2 (79.6, 106.1)	97.2 (88.4, 106.1)	0.002
PLT, 10^9/L	269.5 (228.9, 320.2)	261.5 (214.5, 307.5)	0.009
ALT, U/L	21.0 (15.0, 29.0)	17.0 (12.0, 23.0)	< 0.001
AST, U/L	21.0 (18.0, 26.0)	20.0 (17.0, 25.0)	0.056
FIB-4 > 1.3, n (%)	116 (8.3)	480 (41.6)	< 0.001
TyG index	9.0 (8.6, 9.6)	9.2 (8.8, 9.6)	0.001
TyG-BMI index	271.6 (239.3, 321.1)	277.7 (242.0, 320.4)	0.344
TyG-WHtR index	5.5 (4.9, 6.2)	5.8 (5.3, 6.5)	< 0.001
TyG-WWI index	98.9 (91.0, 107.3)	105.4 (98.6, 112.2)	< 0.001
TyG-WC index	929.1 (821.6, 1039.0)	972.1 (879.6, 1083.8)	< 0.001
Overweight or obesity, n (%)	895 (88.2)	1082 (92.5)	0.029
Hypertriglyceridemia, n (%)	505 (56.5)	720 (64.3)	0.027
High blood pressure, n (%)	436 (42.8)	858 (69.9)	< 0.001
Low HDL-C, n (%)	554 (57.8)	657 (60.1)	0.580
diabetes, n(%)	299 (26.3)	597 (44.0)	< 0.001
Heart attack, n (%)	19 (1.7)	118 (10.9)	< 0.001
Antihypertensive medications, n (%)	146 (15.8)	415 (34.0)	< 0.001
Lipid-lowering medications, n (%)	32 (4.4)	84 (8.3)	0.020
Glucose-lowering medications, n (%)	57 (4.6)	165 (12.8)	< 0.001

Data are displayed as the median (interquartile range) or unweighted frequency counts (weighted percentage) as appropriate. The Mann-Whitney test for continuous variables and the chi-square test for categorical variables were used in this analysis

Association between TyG-related indices and mortality in MASLD participants with diabetes or prediabetes

During a median follow-up period of 25.4 years, 2,157 individuals with MASLD combined with prediabetes or diabetes were identified. Among them, 1,163 individuals (53.9%) died, with 329 deaths (15.3%) attributed to cardiovascular cause and 78 (3.6%) to diabetes. In unadjusted model, higher TyG index, TyG-WC index, TyG-WHtR index, and TyG-WWI index were associated with an increased risk of all-cause mortality. The associations remained stable even after adjusting for covariates in model 1, model 2, and model 3 (TyG index, adjusted hazard ratio (aHR): 1.215, $p = 0.007$; TyG-WC index, aHR: 1.001, $p < 0.001$; TyG-WHtR index, aHR: 1.265, $p < 0.001$; TyG-WWI index, aHR: 1.021, $p < 0.001$). The relationship between TyG-BMI index and all-cause mortality was not significant only in unadjusted model (HR: 1.001, $p = 0.308$). Similar results were found between TyG-related indices and cardiovascular mortality. When examing the link between TyG-related indices and diabetes mortality, higher TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI index were all associated with an increased risk of diabetes mortality (TyG-WC index, aHR: 1.006, $p < 0.001$; TyG-BMI index, aHR: 1.015, $p < 0.001$; TyG-WHtR index, aHR: 2.719, $p < 0.001$; TyG-WWI index, aHR: 1.057, $p < 0.001$). However, the relationship between TyG index and diabetes mortality was not significant in model 3 (HR: 1.573, $p = 0.058$) (Table 3).

Table 3 HRs of TyG-related indices for all-cause and cause specific mortality among individuals with MASLD and prediabetes or diabetes

	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
All-cause mortality								
TyG index	1.298 (1.134,1.485)	< 0.001	1.262 (1.105,1.440)	< 0.001	1.330 (1.152,1.536)	< 0.001	1.215 (1.054,1.401)	0.007
TyG-WC index	1.001 (1.001,1.002)	< 0.001	1.002 (1.001,1.002)	< 0.001	1.002 (1.001,1.002)	< 0.001	1.001 (1.001,1.002)	< 0.001
TyG-BMI index	1.001 (0.999,1.002)	0.308	1.003 (1.001,1.005)	0.001	1.003 (1.002,1.005)	< 0.001	1.003 (1.001,1.004)	0.002
TyG-WHtR index	1.258 (1.152,1.375)	< 0.001	1.293 (1.164,1.436)	< 0.001	1.336 (1.204,1.482)	< 0.001	1.265 (1.143,1.400)	< 0.001
TyG-WWI index	1.033 (1.022,1.044)	< 0.001	1.023 (1.015,1.032)	< 0.001	1.026 (1.017,1.035)	< 0.001	1.021 (1.011,1.030)	< 0.001
Cardiovascular mortality								
TyG index	1.476 (1.170,1.862)	0.001	1.495 (1.171,1.909)	0.001	1.575 (1.231,2.016)	< 0.001	1.316 (1.006,1.722)	0.001
TyG-WC index	1.002 (1.001,1.003)	< 0.001	1.002 (1.001,1.003)	< 0.001	1.002 (1.001,1.004)	< 0.001	1.002 (1.001,1.003)	0.002
TyG-BMI index	1.002 (1.000,1.004)	0.087	1.005 (1.002,1.008)	< 0.001	1.006 (1.003,1.009)	< 0.001	1.005 (1.001,1.008)	0.006
TyG-WHtR index	1.339 (1.165,1.539)	< 0.001	1.444 (1.201,1.737)	< 0.001	1.506 (1.247,1.819)	< 0.001	1.388 (1.118,1.722)	0.003
TyG-WWI index	1.038 (1.022,1.053)	< 0.001	1.030 (1.013,1.047)	< 0.001	1.032 (1.014,1.050)	< 0.001	1.024 (1.006,1.043)	0.009
Diabetes-specific mortality								
TyG index	1.973 (1.379,2.824)	< 0.001	2.028 (1.388,2.962)	< 0.001	2.137 (1.504,3.035)	< 0.001	1.573 (0.986,2.511)	0.058
TyG-WC index	1.005 (1.004,1.006)	< 0.001	1.006 (1.004,1.008)	< 0.001	1.007 (1.005,1.008)	< 0.001	1.006 (1.004,1.009)	< 0.001
TyG-BMI index	1.010 (1.006,1.015)	< 0.001	1.014 (1.009,1.019)	< 0.001	1.015 (1.010,1.020)	< 0.001	1.014 (1.008,1.020)	< 0.001
TyG-WHtR index	2.242 (1.816,2.768)	< 0.001	2.716 (2.164,3.409)	< 0.001	3.005 (2.423,3.725)	< 0.001	2.719 (1.917,3.858)	< 0.001
TyG-WWI index	1.063 (1.039,1.087)	< 0.001	1.067 (1.044,1.091)	< 0.001	1.072 (1.051,1.093)	< 0.001	1.057 (1.027,1.088)	< 0.001

Survey weight-adjusted multivariable cox proportional hazard models were performed for all-causes and cause-specific mortality

Model 1 was adjusted for age, sex, and ethnicity

Model 2 was adjusted for age, sex, ethnicity, family income ratio, marital status, education level, smoking status, and FIB-4

Model 3 was adjusted for age, sex, ethnicity, family income ratio, marital status, education level, smoking status, FIB-4, creatinine, heart attack, antihypertensive medications, lipid-lowering medications, and glucose-lowering medications

RCS analysis

In our study, we further investigated the potential nonlinear relationship between TyG-related indices and all-cause mortality in MASLD patients with prediabetes or diabetes using restricted cubic splines (RCS). After adjusting for age, sex, ethnicity, family income ratio, marital status, education level, smoking status, and FIB-4, We observed positive linear relationships between TyG and TyG-WWI with all-cause mortality (p for nonlinear = 0.920; $p = 0.525$, respectively). In contrast, TyG-BMI, TyG-WHtR, and TyG-WC demonstrated positive nonlinear relationships with all-cause mortality (p for nonlinear = 0.003; $p = 0.007$; $p = 0.001$, respectively) (Fig. 2).

Predictive power of TyG-related indices for all-cause and cause-specific mortality in MASLD participants with prediabetes or diabetes

Time-dependent AUC curves indicated that TyG-WWI demonstrated the strongest predictive ability for all-cause and cardiovascular mortality across various time intervals compared to other indices. However, it was less effective in predicting diabetes-related mortality (Fig. 3).

Subgroup analysis

To assess the applicability of these metrics across diverse populations, we performed subgroup analyses. The correlation between TyG, TyG-BMI, TyG-WHtR, TyG-WC, and TyG-WWI and all-cause mortality was consistent across various subgroups, including age, sex, smoking status, levels of liver fibrosis, and diabetes status (p for interaction > 0.01) (Fig. 4). Furthermore, we performed subgroup analyses focusing on MASLD women with

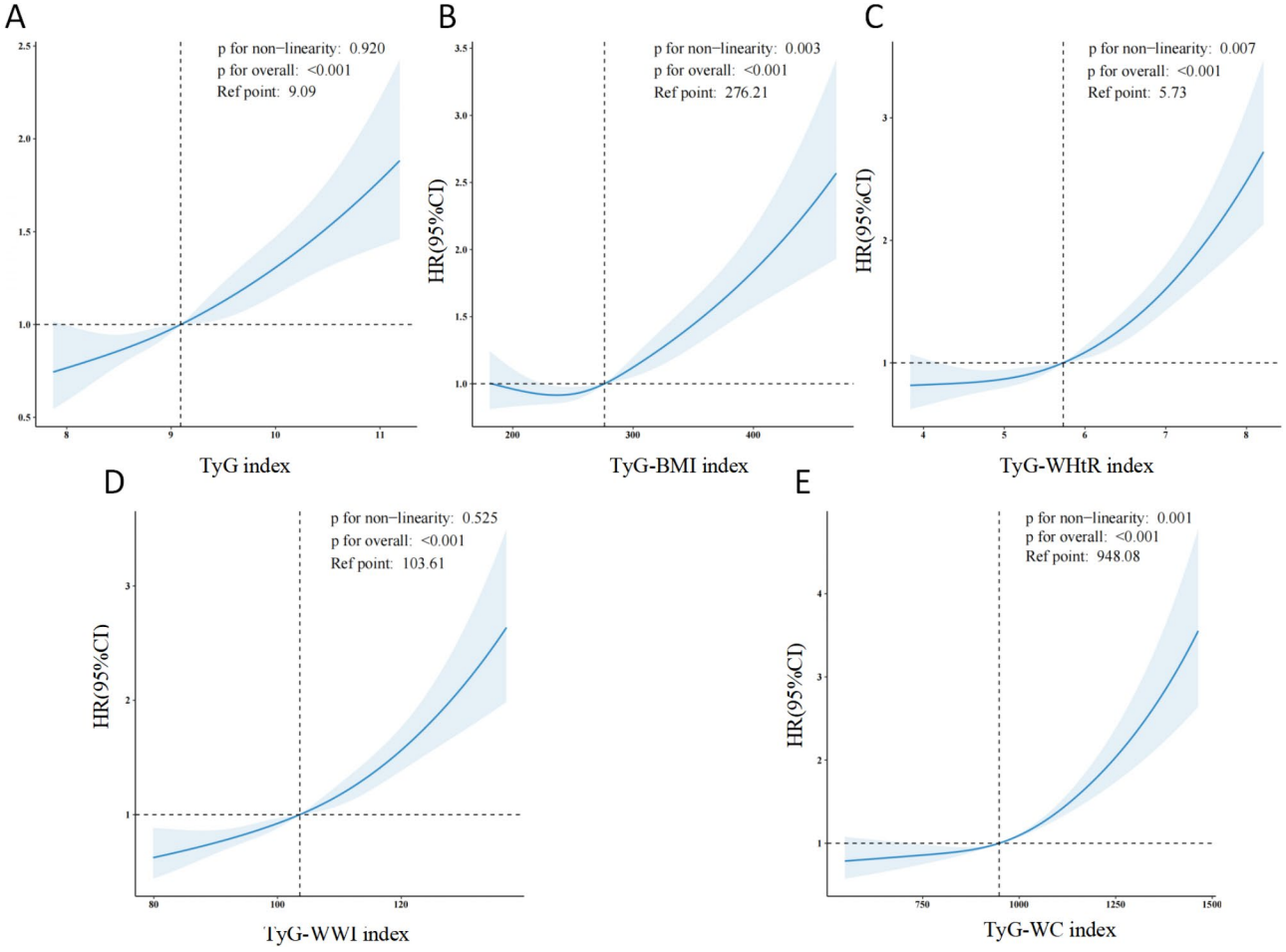

Fig. 2 RCS curves were employed to illustrate the correlation between TyG-related indices and all-cause mortality in MASLD patients with prediabetes or diabetes, adjusting for factors such as age, sex, ethnicity, family income ratio, marital status, education level, smoking, and FIB-4. **A** TyG index; **B** TyG-BMI index; **C** TyG-WHtR index; **D** TyG-WWI index; **E** TyG-WC index. Abbreviations: MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; TyG, Triglyceride-glucose; BMI, Body mass index; WHtR, Waist-height ratio; WWI, Weight-adjusted waist index; WC, waist circumference; RCS, Restricted cubic spline; FIB-4, Fibrosis-4 index.

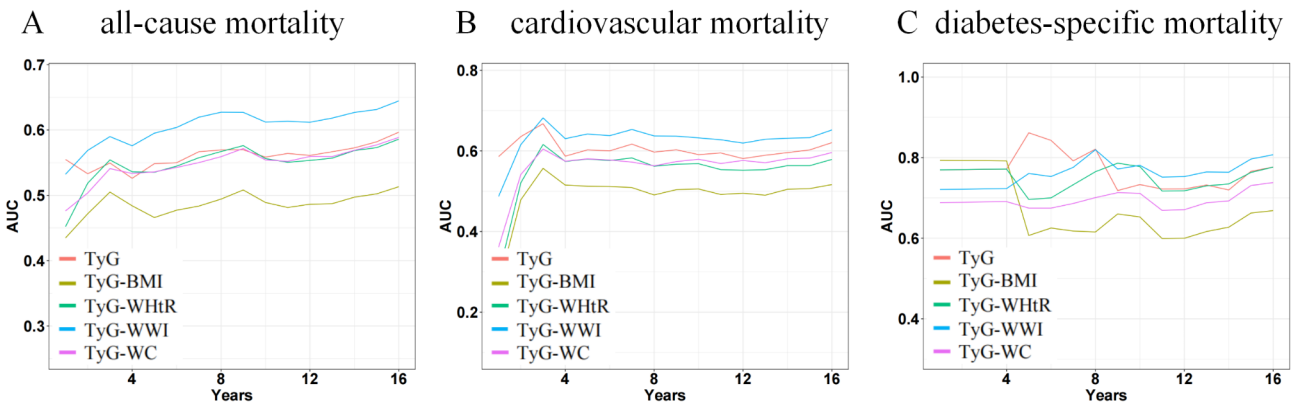

Fig. 3 Time-dependent AUC curves assessing the predictive power of the TyG correlation index for all-cause and cause-specific mortality in MASLD patients with prediabetes or diabetes. **A** All-cause mortality; **B** Cardiovascular mortality; **C** Diabetes mortality. Abbreviations: MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; AUC, Area under the curve; TyG, Triglyceride-glucose; BMI, Body mass index; WHtR, Waist-height ratio; WWI, Weight-adjusted waist index; WC, waist circumference.

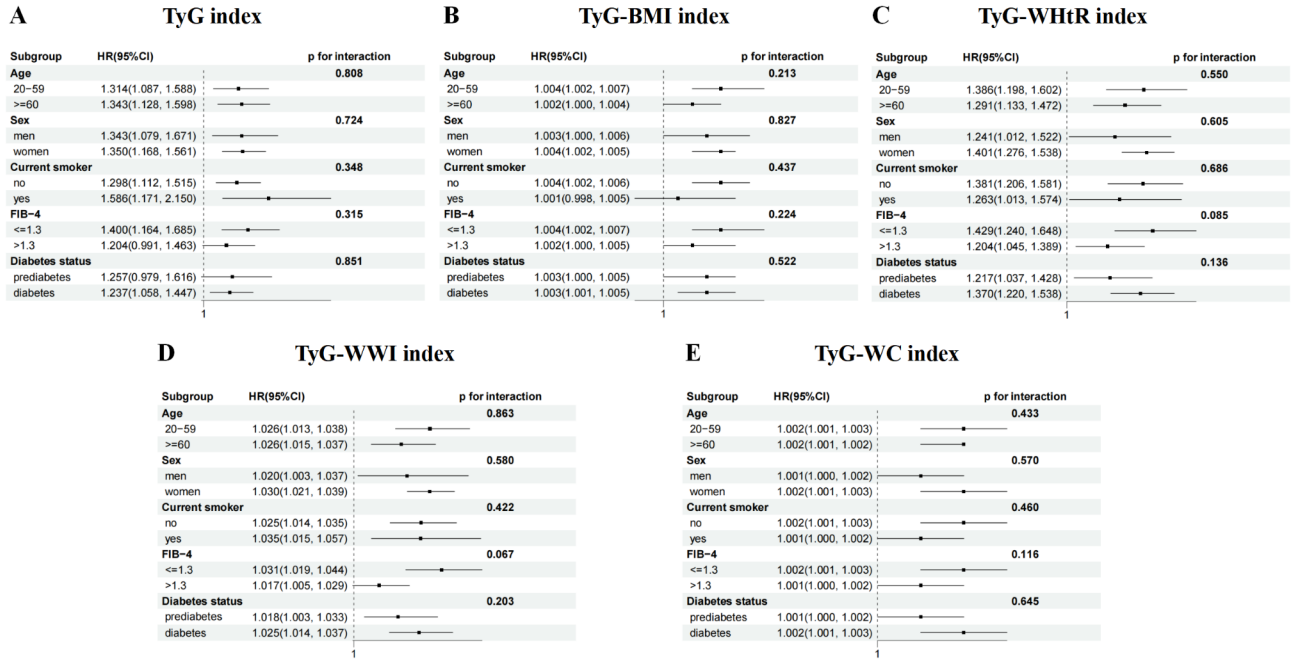

Fig. 4 Subgroup analysis of the correlation between TyG-related indices and all-cause mortality in MASLD patients with prediabetes or diabetes. **A** TyG index; **B** TyG-BMI index; **C** TyG-WHtR index; **D** TyG-WWI index; **E** TyG-WC index. Abbreviations: MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; TyG, Triglyceride-glucose; BMI, Body mass index; WHtR, Waist-height ratio; WWI, Weight-adjusted waist index; WC, waist circumference.

diabetes or prediabetes. The results showed that the effect of TyG indices on all-cause mortality was consistent across pre-menopausal and menopausal subgroups (Table S1).

Discussion

In our study, we identified significant associations between TyG-related indices and MASLD patients with prediabetes or diabetes. Elevated levels of TyG, TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI indices were closely linked to an increased risk of all-cause, cardiovascular, and diabetes-related mortality. TyG-WWI demonstrated the strongest predictive ability for all-cause and cardiovascular mortality across various intervals. These findings underscore the importance of TyG-related indices as cost-effective, early indicators for identifying individuals at risk of cardiovascular events among MASLD patients with diabetes or prediabetes.

MASLD encompassed a variety of conditions characterized by disruptions in glucose and lipid metabolism [19]. IR had been identified as a potential underlying mechanism [20]. Studies on rat models with MASLD had shown that the progression of IR was closely linked to the development of hepatic steatosis, further supporting this

theory [21]. Clinically, the TyG index served as a practical and effective indicator for assessing IR due to its simplicity and applicability [22]. IR was associated with chronic low-grade inflammation, which could, in turn, exacerbate IR and contribute to the development of type 2 diabetes, as well as other metabolic and cardiovascular conditions [23, 24]. Additionally, increased glucose and fatty acid oxidation could result in the production of reactive oxygen species (ROS). These ROS could lead to oxidative stress, which damaged cells and tissues, causing further metabolic complications [25, 26]. Recent studies had linked the TyG index to prognosis in populations with various diseases, including acute coronary syndrome, hypertension, stroke, and type 2 diabetes mellitus [27–30]. Moreover, combining the TyG index with adiposity indicators, such as TyG-BMI and TyG-WC, has demonstrated enhanced predictive performance compared to the TyG index alone [12, 13, 31, 32]. Similar to previous studies, our findings suggest that elevated levels of TyG, TyG-BMI, TyG-WHtR, and TyG-WWI indices were associated with a poorer prognosis in MASLD patients with diabetes or prediabetes, with TyG-WWI being the strongest predictor.

There appeared to be a threshold effect in the relationship between the TyG-related index and mortality risk, suggesting that both excessively high and low TyG-related levels may adversely impact health prognosis [13–16]. However, our study observed that TyG-WHtR, TyG-WC, and TyG-BMI showed similar effects, while TyG and TyG-WWI demonstrated a positive linear relationship, differing from studies that found no link between the TyG index and MASLD prognosis [14]. Previous research had established WWI as a more effective predictor of all-cause and cardiovascular mortality compared to BMI and WC [33]. In line with this finding, our results demonstrated that TyG-WWI offers the strongest predictive capability for all-cause and cardiovascular mortality across various time intervals. This could be explained by the fact that TyG-WHtR and TyG-WWI, by adjusting for height or weight, may more accurately reflect the degree of fat involvement in the disease. Additionally, this relationship might be influenced by the interplay of diabetes and other comorbid conditions.

To our knowledge, this is the first study utilizing NHANES III, the only survey with liver ultrasonography data and extended follow-up, to assess the relationship between TyG-related indices and mortality in MASLD patients with diabetes or prediabetes. We discovered that TyG-related indices provide valuable prognostic evaluations. Subgroup analyses demonstrated that TyG, TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI indices are reliable for assessing and prognosticating MASLD patients with diabetes or prediabetes across diverse demographics, including age, sex, smoking status, degrees of hepatic fibrosis, and diabetes status indicating their wide applicability. It is worth noting that for women, in addition to traditional cardiovascular disease (CVD) risk factors, some studies have reported that new risk factors, such as breast fat density, are associated with cardiovascular events independently of classical CVD risk factors in premenopausal women. However, due to the limitations of the database, our study suggests that the effect of TyG-related indices on all-cause mortality is independent of sex and menopausal status. Whether the impact of TyG-related indices on all-cause mortality is influenced by new risk factors such as breast fat density requires further investigation [34, 35].

However, the study has some limitations. Firstly, it only examined the correlation between baseline TyG and its derived indices with all-cause or cause-specific mortality, without tracking their dynamic changes or evaluating the impact of interventions on outcomes. Secondly, the study's findings, limited to a U.S. population, require validation across diverse populations to establish broader generalizability. Thirdly, the lack of data on anti-CVD medications, which are known to improve prognosis [36–38], may influence the clinical outcomes. Lastly, as with any observational study, unmeasured and unobserved confounding factors cannot be entirely ruled out. Future research could benefit from including a more comprehensive list of potential confounders to enhance the study's robustness.

Conclusion

The study revealed that elevated levels of TyG, TyG-WC, TyG-BMI, TyG-WHtR, and TyG-WWI indices were linked to a poorer prognosis for MASLD combined with prediabetes or diabetes, with TyG-WWI showing the highest predictive power. These results are significant, as they are applicable to a wider population and provide essential markers for clinicians in identifying and managing these health conditions.

Abbreviations

NAFLD	Non-Alcoholic Fatty Liver Disease
MAFLD	Metabolic Dysfunction-Associated Fatty Liver Disease
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
CMRFs	Cardiometabolic risk factors
IR	Insulin resistance
TyG	Triglyceride-glucose index
BMI	Body mass index
WHtR	Waist-height ratio
WC	Waist circumference
WWI	Weight-adjusted waist index
NHANES	National Health and Nutrition Examination Survey
NDI	National Death Index
NCHS	National Center for Health Statistics
TG	Triglycerides
FBG	Fasting blood glucose
HbA1c	Glycated hemoglobin
HCV	Hepatitis C virus
HBV	Hepatitis B virus
SLD	Steatotic liver disease

HDL-c	High-density lipoprotein cholesterol
FIB-4	Fibrosis-4 index
ALT	Aspartate aminotransferase
AST	Alanine aminotransferase
PLT	Platelet
HR	Hazard ratios
CI	Confidence intervals
RCS	Restricted cubic spline
AUC	Area under the curve
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ROS	Reactive oxygen species
CVD	Cardiovascular disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02616-9.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Yiheng Zhang and Juanli Wu: data collection, analysis and writing; Tao Li, Yundong Qu, Yan Wang: interpretation of the results and revision, review and final approval. All authors reviewed the manuscript.

Funding
No funding for this study.

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

Declarations

Ethics approval and consent to participate
NHANES was conducted with approval by the National Center for Health Statistics Ethics Review Board, and obtained informed written consent from all the individuals involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 November 2024 / Accepted: 27 January 2025
Published online: 01 February 2025

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