Cardiovascular Diabetology

RESEARCH

Open Access

Association of triglyceride glucose-related parameters with all-cause mortality and cardiovascular disease in NAFLD patients: NHANES 1999–2018

Yusha Zhang[1†], Fengjiao Wang[1†], Jianjun Tang[1], Li Shen[1], Jia He[1] and Yaqin Chen[1*]

Abstract

Background The relationship between the triglyceride-glucose (TyG) index and its derived index, the triglyceride glucose-waist height ratio (TyG-WHtR), with mortality and cardiovascular diseases (CVDs) in patients with non-alcoholic fatty liver disease (NAFLD) remains unclear.

Methods This study enrolled 6627 adults aged 18 and above diagnosed NAFLD from the National Health and Nutrition Examination Survey (NHANES, 1999–2018). Binary weighted logistic regression analyses, cox proportional hazards model and restricted cubic spline (RCS) were used to analyze the relationship between TyG and TyG-WHtR with all-cause mortality, CVD mortality and CVDs. Mediation analysis explored the mediating role of glycohemoglobin, insulin and hypertension in the above relationships. Meanwhile, the incremental predictive value of the TyG index and TyG-WHtR was further assessed.

Results Except for no significant association between the TyG index and both all-cause mortality and chronic heart failure (CHF), both TyG and TyG-WHtR exhibited significant positive correlations or trends of positive correlation with all-cause mortality, CVD mortality, total-CVD, CHF, coronary heart disease (CHD) and angina pectoris. For all-cause mortality, CVD mortality and CHF, TyG-WHtR was a better predictor than TyG (TyG-WHtR: HR 1.31, 95%CI 1.03–1.66; HR 2.22, 95%CI 1.42–3.47; OR 3.99, 95%CI 1.79–8.93). In contrast, TyG index demonstrated a stronger association with total-CVD, CHD and angina pectoris (TyG index: OR 2.00, 95%CI 1.26–3.18; OR 1.85, 95%CI 1.19–2.91; OR 2.93, 95%CI 1.23-7.00). RCS analysis showed that after adjusting for covariates, most of the aforementioned relationships were linear(P overall < 0.0001, P-nonlinear > 0.05), while the associations of the TyG index and TyG-WHtR with all-cause mortality and CHF were non-linear(P overall < 0.0001, P nonlinear < 0.05). The addition of the TyG index and TyG-WHtR to the basic model for outcomes improved the C-statistics, net reclassification improvement value, and integrated discrimination improvement value.

[†]Yusha Zhang and Fengjiao Wang contributed equally to this work.

*Correspondence:
Yaqin Chen
Aviva9903@csu.edu.cn

Full list of author information is available at the end of the article

Conclusions The predictive value of TyG or TyG-WHtR for all-cause mortality and cardiovascular risk in NAFLD patients was significant. The TyG index and TyG-WHtR might be valid predictors of cardiovascular outcomes of patients with NAFLD.

Keywords Triglyceride-glucose index, Triglyceride glucose-waist height ratio, NAFLD, All-cause mortality, Cardiovascular disease, NHANES

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a systemic metabolic disorder characterized by excessive accumulation of fat in the liver, insulin resistance (IR), and systemic inflammation [1]. Most studies have demonstrated a robust correlation between NAFLD and cardiovascular disease (CVD) [2]. NAFLD is closely associated with an increased risk of major cardiovascular events and cardiac complications, independent of traditional cardiovascular risk factors [3]. Nowadays, numerous models have been developed to predict the risk of CVD in individuals with NAFLD. However, the practicability of most prediction models remains to be confirmed, given the absence of external validation and simulated impact studies [4]. Therefore, reliable indicators for predicting mortality risk and CVD in NAFLD patients are still lacking in clinical practice.

IR refers to the reduced sensitivity of target tissues to normal circulating levels of insulin. This results in ineffective glucose transport into target cells, which in turn leads to the development of metabolic abnormalities such as hyperglycemia [5]. IR is associated with the onset and prognosis of diverse CVDs. A 12-year follow-up cohort study demonstrated a positive correlation between fasting insulin levels and adverse echocardiographic characteristics, as well as an increased risk of heart failure (HF) in patients who had not previously suffered from myocardial infarction or HF [6].

The triglyceride-glucose (TyG) index, derived from the levels of triglycerides (TG) and fasting blood glucose (FBG), serves as a valuable assessment tool for evaluating insulin sensitivity. Although the hyperinsulinemic-euglycemic clamp test remains the gold standard for measuring IR, TyG index have exhibited higher sensitivity and specificity in identifying IR [7, 8]. Moreover, recent studies have highlighted the importance of TyG index as a biomarker for predicting the risk and prognosis of various CVD, including decompensated HF, stroke, and coronary artery disease [9–11].

Obesity is frequently accompanied by hypertension and abnormal lipid metabolism, which significantly increases the risk of developing CVD. Additionally, central obesity can serve as a key indicator for assessing the risk of various obesity-related chronic diseases [12–14]. The indicators for measuring central obesity include waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). However, since WC can not reflect internal fat distribution and measuring hip circumference for calculating WHR is often challenging, WHtR offers a more direct and straightforward method for assessing central obesity and internal fat content [15]. Researches indicate that TyG and TyG-WHtR are superior to other TyG-related parameters in predicting the risk of NAFLD in general populations [16, 17]. And TyG-WHtR was superior to the TyG index alone in identifying the risk of early diabetes [18, 19] and predicting CVD-related mortality [5]. However, there is currently a deficiency in comparative studies on the correlation between TyG and TyG-obesity index with CVD in patients with NAFLD. This study aims to analyze the association between the TyG index and its combined obesity index, TyG-WHtR, and all-cause mortality, CVD mortality, total CVD, congestive heart failure (CHF), coronary heart disease (CHD) and angina pectoris.

Method

Study population

National Health and Nutrition Examination Survey (NHANES) is a national survey of children and adults in the United States. Data of NHANES were collected through personal structured interviews at home, health examinations at a mobile examination center, and specimen analyses in the laboratory (https://www.cdc.gov/nchs/nhanes/index.html). 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.

We enrolled adult participants aged 18 years and older with NAFLD who underwent mobile examinations from NHANES 1999–2018, which provided comprehensive data for blood and physical measurements. NAFLD was defined by a US fatty liver index (USFLI) of 30 or higher, a well-established definition with an area under the receiver operating characteristic curve (AUROC) of 0.80 (95% CI: 0.77–0.83) in predicting ultrasound-confirmed NAFLD [20]. The following groups of patients were excluded from the study: (1) excessive alcohol consumption (>3 drinks per day for the male and >2 drinks per day for the female); (2) participants with hepatitis B (positive hepatitis B surface antigen) or hepatitis C infection (positive hepatitis C antibody or HCV RNA); (3) pregnant women; (4) use of steatogenic medication for more than 90 days (such as amiodarone, corticosteroids,

methotrexate, valproate and tamoxifen). The patient selection process is illustrated in Fig. 1.

Data collection

Demographic, physical examination, laboratory blood test, and medical history data of participants were collected. (1) Demographic data included age, gender, race, education level, smoking status, drinking status and income -poverty ratio (PIR). Race was divided into five sections of Mexican America, non-Hispanic white, non-Hispanic black, other Hispainc and other. Educational levels were classified as less than high school, high school or equivalent, and college or above. PIR are divided into 0–1.3, 1.31–3.5, or >3.5. Smoking status was defined as never smoker, former smoker and current smoker. Drinking status was recorded as non-drinkers, mild to moderate drinkers. (2) Physical examination included BMI, systolic blood pressure (SBP), weight, height, and WC. BMI was calculated as weight in kilograms divided by height in meters squared. SBP is calculated as the average of four measurements. (3) Clinical indicators such as aspartate aminotransferase (ALT), alanine aminotransferase (AST), gamma-glutamyltransferase (GGT), TG, total cholesterol (TC), FBG and glycohemoglobin (HbA1c) were collected. (4) Medical history included diabetes, hypertension and family history of heart disease. The definition of diabetes was self-reported diagnosis, use of insulin or oral hypoglycemic agents, fasting glucose≥7 mmol/L, or HbA1c≥6.5%. The definition of hypertension was self-reported diagnosis or based on multiple measurements, the average SBP≥140 mmHg, and the average diastolic blood pressure≥90 mmHg. Family history of heart disease was established by self-reported physician diagnoses using a standardized medical condition

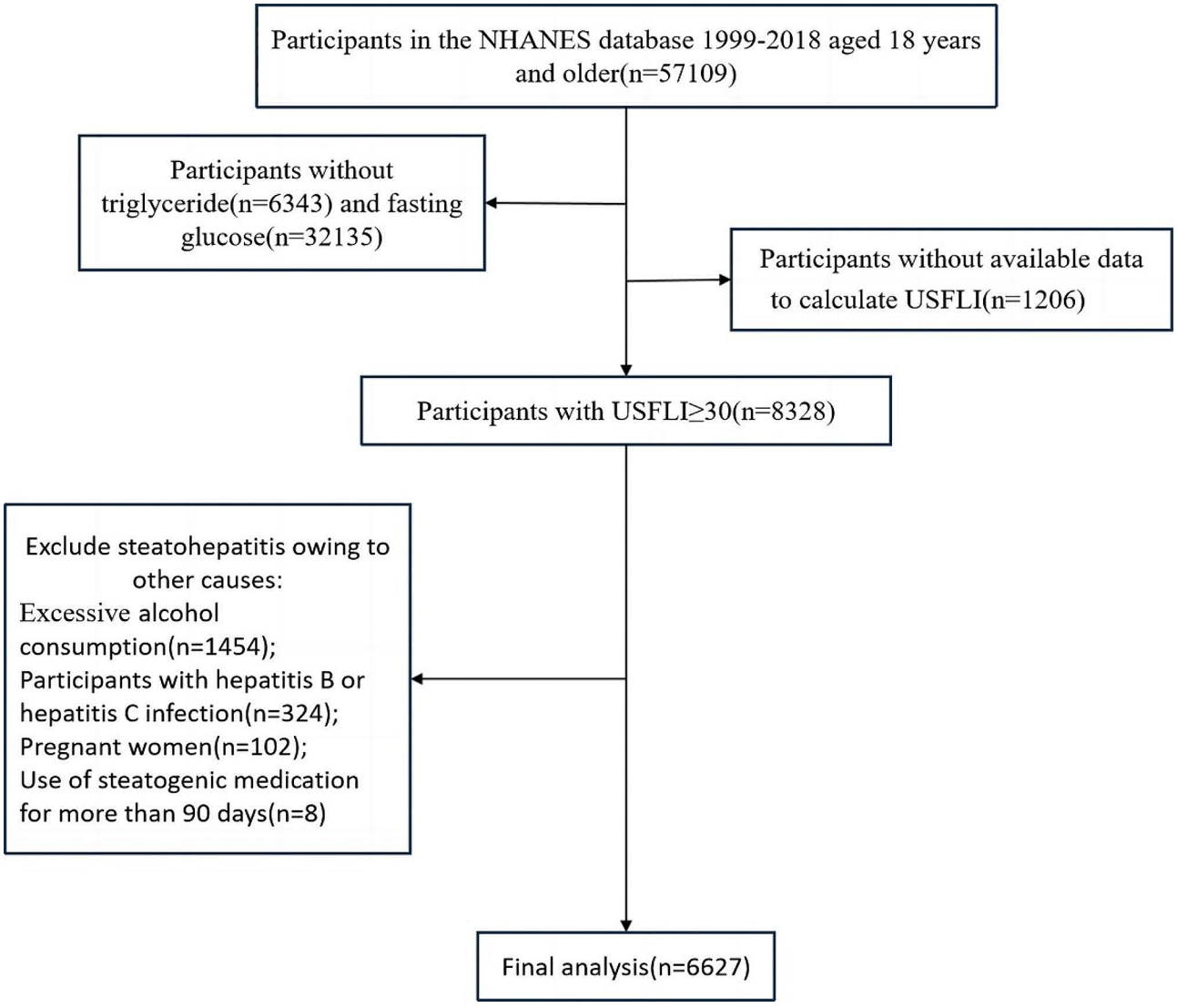

Fig. 1 Flowchart depicting the selection of participants

questionnaire. The participants were asked: "Close relative had heart attack?" or "Blood relative w/hypertension/stroke?" or "Blood relatives have angina" and answered by yes or no.

Assessment of TyG index and TyG-WHtR

The TyG index was calculated as Ln [fasting TG (mg/dL) × fasting glucose (mg/dL)/2]. TyG-WHtR = TyG × WC/height. The participants were classifed into four groups (Q1, Q2, Q3, Q4) by the quartiles of TyG index or TyG-WHtR, and the Q1 group was used as the reference group.

Outcome definitions

We linked the National Death Index (NDI) from the National Center for Health Statistics (NCHS) to obtain the survival status of the participants. Moreover, we utilized the International Statistical Classification of Diseases, 10th Revision (ICD-10) to identify disease-specific deaths, with the NCHS categorizing heart diseases (ICD-10 codes 054–064), malignant neoplasms (ICD-10 codes 019–043), and all other causes (ICD-10 code 010) for our study.

The diagnosis of CVD was established by self-reported physician diagnoses using a standardized medical condition questionnaire. The participants were asked, "Has a doctor or other health professional ever told [you/SP] that [you/s/he]…had congestive heart failure/coronary heart disease/angina pectoris?" A person was considered to have CVD if they answered "yes" to any of the aforementioned questions.

Statistical analysis

Due to the intricate sampling design of NHANES, our analyses incorporated sample weights, clustering, and stratification to fulfill the necessary criteria for analyzing NHANES data. Study population characteristics were stratified into four groups based on quartiles (Q1-Q4) of the TyG index or TyG-WHtR. Baseline characteristics were presented as median (25th-75th percentile) for continuous variables and as number (percentage) for categorical variables. The four groups were compared using analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the $\chi 2$ test for categorical variables.

Three models were established with incremental degrees of adjustment for potential confounders of outcome: crude was unadjusted, model 1 was adjusted for age, gender and race, model 2 was adjusted for age, gender, race, smoke, education, PIR, SBP, TC, family history of heart disease and diabetes. To evaluate the independent predictive value of the TyG index and TyG-WHtR, we established multivariable Cox proportional hazards regression models and binary weighted logistic regression models. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs for the association between TyG index and TyG-WHtR and all-cause mortality and CVD mortality. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between TyG index and TyG-WHtR and total-CVD, CHF, CHD and angina pectoris. Furthermore, linear trends between TyG and TyG-WHtR quartiles were evaluated using the median value within each quartile as a continuous variable.

To determine whether there was a nonlinear dose-response relationship of the TyG index and TyG-WHtR with the risk of mortality and CVD after multivariable-adjustment, restricted cubic splines (RCS)were fitted, with four knots placed at the 5th, 35th, 65th, and 95th percentiles and the 1% highest and lowest TyG index and TyG-WHtR observations were trimmed. Mediation analyses were used to investigate whether the relevance of TyG and TyG-WHtR to all-cause/ CVD mortality or CVD could be explained by HbA1c, insulin or hypertension after adjusting for covariates in the primary analysis model 2. Stratified analysis was carried out for significant covariates, considering potential effect modifiers such as age, gender, race, PIR, smoke, drink, education, SBP, HbA1c and diabetes. In addition, to evaluate the incremental predictive performance of outcomes following the addition of the TyG index and TyG-WHtR to the basic model, we used the C statistic, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).The statistical analysis was performed using R software (version 4.3.2), and statistical significance was determined using a two-tailed P value of 0.05.

Results

Demographic and clinical characteristics in NAFLD and NAFLD with all-cause mortality/CVD mortality/CVD groups

Demographic and clinical characteristics of NAFLD patients and NAFLD with all-cause mortality/CVD mortality/CVD patients were compared in Table 1 and Table S1. Compared with NAFLD patients, NAFLD with all-cause mortality/ CVD mortality/CVD patients tended to be older, male, non-Hispanic white, middle-PIR, smoker, non-drinker and had a family history of CVD. Meanwhile, these groups showed higher levels of SBP, FBG, HbA1c, TyG index and TyG-WHtR and lower levels of BMI, ALT/AST and TC. Interestingly, NAFLD patients with CVD were more likely to be observed in those with a history of diabetes. Conversely, the incidence of all-cause mortality and CVD mortality events in NAFLD patients tended to be higher among those without a history of diabetes.

Table 1 Characteristics of NAFLD patients by the presence of all-cause mortality and CVD mortality

	All-cause mortality			CVD mortality		
	NAFLD *N* = 5283	All-cause mortality + NAFLD *N* = 1335	P Value[2]	NAFLD *N* = 5274	CVD mortality + NAFLD *N* = 459	P Value[1]
Age, year	53(40,64)	72(64,79)	< 0.001	53(40,64)	73(64,80)	< 0.001
Gender, n (%)			< 0.001			0.001
Female	2,580(49)	544(41)		2,576(49)	188(41)	
Male	2,703(51)	791(59)		2,698(51)	271(59)	
Race, n (%)			< 0.001			< 0.001
Mexican America	1,029(19)	206(15)		1,026(19)	69(15)	
Other Hispainc	507(9.6)	62(4.6)		507(9.6)	23(5.0)	
Non-Hispanic white	2,097(40)	784(59)		2,094(40)	263(57)	
Non-Hispanic black	1,231(23)	242(18)		1,230(23)	90(20)	
Other	419(7.9)	41(3.1)		417(7.9)	14(3.1)	
Education, n (%)			< 0.001			< 0.001
Less than high school	1,498(28)	563(42)		1,496(28)	187(41)	
High school or equivalent	1,204(23)	323(24)		1,204(23)	109(24)	
College or above	2,579(49)	446(33)		2,572(49)	163(36)	
Family poverty income ratio, n (%)			< 0.001			< 0.001
≤ 1.3	1,406(30)	421(35)		1,403(30)	135(32)	
1.31–3.5	1,816(38)	535(44)		1,814(38)	199(47)	
> 3.5	1,541(32)	247(21)		1,537(32)	88(21)	
Smoke, n (%)			< 0.001			0.003
Never	95(4.2)	30(3.7)		94(4.2)	13(5.0)	
Former	730(33)	197(25)		729(33)	58(22)	
Now	1,416(63)	574(72)		1,416(63)	189(73)	
Drink, n (%)			< 0.001			< 0.001
Never	2,549(48)	790(59)		2,548(48)	263(57)	
Mild-Moderate	2,734(52)	545(41)		2,726(52)	196(43)	
BMI, kg/m^2	33(29,38)	31(27,35)	< 0.001	33(29,38)	31(27,35)	< 0.001
Systolic blood pressure, mmHg	125(116,137)	133(121,148)	< 0.001	125(116,137)	135(122,153)	< 0.001
ALT/AST	1.07(0.89,1.30)	0.92(0.77,1.10)	< 0.001	1.07(0.89,1.30)	0.92(0.78,1.11)	< 0.001
GGT, U/L	28(20,42)	28(20,45)	0.12	28(20,42)	28(20,46)	0.3
TG, mg/dl	140(99,199)	140(98,205)	0.6	140(99,199)	143(100,213)	0.054
Total cholesterol, mg/dl	193(167,222)	188(161,220)	< 0.001	193(167,222)	187(162,224)	0.12
Fasting Glucose, mg/dl	102(94,118)	111(98,142)	< 0.001	102(94,118)	113(98,150)	< 0.001
Glycohemoglobin, %	5.70(5.40,6.30)	6.00(5.60,6.80)	< 0.001	5.70(5.40,6.30)	6.00(5.60,7.00)	< 0.001
Diabetes, n (%)	1,694(32)	647(48)	< 0.001	1,688(32)	228(50)	< 0.001
Family history of heart disease, n (%)	991(20)	281(22)	0.038	990(20)	101(23)	0.072
TyG	8.98(8.59,9.39)	9.05(8.65,9.52)	< 0.001	8.98(8.59,9.39)	9.11(8.71,9.61)	< 0.001
TyG-WHtR	5.93(5.41,6.55)	5.97(5.47,6.57)	0.2	5.93(5.41,6.55)	6.06(5.57,6.62)	0.004

Median(IQR) for continuous; n() for categorical

[1]Wilcoxon rank sum test; Pearson's Chi-squared test

Characteristics of NAFLD patients based on the quartile of TyG index and TyG-WHtR

To characterize the baseline traits of NAFLD patients across different TyG and TyG-WHtR levels, we categorized them into four quartiles(Q) according to the TyG and TyG-WHtR values (TyG index: Q1 ≤ 8.60, Q2:8.60-9.00, Q3:9.00-9.42, Q4 > 9.42; TyG-WHtR: Q1 ≤ 5.42, Q2:5.42–5.94, Q3: 5.94–6.55, Q4 > 6.55). The mean TyG index and TyG-WHtR in the enrolled patients was 9.05 ± 0.71 and 6.03 ± 0.90. The characteristics of the NAFLD patients according to quartiles of TyG and TyG-WHtR are shown in Table 2 and Table S2.

Patients with higher TyG index are likely to be older, male, non-Hispanic white, middle-PIR, non-drinker, and to be higher SBP, GGT, TG, TC, FBG, HbA1c and lower BMI. Meanwhile, they also exhibited higher rates of all-cause mortality, CVD mortality, diabetes, total-CVD, CHF, CHD and angina pectoris events. Participants with higher TyG-WHtR tended to be female, non-Hispanic white, middle-PIR, smoker, and to have higher BMI, SBP, TG, TC, FBG, HbA1c and lower GGT. And higher

Table 2 Baseline characteristics according to TyG index quartiles

	TyG				P Value[1]
	Q1(≤ 8.60)	Q2(8.60-9.00)	Q3(9.00-9.42)	Q4(>9.42)	
Age, year	54(37,67)	57(42,69)	60(46,70)	59(46,68)	< 0.001
Gender, n (%)					0.004
Female	820(49)	792(47)	799(48)	715(44)	
Male	837(51)	877(53)	853(52)	928(56)	
Race, n (%)					< 0.001
Mexican America	210(13)	308(18)	324(20)	393(24)	
Other Hispainc	113(6.8)	143(8.6)	160(9.7)	152(9.3)	
Non-Hispanic white	555(33)	744(45)	803(49)	778(47)	
Non-Hispanic black	691(42)	348(21)	249(15)	186(11)	
Other	88(5.3)	126(7.5)	116(7.0)	134(8.2)	
Education, n (%)					< 0.001
Less than high school	442(27)	482(29)	554(34)	581(35)	
High school or equivalent	390(24)	373(22)	389(24)	376(23)	
College or above	825(50)	812(49)	706(43)	686(42)	
Family poverty income ratio, n (%)					0.003
≤ 1.3	430(28)	446(30)	441(30)	508(34)	
1.31–3.5	609(40)	578(38)	592(40)	574(39)	
> 3.5	476(31)	486(32)	430(29)	395(27)	
Smoke, n (%)					0.6
Never	27(4.0)	34(4.5)	34(4.5)	30(3.5)	
Former	215(32)	222(29)	218(29)	273(32)	
Now	428(64)	503(66)	510(67)	549(64)	
Drink, n (%)					0.009
Never	792(48)	822(49)	850(51)	876(53)	
Mild-Moderate	865(52)	847(51)	802(49)	767(47)	
BMI, kg/m^2	33(29,38)	33(29,37)	32(29,37)	32(29,36)	< 0.001
Systolic blood pressure, mmHg	125(115,137)	125(116,137)	127(117,140)	129(120,142)	< 0.001
ALT/AST	1.00(0.83,1.19)	1.04(0.85,1.24)	1.04(0.86,1.27)	1.09(0.90,1.32)	< 0.001
GGT, U/L	25(19,38)	26(19,38)	28(20,42)	32(23,52)	< 0.001
TG, mg/dl	79(66,93)	124(109,139)	172(149,196)	264(210,344)	< 0.001
Total cholesterol, mg/dl	180(154,206)	189(165,217)	196(168,224)	207(179,239)	< 0.001
Fasting Glucose, mg/dl	97(90,105)	101(94,112)	105(96,123)	129(103,192)	< 0.001
Glycohemoglobin, %	5.60(5.30,5.90)	5.70(5.40,6.10)	5.80(5.50,6.30)	6.40(5.70,8.10)	< 0.001
Diabetes, n (%)	289(17)	427(26)	621(38)	1,003(61)	< 0.001
Family history of heart disease, n (%)	1,254(81)	1,252(79)	1,249(80)	1,220(79)	0.5
All-cause mortality, n (%)	295(18)	322(19)	329(20)	387(24)	< 0.001
CVD mortality, n (%)	87(6.0)	103(7.1)	122(8.5)	147(11)	< 0.001
Total-CVD, n (%)	176(11)	224(14)	252(16)	301(19)	< 0.001
CHF, n (%)	75(4.7)	80(4.9)	98(6.1)	126(7.8)	< 0.001
CHD, n (%)	88(5.5)	102(6.3)	116(7.2)	154(9.5)	< 0.001
Angina pectoris, n (%)	48(3.0)	81(5.0)	90(5.5)	114(7.0)	< 0.001

Median(IQR) for continuous; n() for categorical

CVD mortality, Cardiovascular mortality; Total-CVD, Total cardiovascular disease; CHF, Congestive heart failure; CHD, Coronary heart disease

[1]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

TyG-WHtR groups demonstrated elevated rates of CVD mortality, diabetes, total-CVD, CHF, CHD and angina pectoris events.

Associations of TyG index and TyG-WHtR with all-cause mortality/CVD mortality/total-CVD/CHF/CHD/angina pectoris

Figure 2 illustrates the relationship of TyG and TyG-WHtR with mortality and cardiovascular disease (CVD). Detailed information on all the aforementioned associations is available in Table S3-S8. After adjusting for age, gender, race, smoke, education, PIR, SBP, TC, family history of heart disease and diabetes in Model 2, the results showed that except for no significant association between TyG and all-cause mortality and CHF, both TyG and TyG-WHtR exhibited significant positive correlations or trends of positive correlation with all-cause mortality, CVD mortality, total-CVD, CHF, CHD and angina pectoris incidence. (p trend < 0.05, TyG-CVD mortality: p trend = 0.07, TyG- angina pectoris: p trend = 0.078)

For all-cause mortality, CVD mortality and CHF, TyG-WHtR had higher predictive power (HR:1.31, 95%CI 1.03–1.66; HR:2.22, 95%CI 1.42–3.47; OR:3.99, 95%CI 1.79–8.93). And TyG index demonstrated a stronger association with total-CVD, CHD and angina pectoris (OR:2.00, 95%CI 1.26–3.18; OR:1.85, 95%CI 1.19–2.91; OR:2.93, 95%CI 1.23-7.00).

Using RCS analysis to explore the relationship between TyG and TyG-WHtR, and all-cause mortality/CVD mortality/Total-CVD/CHF/CHD and angina pectoris

Figure 3 shows the association between TyG, TyG-WHtR, and all-cause mortality, CVD mortality, total-CVD, CHF, CHD and angina pectoris using RCS analysis. After adjusting for all covariates in the master analytical model 2 above, a linear correlation was observed between TyG, TyG-WHtR and CVD mortality, total-CVD, CHD and angina pectoris (P-overall < 0.0001, P-nonlinear > 0.05). In contrast, TyG and TyG-WHtR showed nonlinear associations with all-cause mortality and CHF (P-overall < 0.0001, P-nonlinear < 0.05). Therefore, it is evident that both excessively high and low levels of TyG and TyG-WHtR increase the risk of all-cause mortality and the incidence of CHF in NAFLD patients.

Mediation analysis of TyG, TyG-WHtR and all-cause mortality, CVD mortality, total-CVD, CHF, CHD and angina pectoris

Mediation analyses indicated that HbA1c, insulin, and hypertension indirectly mediated the associations between TyG, TyG-WHtR and all-cause mortality, CVD mortality, total CVD, CHF, CHD and angina pectoris (Fig. S1). For TyG, the HbA1c-mediated indirect effects of CVD mortality, total-CVD, and CHD accounted for 40.9, 25.5, and 26.1%, respectively; for TyG-WHtR, the HbA1c-mediated effects of all-cause mortality, total-CVD, CHF, CHD and angina pectoris were −76.7, 26.3, 9.9, 59.8, and 32.5%, respectively. The indirect effects of the insulin-mediated association of TyG with all-cause mortality, CVD mortality, total-CVD, CHF, and CHD accounted for 9.9, 2.9, 0.4, 5.6 and 2.6%, respectively. The indirect effects of the insulin-mediated association of TyG-WHtR with all-cause mortality, total-CVD, CHF, and CHD accounted for −18.9, 7.5, 5.6, and 11.7%, respectively.

For TyG, the hypertension-mediated indirect effects of all-cause mortality, CVD mortality, total-CVD, CHF, CHD and angina pectoris accounted for 7.8, 0.8, 7.8, 9.1, 4.9 and 7.7%, respectively. The percentages of indirect effects for the association between hypertension-mediated TyG-WHtR and all-cause mortality, total-CVD, CHF, CHD, and angina pectoris were −15.7, 7.3, 15.4, 23.3 and 20.1%, respectively.

Stratification of TyG, TyG-WHtR in relation to all-cause mortality, CVD mortality, total-CVD, CHF, CHD and angina pectoris. angina pectoris, and coronary heart disease

After controlling for variables, stratified analyses based on age, gender, PIR, race, smoking, drinking, education, SBP, HbA1c, and diabetes (Table S9-S20)indicated that significant associations of TyG with total-CVD events, and TyG-WHtR with CVD mortality, and CHF were more frequently observed in individuals aged < 60 years; Significant correlations of TyG-WHtR with total-CVD events, CHF, and angina pectoris were more likely to be observed in individuals with HbA1c ≥ 6.5; In addition, the significance of TyG with total-CVD events was more frequent in individuals without diabetes, whereas the significance of TyG-WHtR with angina pectoris was more frequent in individuals with diabetes.

Incremental predictive value of TyG index and TyG-WHtR

The incremental predictive values of the TyG index and TyG-WHtR for all-cause mortality, CVD mortality, and the mentioned CVDs are summarized in Table 3. The addition of the TyG index and TyG-WHtR significantly improved the C-statistics of the base model (except for the added TyG index for CHF, all others $p < 0.05$). Moreover, the improvement capabilities of the TyG and TyG-WHtR are comparable (Fig. 4; Table 3). Additionally, risk reclassification and discriminative power also improved for most outcomes after the inclusion of these two indices in the base model.

Discussion

Our analysis showed that except for no significant association between TyG and CVD mortality and CHF, both TyG and TyG-WHtR were positively associated with all-cause mortality, CVD mortality, total-CVD, CHF, CHD

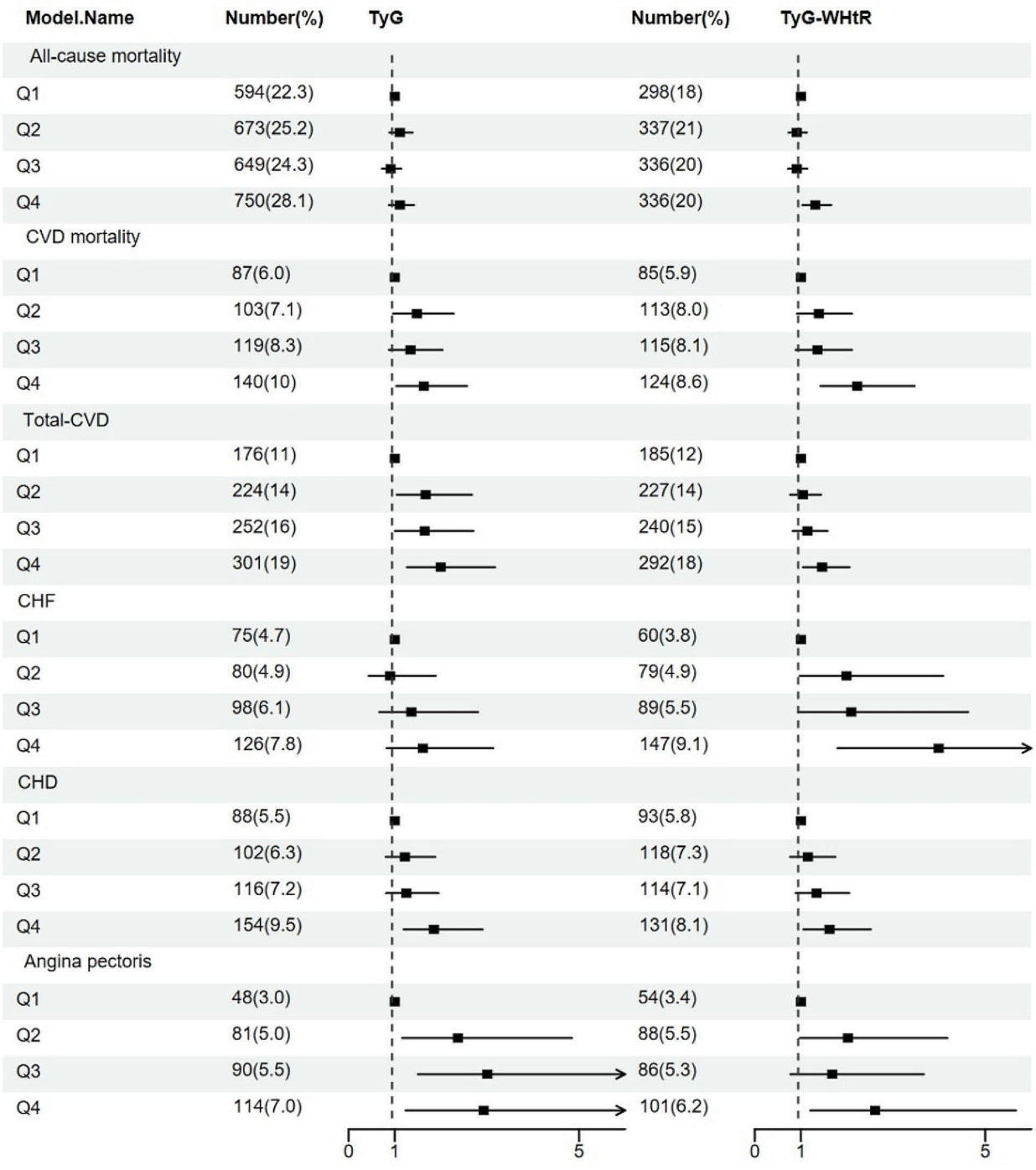

Fig. 2 Forest plot of the TyG index and TyG-WHtR association with all-cause mortality, CVD mortality, total-CVD, congestive heart failure, coronary heart disease and angina pectoris

and angina pectoris ($P<0.05$). In particular, TyG showed a better correlation with total-CVD, CHD, and angina, whereas TyG-WHtR showed a higher association with all-cause mortality, CVD mortality and CHF.

The TyG index has a high sensitivity and specificity in detecting IR [8, 21]. The reason for TyG index to effectively predict IR may be that glucotoxicity and lipotoxicity are key mechanisms to mediate IR [21]. After adjusting for covariates, our study showed that TyG and TyG-WHtR were significantly and positively associated with all-cause mortality, CVD mortality, total-CVD, CHF, angina pectoris, and CHD. RCS analysis showed that most of the aforementioned associations were linear after adjustment for all covariates. However, in patients

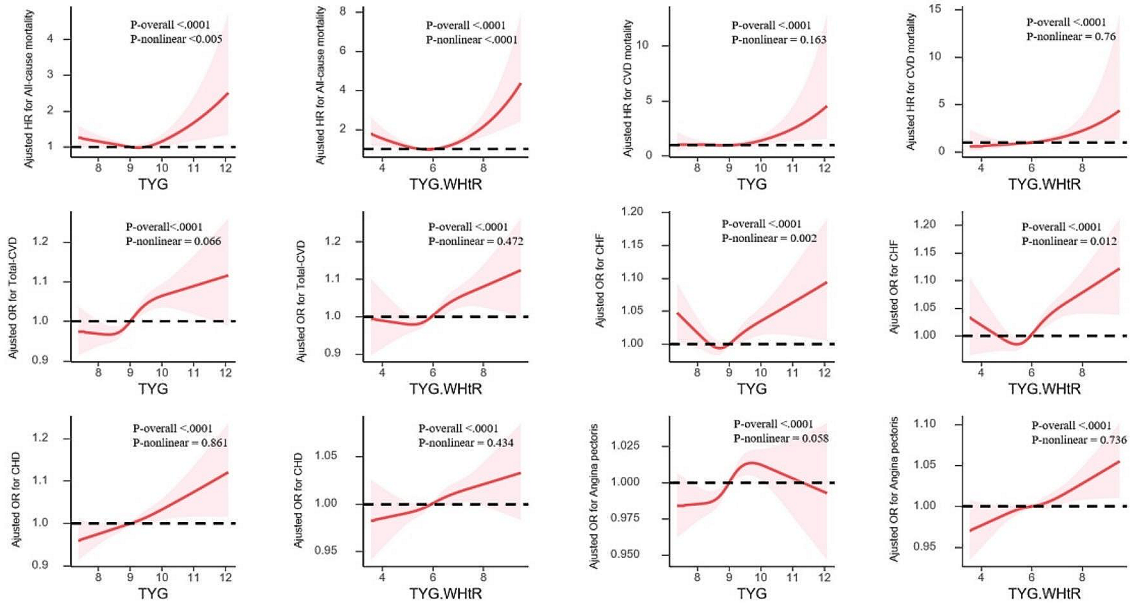

Fig. 3 Associations between TyG and TyG-WHtR with all-cause mortality, CVD mortality, total-CVD, congestive heart failure, coronary heart disease and angina pectoris were evaluated by RCS after adjustment for the covariables

Table 3 Incremental predictive value of the cumulative TyG index

	C-statistic (95%CI)	*P* value	Continunous NRI (95%CI)	*P* value	IDI(95%CI)	*P* value
All-cause mortality						
Basic model	0.810(0.798–0.821)		ref		ref	
Basic model + TyG	0.812(0.800-0.823)	0.004	0.267(-0.011-0.462)	0.054	0.020(-0.024-0.046)	0.07
Basic model + TyG-WHtR	0.810(0.790–0.825)	0.01	0.185(-0.093-0.40	0.08	0.005(-0.001-0.014)	0.08
CVD mortality						
Basic model	0.812(0.800-0.824)		ref		ref	
Basic model + TyG	0.813(0.802–0.825)	0.01	0.142(-0.277-0.375)	0.18	0.003(-0.006-0.015)	0.26
Basic model + TyG-WHtR	0.814(0.802–0.826)	0.02	0.127(0.022–0.195)	0.01	0.005(0.001–0.011)	0.01
Total-CVD						
Basic model	0.749(0.725–0.770)		ref		ref	
Basic model + TyG	0.766(0.744–0.788)	< 0.001	0.162(0.094–0.230)	< 0.001	0.002(0.0006–0.004)	0.008
Basic model + TyG-WHtR	0.767(0.745–0.789)	< 0.001	0.190(0.122–0.259)	< 0.001	0.004(0.001–0.006)	0.001
CHF						
Basic model	0.736(0.705–0.769)		ref		ref	
Basic model + TyG	0.750(0.718–0.782)	0.08	0.173(0.071–0.276)	< 0.001	0.007(-0.005-0.002)	0.23
Basic model + TyG-WHtR	0.764(0.731–0.796)	0.01	0.311(0.208–0.414)	< 0.001	0.008((0.003–0.012)	< 0.001
CHD						
Basic model	0.755(0.724–0.784)		ref		ref	
Basic model + TyG	0.775(0.746–0.803)	0.003	0.235(0.142–0.329)	< 0.001	0.005(0.002–0.007)	0.003
Basic model + TyG-WHtR	0.772(0.724–0.784)	0.005	0.170(0.077–0.265)	< 0.001	0.002(0.0004–0.004)	0.04
Angina pectoris						
Basic model	0.710(0.665–0.739)		ref		ref	
Basic model + TyG	0.733(0.698–0.767)	0.019	0.149(0.040–0.259)	0.007	0.002(0.0001–0.003)	0.04
Basic model + TyG-WHtR	0.735(0.700-0.769)	0.02	0.129(0.020–0.239)	0.02	0.002(0.0003–0.004)	0.02

The conventional model was adjusted for age, gender, race, smoke, education, income-poverty ratio, systolic blood pressure, total cholesterol, family history of heart disease and diabetes

CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improve; CVD mortality, cardiovascular mortality; CHF, chronic heart failure; CHD, coronary heart disease

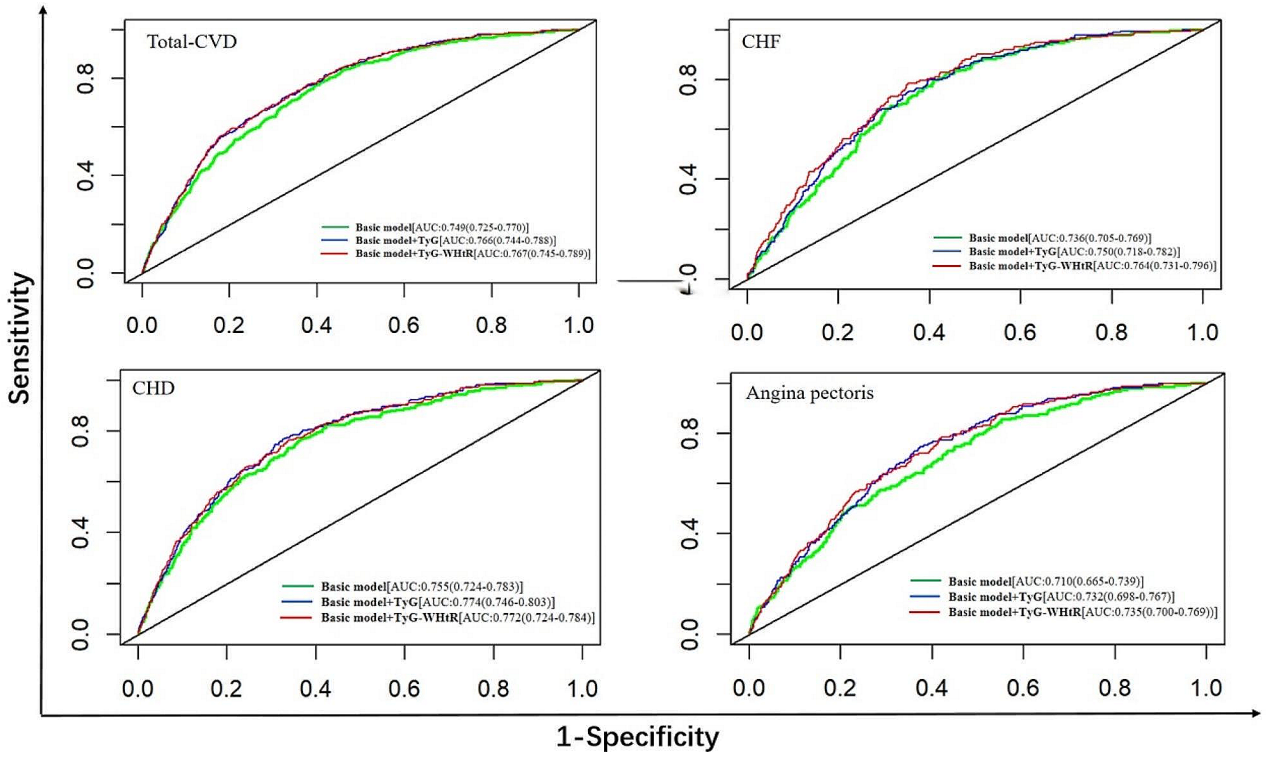

Fig. 4 ROC Curve analysis for TyG index and TyG-WHtR predicted total-CVD, congestive heart failure, coronary heart disease and angina pectoris

with NAFLD, TyG and TyG-WHtR were nonlinearly correlated with all-cause mortality and CHF, indicating that both excessively high and low levels of TyG and TyG-WHtR increase the risk for these outcomes. The nonlinear relationship between TyG and all-cause mortality is consistent with the findings of the previous studies [22]. This may be related to excessively high or low IR, inflammatory response, oxidative stress and vascular endothelial function [5]. Meanwhile, TyG and TyG-WHtR exhibit non-linear correlations in patients with NAFLD and CHF, which may be attributed to the complexity of the disease, the parameter settings of the RCS curves in statistical analyses, and the choice of statistical model [10, 23–25].

NAFLD is defined as excessive fat accumulation in the liver and elevated levels of free fatty acids are thought to contribute to IR in skeletal muscle [26]. In addition to lipid accumulation, hepatic inflammation, activation of pro-inflammatory cytokines and related transcription factors are key mechanisms that disrupt insulin signaling and contribute to IR [27]. In recent years, it has been established that 90% of NAFLD patients are accompanied by metabolic dysfunction, obesity, and obesity-related diseases such as type 2 diabetes mellitus [28]. Therefore, NAFLD is often characterized by lipotoxicity and metabolic syndromes such as IR, which are predominantly associated with obese individuals [1]. Meanwhile, CVD is a common cause of death in patients with NAFLD, making NAFLD a potential independent predictor of CVD [29, 30]. The related mechanisms of CVD in NAFLD patients have been extensively investigated [2, 31, 32] and mainly involve IR, endothelial dysfunction, glyco-lipotoxicity and oxidative stress. Under physiological conditions, insulin plays an important role in balancing contractile and diastolic functions in vascular endothelial cells through phosphatidylinositol 3 -kinase (PI3K) and mitogen-activated protein kinase (MAPK) dependent signaling pathways. However, this balance is disturbed in IR, resulting in endothelial dysfunction and causing glyco-lipotoxicity in the organism. Meanwhile, excessive fat accumulation in the liver promotes the generation of reactive oxygen species (ROS) in the mitochondria, resulting in large amounts of oxidized low-density lipoproteins in the circulation, leading to endothelial oxidative stress injury and impaired vascular function [33, 34]. These abnormal physiological processes are common in NAFLD patients, which partially explain the high incidence of CVD. Meanwhile, a meta-analysis of 34,043 patients with NAFLD showed an increased risk of lethal and non-lethal CVD in patients with NAFLD compared with non-NAFLD patients [35]. Therefore, it is useful to combine the TyG index and indicators of obesity to predict the occurrence of CVD and death in patients with NAFLD.

In numerous studies, TyG and its combined obesity-related indices, such as TyG-BMI, TyG-WC, TyG-WHR,

and TyG-WHtR can be used as surrogate indices for IR, which are associated with increased risk of NAFLD and other metabolic disorders [17, 36, 37], and can better characterize IR status in NAFLD patients [38, 39]. However, an Indian study in 2023 showed that TyG is not superior to FIB-4 for the assessment of fibrosis in NAFLD patients [40]. Therefore, it is prudent to assess the degree of liver fibrosis in patients with NAFLD using the TyG correlation index. In addition, TyG and its combined obesity-related indicators can better reflect cardiovascular events. A cross-sectional study including 424 patients with NAFLD showed that TyG and TyG-BMI were risk factors for CHD in patients with NAFLD after adjustment for age, sex, hypertension, and diabetes mellitus [9]. A study from NHANES 2003–2018 indicated that the correlation and diagnostic efficacy of TyG-WC and TyG-WHtR in relation to CVD and death was superior to TyG index to some extent [5]. Moreover, TyG and its related indices are also associated with NAFLD patients in adolescents. Two Korean retrospective analyses of participants aged 10–19 years showed that TyG and TyG-WHtR were predictors of NAFLD in adolescents and TyG-WHtR was superior to TyG, especially in females [41, 42]. The exact mechanism of the close relationship between the TyG index and NAFLD and CVD has not been fully elucidated. However, factors such as IR, endothelial dysfunction, inflammation, dysregulated glycolipid metabolism and thrombosis are known to be involved [43, 44]. These factors may explain the occurrence of many CVDs in NAFLD patients with elevated TyG levels.

Among these TyG-related indices, BMI cannot distinguish between increases due to muscle and fat. Higher muscle mass may reduce the risk of premature death. Thus, although a higher BMI is associated with an increased risk of morbidity and mortality, this correlation requires further verification. Therefore, we chose TyG-WHtR as an indicator of obesity to predict cardiovascular prognosis in NAFLD patients because of its ease of acquisition, high efficacy, and ability to reflect body fat accumulation.

Our study is the first to investigate the relationship between TyG and the combined obesity indicator TyG-WHtR and all-cause mortality, CVD mortality, total-CVD, CHF, CHD, and angina pectoris in NAFLD patients. Significant associations of TyG with total-CVD events and TyG-WHtR with CVD mortality, and CHF were more frequently observed in individuals aged < 60 years; significant correlations of TyG-WHtR with totalCVD events, CHF, and angina pectoris were more easily observed in individuals with HbA1c ≥ 6.5; In addition, the association of TyG with total CVD events was predominant among individuals without diabetes, whereas the association of TyG-WHtR with angina pectoris was more pronounced among those with diabetes. Some findings also revealed that the association of TyG, TyG-WHtR with CVD and CVD mortality was higher in the absence of diabetes [5], which may be related to the use of hypoglycemic drugs in diabetic patients and directly affect the TyG index by lowering blood glucose levels. Moreover, a study involving 7,521 Iranian individuals found that the TyG index was significantly associated with CVD risk, particularly in younger individuals [25]. Additionally, a study based on NHAENS reported that TyG and TyG-WHtR were more strongly associated with cardiovascular events and CVD mortality in younger patients [5]. Similarly, another study of the US population found that the TyG index was more strongly associated with HF in patients under 60 years old, which aligns with our findings [45]. This may be due to the relatively diminished predictive power of TyG and TyG-WHtR with increasing age, likely because of the accumulation of additional CVD risk factors. There have been conflicting reports on gender differences in TyG, TyG-WHtR and CVD, CHF, CHD and CVD mortality [46, 47]. These discrepancies may be related to socio-economic differences between genders. Overall, men exhibited a slightly higher event rate, which may be related to their greater exposure to chemicals and environmental factors that could amplify their association with CVD [25].

Our study also demonstrated that HbA1c, insulin, and hypertension partially mediate the association between TyG, TyG-WHtR, and CVD mortality, total-CVD, CHF, angina pectoris, and CHD. Our findings revealed that hypertension primarily mediated the association between TyG-WHtR and CHF, while the majority of the remaining associations were largely mediated by HbA1c. This suggests that effective interventions can be developed to target these mediators in order to reduce the risk of CVD in patients with NAFLD.

Strengths and limitations

The strength of this study lies in the adjustment of covariates to investigate the relationships between TyG, TyG-WHtR, and various outcomes including all-cause mortality, CVD mortality, total-CVD, CHF, angina pectoris, and CHD. Furthermore, the study examines the intermediate roles of HbA1c, insulin, and hypertension in the associations between TyG and TyG-WHtR with these diseases. This provides valuable clinical guidance for the management of patients with NAFLD who also have CVDs. However, there are also some limitations to this study. Firstly, data on CVD were collected from participants by self-reporting, which may have some false positives or the omission of patients with undiagnosed CVD. Secondly, our study is based on the data from the United States, and further research is necessary to investigate whether these discoveries can be widely applied to other regions. Thirdly, although TyG and TyG-WHtR can

be used as surrogate indicators of visceral fat, they do not take into account metabolic factors and may have limited application [18].Finally, according to our study, although TyG and TyG-WHtR can be used as preliminary predictors of cardiovascular events and mortality in patients with NAFLD, their diagnostic value needs to be further investigated.

Conclusions

The study revealed that patients with NAFLD and CVD exhibited elevated levels of both TyG and TyG-WHtR. Additionally, TyG-WHtR can serve as a simple complementary indicator alongside TyG to predict CVD mortality, as well as conditions such as CHF, angina pectoris, and CHD.Furthermore, the two indices can be widely used in primary hospitals and communities for screening and prediction in patients with potential NAFLD combined with CVD due to their simplicity and inexpensiveness.

Abbreviations

TyG	Triglyceride-glucose index
CVD	Cardiovascular disease
NAFLD	Non-alcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
ANOVA	Analysis of variance
CHF	Chronic heart failure
IR	Insulin resistance
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
CHD	Coronary Heart Disease
USFLI	US fatty liver index
AUROC	Area under the receiver operating characteristic curve
PIR	Income -poverty ratio
SBP	Systolic blood pressure
ALT	Aspartate aminotransferase
AST	Alanine aminotransferase
GGT	Gamma-glutamyltransferase
TG	Triglycerides
TC	Total cholesterol
FBG	Fasting blood glucose
HbA1c	Glycohemoglobin
NDI	National Death Index
NCHS	National Center for Health Statistics
ICD-10	International Statistical Classification of Diseases,10th Revision
HR	Hazard ratio
OR	Odds ratios
CI	Confidence intervals
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
PI3K	Phosphatidylinositol 3 -kinase
MAPK	Mitogen-activated protein kinase
ROS	Reactive oxygen species

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02354-4.

Supplementary Material 1

Supplementary Material 2

Author contributions

YZ and FW: data analysis and writing; JT: data collection; LS and JH: interpretation of the results and revision; YC: review and final approval. All authors reviewed the manuscript.

Funding

This work was supported by National Natural Science Foundation of China (grant No: 81500359); Natural Science Foundation of Hunan Province (grant No: 2016JJ4100); the Research project of Hunan Provincial Health Commission (grant No. 20200768), Chinese Cardiovascular Association- Access fund (grant No. 2020-CCA-ACCESS-115), the Fundamental Research Funds for the Central Universities of Central South University (grant No. 512340072).

Data availability

The data were obtained from publicly available sources.

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.

Author details

[1]Department of Cardiology, The Second Xiangya Hospital, Central South University, Hunan Province, Changsha 410011, Hunan, China

Received: 2 May 2024 / Accepted: 8 July 2024
Published online: 18 July 2024

References

1. Grander C, Grabherr F, Tilg H. Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options. [Cardiovasc Res. 2023;119(9):1787–98.
2. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. [Gut. 2020;69(9):1691–705.
3. Keen H, Jarrett RJ, Alberti KG. Diabetes mellitus: a new look at diagnostic criteria. [Diabetologia. 1980;18(1):81.
4. Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population. Syst review[Bmj. 2016;353:i2416.
5. Dang K, Wang X, Hu J, et al. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003–2018[. Cardiovasc Diabetol. 2024;23(1):8.
6. Banerjee D, Biggs ML, Mercer L, et al. Insulin resistance and risk of incident heart failure. Cardiovasc Health Study[Circ Heart Fail. 2013;6(3):364–70.
7. Alizargar J, Bai CH, Hsieh NC, et al. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. [Cardiovasc Diabetol. 2020;19(1):8.
8. Er LK, Wu S, Chou HH, et al. Triglyceride glucose-body Mass Index is a simple and clinically useful surrogate marker for insulin resistance in nondiabetic Individuals[. PLoS ONE. 2016;11(3):e0149731.
9. Zhao J, Fan H, Wang T, et al. TyG index is positively associated with risk of CHD and coronary atherosclerosis severity among NAFLD. patients[Cardiovasc Diabetol. 2022;21(1):123.
10. Tao LC, Xu JN, Wang TT, et al. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations[. Cardiovasc Diabetol. 2022;21(1):68.
11. Huang R, Wang Z, Chen J, et al. Prognostic value of triglyceride glucose (TyG) index in patients with acute decompensated heart failure. [Cardiovasc Diabetol. 2022;21(1):88.
12. Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with

cardiovascular disease: collaborative analysis of 58 prospective studies. [Lancet. 2011;377(9771):1085–95.
13. Yusuf S, Anand S. Body-mass index, abdominal adiposity, and cardiovascular. risk[Lancet. 2011;378(9787):226–7. author reply 228.
14. Tian X, Chen S, Wang P, et al. Insulin resistance mediates obesity-related risk of cardiovascular disease: a prospective cohort study. [Cardiovasc Diabetol. 2022;21(1):289.
15. Jayedi A, Soltani S, Zargar MS, et al. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. [Bmj. 2020;370:m3324.
16. Sheng G, Lu S, Xie Q, et al. The usefulness of obesity and lipid-related indices to predict the presence of non-alcoholic fatty liver disease[. Lipids Health Dis. 2021;20(1):134.
17. Malek M, Khamseh ME, Chehrehgosha H, et al. Triglyceride glucose-waist to height ratio: a novel and effective marker for identifying hepatic steatosis in individuals with type 2 diabetes mellitus. [Endocrine. 2021;74(3):538–45.
18. Li X, Sun M, Yang Y, et al. Predictive effect of triglyceride glucose-related parameters, obesity indices, and lipid ratios for diabetes in a Chinese Population: a prospective cohort Study[. Front Endocrinol (Lausanne). 2022;13:862919.
19. Xuan W, Liu D, Zhong J, et al. Impacts of triglyceride glucose-Waist to height ratio on diabetes incidence: a secondary analysis of a Population-based Longitudinal Data[. Front Endocrinol (Lausanne). 2022;13:949831.
20. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey[. Aliment Pharmacol Ther. 2015;41(1):65–76.
21. Du T, Yuan G, Zhang M, et al. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance[. Cardiovasc Diabetol. 2014;13:146.
22. Zhang Q, Xiao S, Jiao X, et al. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001–2018[. Cardiovasc Diabetol. 2023;22(1):279.
23. Wang X, Xu W, Song Q, et al. Association between the triglyceride-glucose index and severity of coronary artery disease. [Cardiovasc Diabetol. 2022;21(1):168.
24. Zhou Q, Yang J, Tang H, et al. High triglyceride-glucose (TyG) index is associated with poor prognosis of heart failure with preserved ejection fraction. [Cardiovasc Diabetol. 2023;22(1):263.
25. Barzegar N, Tohidi M, Hasheminia M, et al. The impact of triglyceride-glucose index on incident cardiovascular events during 16 years of follow-up: Tehran lipid and glucose study. Cardiovasc Diabetol. 2020;19(1):155.
26. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle. Its role Insulin Sensit Metabolic Disturbances Diabetes mellitus[Lancet. 1963;1(7285):785–9.
27. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease[. J Clin Invest. 2017;127(1):1–4.
28. Tilg H, Adolph TE, Dudek M, et al. Non-alcoholic fatty liver disease: the interplay between metabolism. Microbes immunity[Nat Metab. 2021;3(12):1596–607.
29. Tana C, Ballestri S, Ricci F et al. Cardiovascular Risk in non-alcoholic fatty liver disease: mechanisms and therapeutic Implications[. Int J Environ Res Public Health 2019;16(17).
30. Ma J, Hwang SJ, Pedley A, et al. Bi-directional analysis between fatty liver and cardiovascular disease risk factors[. J Hepatol. 2017;66(2):390–7.
31. Kim JA, Montagnani M, Koh KK, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. [Circulation. 2006;113(15):1888–904.
32. Potenza MA, Marasciulo FL, Chieppa DM, et al. Insulin resistance in spontaneously hypertensive rats is associated with endothelial dysfunction characterized by imbalance between NO and ET-1 production[. Am J Physiol Heart Circ Physiol. 2005;289(2):H813–822.
33. Yesilova Z, Yaman H, Oktenli C, et al. Systemic markers of lipid peroxidation and antioxidants in patients with nonalcoholic fatty liver disease[. Am J Gastroenterol. 2005;100(4):850–5.
34. Cavalca V, Cighetti G, Bamonti F, et al. Oxidative stress and homocysteine in coronary artery disease. [Clin Chem. 2001;47(5):887–92.
35. Targher G, Byrne CD, Lonardo A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis[. J Hepatol. 2016;65(3):589–600.
36. Behboudi-Gandevani S, Ramezani Tehrani F, Cheraghi L, et al. Could a body shape index and waist to height ratio predict insulin resistance and metabolic syndrome in polycystic ovary syndrome?[. Eur J Obstet Gynecol Reprod Biol. 2016;205:110–4.
37. Hou X, Chen S, Hu G, et al. Stronger associations of waist circumference and waist-to-height ratio with diabetes than BMI in Chinese adults[. Diabetes Res Clin Pract. 2019;147:9–18.
38. Xue Y, Xu J, Li M, et al. Potential screening indicators for early diagnosis of NAFLD/MAFLD and liver fibrosis: triglyceride glucose index-related parameters. [Front Endocrinol (Lausanne). 2022;13:951689.
39. Lim J, Kim J, Koo SH, et al. Comparison of triglyceride glucose index, and related parameters to predict insulin resistance in Korean adults: an analysis of the 2007–2010 Korean National Health and Nutrition Examination Survey[. PLoS ONE. 2019;14(3):e0212963.
40. Jeji PS, Mishra D, Shukla M et al. Comparison of Triglyceride-glucose Index (TyG index) and FIB-4 for Assessing Fibrosis in NAFLD[*Journal of Clinical and Experimental Hepatology* 2023;13.
41. Song K, Park G, Lee HS, et al. Comparison of the triglyceride glucose index and modified triglyceride glucose indices to predict nonalcoholic fatty liver disease in Youths[. J Pediatr. 2022;242:79–e8571.
42. Song K, Lee HW, Choi HS et al. Comparison of the modified TyG indices and other parameters to Predict non-alcoholic fatty liver Disease in Youth[*Biology*. (Basel). 2022;11(5).
43. Shahavandi M, Djafari F, Shahinfar H, et al. The association of plant-based dietary patterns with visceral adiposity, lipid accumulation product, and triglyceride-glucose index in Iranian adults[. Complement Ther Med. 2020;53:102531.
44. Wang A, Tian X, Zuo Y, et al. Association between the triglyceride-glucose index and carotid plaque stability in nondiabetic adults[. Nutr Metab Cardiovasc Dis. 2021;31(10):2921–8.
45. Wang H, He S, Wang J, et al. Hyperinsulinemia and plasma glucose level independently associated with all-cause and cardiovascular mortality in Chinese people without diabetes-A post-hoc analysis of the 30-year follow-up of Da Qing diabetes and IGT study[. Diabetes Res Clin Pract. 2023;195:110199.
46. Li X, Chan JSK, Guan B, et al. Triglyceride-glucose index and the risk of heart failure: evidence from two large cohorts and a mendelian randomization analysis. [Cardiovasc Diabetol. 2022;21(1):229.
47. Qu H, Long LZ, Chen L, et al. Triglyceride-glucose index and estimated 10-year risk of a first hard cardiovascular event[. Front Cardiovasc Med. 2022;9:994329.

Publisher's Note