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Original Article

Nonlinear relationship between TyG index and the risk of non-alcoholic fatty liver disease in Chinese population: a cross-sectional study

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Abstract: Background: There is insufficient evidence on the link between the triglyceride-glucose index (TyG) and non-alcoholic fatty liver disease (NAFLD) in the Chinese population. This study aims to investigate the association between TyG and the risk of NAFLD. Methods: A cross-sectional study was conducted with 994 participants who underwent health examinations. Demographic information, blood biochemistry profiles, and ultrasonics results were collected. Logistic regression and restricted cubic spline (RCS) analysis was used to assess the nonlinear relationship between TyG and NAFLD risk. Subgroup analysis was performed to examine possible interaction effects. Results: Overall, 31.2% (n = 314) of the general population had NAFLD. Age, male gender, BMI, blood pressure, alanine aminotransferase, fasting blood glucose, uric acid, triglycerides and TyG levels were associated with NAFLD. RCS analysis showed a significant nonlinear dose-response relationship between TyG index and NAFLD. The risk of developing NAFLD increases significantly with a higher TyG index. This association persists even after adjustment for relevant risk factors [odds ratio (OR): 4.70, 95% CI 3.24 to 6.83]. Furthermore, compared to the lowest quartile of TyG (Q1), the NAFLD risk of subjects in the Q2, Q3, and Q4 quartiles increased 1.53, 3.84, and 16.07 times, respectively (P for trend < 0.001). Furthermore, statistically significant interactions were observed between TyG index and gender, BMI, and hypertension in predicting NAFLD risk (P < 0.05). Conclusions: This study highlights the impact of an elevated TyG index on the risk of developing NAFLD. Elevated TyG levels may serve as a risk factor for NAFLD in the Chinese population.

Keywords: Non-alcoholic fatty liver disease, triglyceride-glucose index, insulin resistance, sex difference, hypertension

Introduction

Overindulgence in fat accumulation in the liver, which can result in hepatocellular carcinoma, liver fibrosis, and steatohepatitis, is the hallmark of nonalcoholic fatty liver disease (NAFLD), a condition that is common throughout the world [1]. A complex interaction between genetic, environmental, and lifestyle factors plays a role in the pathogenesis of NAFLD [2, 3]. Currently, over 25-30% of people on the planet are impacted [4]. It is important to detect and treat NAFLD early in order to minimize its detrimental effects on health outcomes, as it is linked to an elevated risk of cardiovascular death [5].

Systemic insulin resistance can be quantitatively assessed using the triglyceride glucose index (TyG), an effective anthropometric measure. It provides important information about metabolic health and disease risk and is derived from measurements of fasting blood glucose and triglyceride levels [6]. Diabetes, metabolic diseases, and nutritional deficiencies are a few examples of underlying health issues that may be indicated by abnormal TyG levels [7, 8]. Studies have indicated the practical significance of TyG as a predictor of multiple health consequences, such as hypertension, diabetes, and specific cancer types [6, 8, 9]. Because it may shed light on TyG's possible predictive role in the

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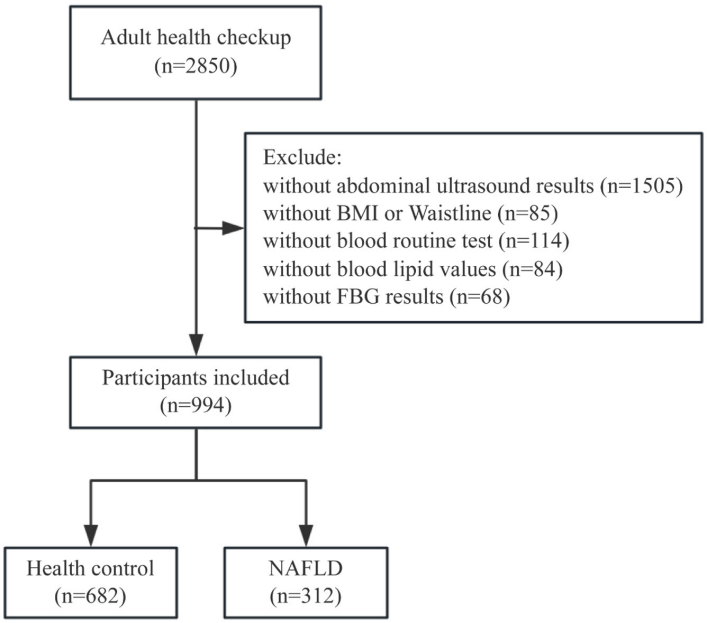

Figure 1. Inclusion and exclusion process of the study participants.

development of NAFLD, the relationship between TyG and NAFLD is particularly interesting [10-12].

In this single-center cross-sectional study, participants were gathered retrospectively during our hospital's health examinations between May 1, 2022 and December 31, 2022. The primary aim of this study is to explore the diagnostic value of the TyG index in the risk of developing NAFLD. Furthermore, the research endeavors to examine if there is a nonlinear pattern in the association between the TyG index and the risk of NAFLD in order to provide additional insight into this intricate relationship. A cross-sectional study involving 994 participants who underwent general health examinations was carried out in order to accomplish these research goals. The findings of this investigation may open the door for more in-depth studies in this field and offer insightful information about the management and prevention of NAFLD.

Methods

Study population

In this cross-sectional study, we retrospectively reviewed the records of 2850 adults who underwent routine health examinations at the Health Examination Center in the Second Affiliated Hospital of Xi'an Jiaotong University from May 1, 2022 to December 31, 2022. Individuals were excluded with one or more of the following: (1) no ultrasound examination, (2) missing essential anthropological data such as body mass index (BMI) and waist circumference, (3) no routine blood test, (4) incomplete results for lipid or fasting blood glucose levels (FBG), (5) significant alcohol consumption (≥40 g/day for ≥5 years). Finally, the 994 remaining examinees were divided into two groups according to their ultrasound characteristics: NAFLD and health control (**Figure 1**). The present study was exempt from informed consent because the dataset consists of deidentified data for research purposes only. The study complied with the Helsinki Declaration and was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University under number 2022202.

Data collection and measurements

Age, gender, smoking and medical history were assessed using a structured medical questionnaire. After an overnight fast, all subjects underwent a physical examination the next morning. Clinical variables such as weight, height, waist, hip line, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded by well-trained personnel. And serological markers were measured using a Sysmex XN-9000 automatic hematology analyzer (Sysmex, Kobe, Japan). Biochemical markers, including total bilirubin, direct bilirubin, indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), FBG, serum uric acid (SUA), blood urine nitrogen (Brea), and serum creatinine (Cr), were measured using the Beckman AU5800 automatic biochemical analyzer (Beckman Coulter, Brea, CA, USA).

SBP ≥140 mmHg, DBP ≥90 mmHg, or the use of antihypertensive medication at the time of diagnosis were considered indicators of hyper-

tension [13]. FPG ≥7.0 mmol/L or the use of hypoglycemic medications at the time of diagnosis was considered diabetes [14]. Treatment with a lipid-lowering agent or TC > 5.2 mmol/L, LDL-C > 3.1 mmol/L, or TG > 1.7 mmol/L were considered indicators of hyperlipidemia [15]. ln [TG (mg/dL) × FBG (mg/dL)/2] was used to calculate the TyG index [16].

Diagnosis of fatty liver

Two highly qualified and experienced clinicians conducted the abdominal ultrasonography examinations. Upon a 12-hour fast, each subject was examined. Utilizing a convex matrix B-type ultrasonic diagnostic instrument (Philips) operating at a frequency of 3 points five megahertz, the examinees assumed a supine position or left and right lateral positions, fully exposing their upper abdomen. By demonstrating hepatic steatosis, ultrasound was able to diagnose fatty liver in the following ways: (a) the liver's near-field echo is diffusely enhanced and stronger than the kidneys'; (b) the structure of the intrahepatic duct is not readily apparent; (c) the liver's far-field echoes gradually weaken; and (d) the liver's hepatic blood flow signal is reduced [14].

Statistical analysis

To reduce potential bias, variables with missing values more than 20 percent were eliminated; those without were imputed using the random forest method. The Kolmogorov-Smirnov test and histogram distribution were used to evaluate the variables' normality. While skewed continuous variables were expressed as median (interquartile range [IQR]), normally distributed continuous variables were reported as mean ± standard deviation. Frequencies and percentages were used to represent categorical variables. Chi-square testing was used to analyze categorical variables, and ANOVA or Kruskal-Walli's test was used for group comparisons of continuous variables, depending on the distribution normalcy. Utilizing the restricted cubic spline (RCS) model, the nonlinear dose-response relationships between TyG index and NAFLD were investigated. TyG was employed in this model as a continuous variable with the four knots - the fifth, 35th, 65th, and 95th. A likelihood ratio test is used to determine the nonlinearity of a model by contrasting its model with only one linear term with one that includes both linear and cubic spline terms. An investigation into the relationship between the TyG index and the risk of NAFLD was done utilizing multivariate logistic regression. The TyG index, which is separated into quantiles Q1-Q4, was included in the analysis as a categorical variable. Confounders were chosen based on their clinical significance, taking into account important covariates found in the univariate analysis. After computing the variance inflation factor (VIF), multicollinearity was indicated by a VIF value of ≥5. Three models were built in order to be analyzed. Model 1 was left unadjusted, while Model 2 was corrected for age, gender, and BMI. Model 3 was further adjusted for smoking, diabetes, hypertension, dyslipidemia and SUA. Based on age, gender, BMI, hypertension, and diabetes status, subgroup analysis and interaction testing were carried out to further investigate any potential changes to the relationship between TyG and NAFLD.

All analyses were performed using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and Free Statistics analysis platform (Version 1.9, Beijing, China, http://www.clinicalscientists.cn/freestatistics). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Demographic and clinical characteristics according to the quartiles of TyG index are detailed in **Table 1**. Of the 994 participants, 312 had NAFLD, with a prevalence of 31.4%. The median age of the participants was 40.0 years, and 67.4% of the subjects were male. Participants in the higher TyG quartiles were generally older and had elevated levels of BMI, SBP, DBP, waistline, WBC, HB, AST, ALT, Alb, TC, TG, LDL-C, FBG and SUA, and lower levels of HDL-C (all $P < 0.001$). In addition, the prevalence of smoking, hypertension, diabetes and hyperlipidemia also showed an increased trend from the lower to higher quartile of TyG index (all $P < 0.001$). With increasing TyG index, the NAFLD prevalence (4.4% vs. 15.7% vs. 37.5% vs. 67.9%, $P < 0.001$) elevated dramatically.

Association of NAFLD with TyG index

The logistic regression model was primarily used to analyze the relationship between TyG and NAFLD. Whether as a continuous or categorical variable, TyG was positively correlated with NAFLD risk in the unadjusted model (**Table**

Table 1. Clinical characteristics among TyG quartiles

Variables	Total (n = 994)	Q1 (n = 249)	Q2 (n = 248)	Q3 (n = 248)	Q4 (n = 249)	*P* value
Age, years	40.0 (33.0, 49.0)	35.0 (29.0, 43.0)	39.0 (33.0, 49.0)	42.0 (34.8, 51.0)	42.0 (35.0, 51.0)	< 0.001
Gender, n (%)						< 0.001
Male	670 (67.4)	104 (41.8)	154 (62.1)	200 (80.6)	212 (85.1)	
Female	324 (32.6)	145 (58.2)	94 (37.9)	48 (19.4)	37 (14.9)	
BMI, kg/m^2	24.2 (22.0, 26.6)	21.6 (20.0, 23.7)	23.4 (21.5, 25.4)	25.0 (23.7, 27.2)	26.0 (24.2, 28.0)	< 0.001
SBP, mmHg	122.0 (112.0, 131.0)	115.0 (107.0, 123.0)	119.0 (110.8, 128.2)	123.0 (115.8, 133.0)	128.0 (121.0, 136.0)	< 0.001
DBP, mmHg	78.0 (70.2, 85.0)	72.0 (66.0, 79.0)	76.0 (68.0, 83.0)	80.0 (73.0, 87.0)	85.0 (77.0, 89.0)	< 0.001
Waistline, cm	84.0 (75.0, 91.0)	74.0 (68.0, 81.0)	81.0 (73.0, 88.0)	88.0 (81.0, 93.0)	90.0 (84.0, 95.0)	< 0.001
Hipline, cm	97.0 (93.0, 100.0)	94.0 (90.0, 97.0)	96.0 (93.0, 99.0)	98.0 (95.0, 102.0)	99.0 (95.0, 102.0)	< 0.001
Smoke, n (%)						< 0.001
No	750 (75.5)	218 (87.6)	185 (74.6)	183 (73.8)	164 (65.9)	
Yes	240 (24.1)	30 (12)	61 (24.6)	65 (26.2)	84 (33.7)	
Hypertension, n (%)						< 0.001
No	796 (80.1)	234 (94)	212 (85.5)	189 (76.2)	161 (64.7)	
Yes	198 (19.9)	15 (6)	36 (14.5)	59 (23.8)	88 (35.3)	
Diabetes, n (%)						< 0.001
No	958 (96.4)	249 (100)	246 (99.2)	237 (95.6)	226 (90.8)	
Yes	36 (3.6)	0 (0)	2 (0.8)	11 (4.4)	23 (9.2)	
Hyperlipidemia, n (%)						< 0.001
No	940 (94.6)	248 (99.6)	245 (98.8)	233 (94)	214 (85.9)	
Yes	54 (5.4)	1 (0.4)	3 (1.2)	15 (6)	35 (14.1)	
WBC, ×10^9/L	5.9 (5.0, 6.8)	5.2 (4.5, 6.2)	5.8 (4.9, 6.7)	6.0 (5.1, 7.1)	6.2 (5.4, 7.2)	< 0.001
HB, g/L	153.0 (138.2, 161.0)	141.0 (131.0, 154.0)	149.5 (135.0, 159.0)	156.0 (146.8, 163.2)	160.0 (151.0, 164.0)	< 0.001
PLT, ×10^9/L	226.5 (195.0, 264.8)	226.0 (198.0, 263.0)	228.5 (195.8, 264.2)	229.0 (196.8, 262.0)	224.0 (191.0, 266.0)	0.933
TBIL, μmol/L	12.8 (10.0, 16.3)	12.4 (9.2, 15.9)	12.9 (10.1, 16.2)	12.9 (10.0, 16.5)	13.3 (10.3, 16.1)	0.316
DBIL, μmol/L	4.6 (3.7, 5.8)	4.7 (3.7, 6.1)	4.8 (3.7, 5.8)	4.6 (3.7, 5.8)	4.5 (3.6, 5.8)	0.483
IBIL, μmol/L	8.1 (6.3, 10.6)	7.5 (5.7, 10.2)	8.1 (6.1, 10.6)	8.2 (6.5, 10.8)	8.7 (6.5, 11.0)	0.007
ALT, IU/L	19.0 (13.0, 29.0)	13.0 (10.0, 19.0)	17.0 (12.0, 24.0)	21.0 (16.0, 31.0)	28.0 (19.0, 39.0)	< 0.001
AST, IU/L	19.0 (16.0, 23.0)	17.0 (15.0, 20.0)	18.0 (16.0, 22.0)	20.0 (17.0, 23.0)	22.0 (17.0, 27.0)	< 0.001
Alb, g/L	46.7 ± 2.6	46.2 ± 2.5	46.6 ± 2.5	46.7 ± 2.6	47.4 ± 2.5	< 0.001
TC, mmol/L	4.4 (3.9, 4.9)	4.1 (3.6, 4.5)	4.4 (3.8, 4.8)	4.4 (4.0, 5.1)	4.7 (4.3, 5.3)	< 0.001
TG, mmol/L	1.3 (0.9, 2.0)	0.7 (0.6, 0.8)	1.1 (1.0, 1.2)	1.6 (1.4, 1.8)	2.5 (2.2, 3.2)	< 0.001
HDL-C, mmol/L	1.2 (1.0, 1.4)	1.5 (1.2, 1.7)	1.3 (1.1, 1.5)	1.1 (1.0, 1.3)	1.0 (0.9, 1.2)	< 0.001
LDL-C, mmol/L	2.7 (2.2, 3.2)	2.4 (2.0, 2.8)	2.7 (2.3, 3.2)	2.8 (2.4, 3.3)	2.9 (2.4, 3.3)	< 0.001
FBG, mmol/L	5.0 (4.7, 5.4)	4.8 (4.5, 5.0)	4.9 (4.7, 5.2)	5.1 (4.8, 5.4)	5.4 (5.0, 6.1)	< 0.001
SUA, mmol/L	335.0 (275.0, 399.0)	288.0 (238.0, 342.0)	318.0 (262.8, 375.0)	356.0 (310.0, 414.0)	375.0 (314.0, 441.0)	< 0.001
Brea, mmol/L	4.6 (4.0, 5.4)	4.5 (3.8, 5.4)	4.7 (4.0, 5.5)	4.6 (3.9, 5.5)	4.7 (4.1, 5.3)	0.301
Cr, mmol/L	75.3 (65.2, 83.8)	70.3 (60.7, 80.1)	73.6 (63.9, 83.5)	78.6 (70.4, 86.3)	77.1 (70.3, 84.8)	< 0.001
TyG	8.6 (8.2, 9.0)	8.0 (7.8, 8.1)	8.4 (8.3, 8.5)	8.8 (8.7, 8.9)	9.3 (9.2, 9.6)	< 0.001
NAFLD, n (%)	312 (31.4)	11 (4.4)	39 (15.7)	93 (37.5)	169 (67.9)	< 0.001

Table 2. Multivariable logistic regression for risk of NAFLD

Variable	Model 1			Model 2			Model 3		
	OR (95% CI)	*P* value	*P* for trend	OR (95% CI)	*P* value	*P* for trend	OR (95% CI)	*P* value	*P* for trend
TyG[a]	8.99 (6.49-12.46)	< 0.001		5.13 (3.59-7.33)	< 0.001		4.70 (3.24-6.83)	< 0.001	
Quartile[b]			< 0.001			< 0.001			< 0.001
Q1 (n = 249)	Ref.			Ref.			Ref.		
Q2 (n = 248)	4.04 (2.02-8.08)	< 0.001		2.62 (1.21-5.66)	0.014		2.53 (1.15-5.57)	0.021	
Q3 (n = 248)	12.98 (6.73-25.04)	< 0.001		5.24 (2.51-10.96)	< 0.001		4.84 (2.27-10.34)	< 0.001	
Q4 (n = 249)	45.71 (23.62-88.46)	< 0.001		19.36 (9.24-40.56)	< 0.001		17.07 (7.96-36.59)	< 0.001	

Model 1: unadjusted; Model 2: adjusted for age, gender, BMI; Model 3: adjusted for age, gender, BMI, smoke, hypertension, diabetes, dyslipidemia and SUA. [a]TyG index as continuous variable; [b]TyG quartile: Q1 (6.970, 8.191), Q2 (8.191, 8.606), Q3 (8.606, 9.027), Q4 (9.027, 11.311).

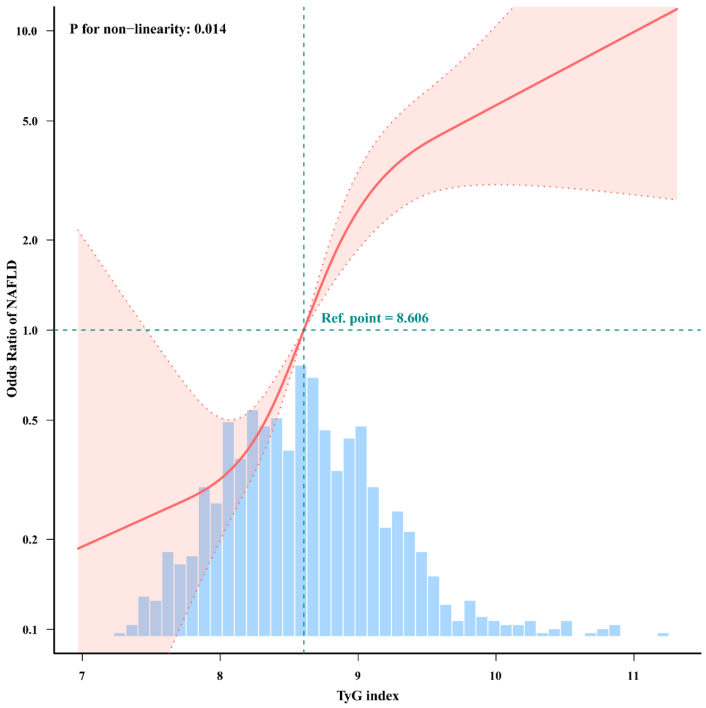

Figure 2. Restricted cubic spline modelling of the association between NAFLD and TyG index among general populations. Red area, 95% CI. Model was adjusted for age, gender, BMI, smoke, hypertension, diabetes, dyslipidemia and SUA.

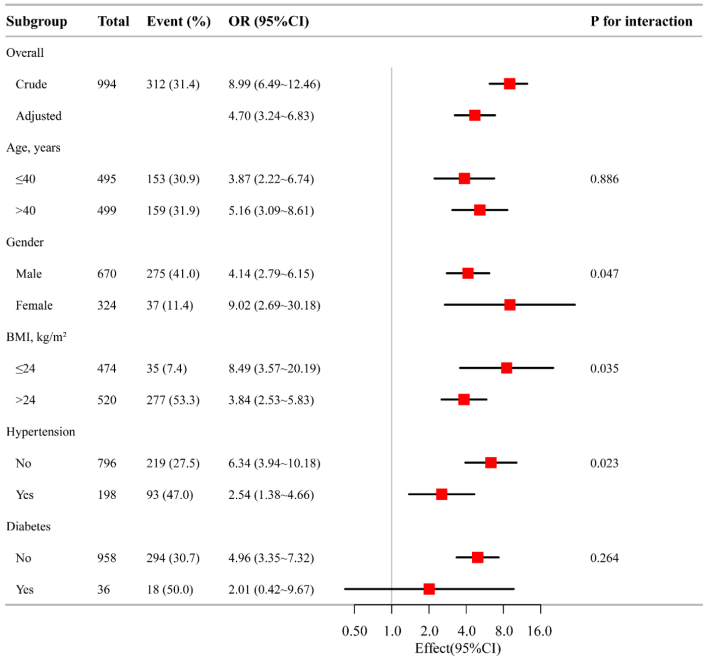

Figure 3. Subgroup analysis.

2). In model 2, the positive correlations between TyG and NAFLD persisted even after controlling for age, gender, and BMI (each $P < 0.05$). Based on model 2, model 3 further adjusted for variables like SUA, smoking, hypertension, diabetes, and dyslipidemia. The outcomes did not alter (each $P < 0.05$). In the higher quartiles, the odds ratio (OR) of NAFLD was significantly higher than that in the lowest quartile (Q2: OR 2.53, 95% CI 1.15-5.57; Q3: OR 4.84, 95% CI 2.27-10.34; Q4: OR 17.07, 95% CI 7.96-36.59, respectively). The dose-response relationships between TyG and the risk of NAFLD were investigated using the RCS analyses (**Figure 2**). With rising TyG levels, the ORs of NAFLD rose non-linearly (P for non-linearity = 0.014).

Subgroup analysis

We further performed exploratory subgroup analyses to assess the associations between TyG and the risk of NAFLD. Consistent results were found in the subgroup analysis. However, the *P* values for interactions for gender, BMI and hypertension were lower than 0.05 (**Figure 3**). The associations between TyG and NAFLD risk seemed to be stronger among female, individuals older than 40 years or without hypertension.

Discussion

In this cross-sectional study, our results showed that the TyG index was an independent predictor of NAFLD among participants who underwent routine health examinations. The major findings of our study are as following: (1) The prevalence of NAFLD among general population was 31.4%, which is even higher than the global average level. (2) With an increasing TyG level, the prevalence of NAFLD dramatically increased and showed a non-linear relationship. (3) Significant interactions were observed between TyG and gender, BMI and hypertension in relation to NAFLD risk. The associations

between TyG and NAFLD risk seemed to be stronger among female, individuals older than 40 years old or without hypertension. Further researches are warranted for the validation of our results here.

NAFLD, which affects at least 25% of adults globally, is currently the most prevalent chronic liver disease [4]. Obesity and metabolic disorders are among the factors that have been linked in previous studies to the onset and progression of NAFLD [17]. NAFLD can be predicted with great accuracy using basic metrics like BMI, waist circumference, and waist-hip ratio. However, those indicators are not very specific, and they typically understated the risk of NAFLD in people who are not obese or diabetic [18, 19]. Cardiovascular and metabolic disorders are closely associated with the TyG index, which is a straightforward proxy measure of insulin resistance [5, 6]. Extensive research has demonstrated that TyG outperformed HOMA-IR in terms of liver fibrosis presence and hepatic steatosis severity [10]. All-cause and cardiovascular mortality in patients with NAFLD were substantially correlated with high levels of TyG and related indices, including TyG-BMI and TyG-WC [12]. The risk and severity of coronary heart disease in patients with NAFLD can be accurately predicted by combining the systemic inflammatory index and TyG [20]. The results of present study were in line with these findings. It was discovered that the frequency of results increased dramatically as the TyG level rose, reaching 67.9% in the highest quartile. The non-linear correlation between the onset of NAFLD and the TyG index was further confirmed by the RCS model and multivariate logistic regression.

Subgroup analysis stratified by age, gender, BMI and comorbidities was conducted to further explore the possible modifications on the association of TyG and NAFLD. Similar results were found in most of the subgroups, except for the diabetic subjects. However, significant interactions were observed for gender, BMI and hypertension. It seems that the associations between TyG and NAFLD risk were stronger among females, individuals older than 40 years or without hypertension. There are gender disparities in NAFLD prevalence, risk factors, fibrosis, and clinical outcomes [21]. According to reports, men are more likely than women to have NAFLD during the reproductive age range, both in terms of frequency and severity. But NAFLD strikes more often in women after menopause, indicating that estrogen may be protective [22]. Regretfully, the majority of clinical and epidemiological studies that have been published do not adequately analyze sex differences. Furthermore, we found that TyG was more significantly associated with the risk of NAFLD among non-hypertensive population. Previous studies had established NAFLD as an independent risk factor of hypertension and other cardiovascular diseases [5, 17]. Recently, it has been found that hypertension was also associated with an increased risk of NAFLD based on a national observational study and Mendelian randomization analyses [23]. It seems to be a bidirectional relationship between hypertension and NAFLD, and thus may modify the association of TyG and NAFLD. Diabetes is closely associated with fatty liver, and it has been reported that nearly 70% of patients with diabetes is combined with NAFLD. However, there was no significant association between the TyG index and the risk of NAFLD among diabetic subgroup. This should be taken into account for the small population of diabetes (n = 36) in our study, as the 95% confidence interval ranges from 0.42 to 9.67.

This study had several limitations. First, this is a cross-sectional study from a single center, and the sample size is relatively small. Second, the diagnosis of NAFLD was based on ultrasound results instead of liver biopsy. Third, variables like occupation, education level, and dietary and exercise habits that are not measured may also be present in this study. In addition, our subjects were limited to the Han peoples and Xi'an area, and whether the findings apply to other peoples or regions remains unclear.

Conclusion

Our research showed that the TyG index is a useful tool for identifying NAFLD in the general population. Elevated TyG levels are a cheap and practical index that could be a helpful marker for NAFLD screening in the Chinese population.

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Disclosure of conflict of interest

None.

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