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The potential of insulin resistance indices to predict non-alcoholic fatty liver disease in patients with type 2 diabetes

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Abstract

Background The triglyceride-glucose (TyG) index and related parameters, as well as the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), have been developed as insulin resistance markers to identify individuals at risk for non-alcoholic fatty liver disease (NAFLD). However, its use for predicting NAFLD in patients with type 2 diabetes mellitus (T2DM) remains unclear. In this study, we aimed to observe the performance of insulin resistance indices in diagnosing NAFLD combined with T2DM and to compare their diagnostic values in clinical practice.

Patients and methods Overall, 268 patients with T2DM from the Endocrinology Department of Jiangsu Provincial Hospital of Traditional Chinese Medicine were enrolled in this study and divided into two groups: an NAFLD group (T2DM with NAFLD) and a T2DM group (T2DM without NAFLD). General information and blood indicators of the participants were collected, and insulin resistance indices were calculated based on these data. Receiver operating characteristic (ROC) analysis was conducted to calculate the area under the curve (AUC) for insulin resistance-related indices, aiming to assess their ability to discriminate between T2DM patients with and without NAFLD.

Results ROC analysis revealed that among the five insulin resistance-related indices, four parameters (TyG, TyG-body mass index [BMI], TyG-waist circumference [WC], and TyG- (waist–hip ratio [WHR]) exhibited high predictive performance for identifying NAFLD, except for HOMA-IR (AUCs:0.710,0.738,0.737 and 0.730, respectivly). TyG-BMI demonstrated superior predictive value, especially in males. For males, the AUC for TyG-BMI was 0.764 (95% confidence interval [CI] 0.691–0.827). The sensitivity and specificity for male NAFLD were 90.32% and 47.89%, respectively. Moreover, in the Generalized linear regression models, there were positive associations of TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR with controlled attenuation parameter (CAP), with β values of 21.30, 0.745, 0.247, and 2.549 (all $P < 0.001$), respectively.

Conclusion TyG-BMI is a promising predictor of NAFLD combined with T2DM, particularly in lean male patients.

Keywords Type 2 diabetes mellitus, Non-alcoholic fatty liver disease, TyG index-related parameters, BMI, ROC curves

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide [1], affecting approximately one-third of the global population and posing a growing public health challenge. As our understanding of NAFLD have deepened, in 2020, an international fatty liver expert group recommended renaming NAFLD as "metabolic dysfunction-associated fatty liver disease (MAFLD)" [2]. Subsequently, in 2023, a multisociety statement led by the American Association for the Study of Liver Diseases (AASLD) proposed renaming NAFLD as "metabolic dysfunction-associated steatotic liver disease (MASLD)" [3]. An epidemiological survey indicated that > 95% of patients with NAFLD met the diagnostic criteria for MAFLD, suggesting that NAFLD epidemiological data can be extrapolated to MAFLD [4]. NAFLD is often asymptomatic in its early stages and has a bidirectional relationship with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), jointly promote the occurrence of multisystem metabolic-related diseases [5]. The prognosis of patients with NAFLD is primarily associated with cardiovascular and non-hepatic malignancies. In the presence of advanced fibrosis, the number of liver-related events increases significantly. Additionally, T2DM poses a higher risk of HCC progression of hepatocellular carcinoma than obesity [6]. Recent studies have indicated that approximately 65.04% of T2DM patients worldwide have NAFLD [7], while other research predicts that over 90% of T2DM patients may eventually develop NAFLD over the course of their disease [8]. Early diagnosis and treatment are critical to prevent worsening progress. However, liver biopsy remains the gold standard for the diagnosis of fatty liver disease. Owing to the invasive nature of this procedure, its use is limited in clinical practice. Therefore, the development of noninvasive diagnostic methods has been highlighted. Early diagnosis and evaluation of NAFLD are vital.

Insulin resistance (IR) and obesity are common contributors to the development of T2DM complicated with NAFLD. The triglyceride-glucose (TyG) index is a reliable marker of IR [9]. These include fasting plasma glucose (FPG) and triglyceride (TG) levels. Moreover, studies have demonstrated that TyG combined with obesity indices, such as triglyceride glucose body mass index(TyG-BMI) and Triglyceride Glucose-Waist Circumference (TyG-WC), has potential predictive utility for insulin resistance (IR), which is closely correlated with obesity [10]. Subsequently, researchers have evaluated the potential of TyG-related indices in diagnosing NAFLD. However, there are significant variations in diagnostic performance. Moreover, the homeostasis model used for the assessment of the insulin resistance index (HOMA-IR) was proposed by Matthews et al. in 1985 and serves as an indirect approach for evaluating insulin resistance (IR) in clinical settings [11]. Notably, this index utilizes fasting plasma insulin and glucose concentrations to evaluate IR and β-cell deficiencies. However, the value of IR-related indices in diagnosing T2DM complicated with NAFLD requires further investigation.

In this study, we aimed to investigate the diagnostic performance of the TyG index and HOMA-IR index in T2DM complicated with NAFLD and compare their diagnostic values in clinical practice.

Participants and methods

Study design and populations

A total of 268 patients with T2DM were admitted to the endocrinology department at Jiangsu Province Hospital of Traditional Chinese Medicine between January 2021 and October 2023 and were enrolled in the study. On admission, all patients were informed that their medical records could be used for research unless they opposed it. In the present study, none of the patients exhibited any oppositions. This study was approved by the Ethics Committee of endocrinology departments at Jiangsu Province Hospital of Traditional Chinese Medicine (Approval Number: 2022NL-071–02). Participants were excluded if they were aged ≤ 18 years, viral hepatitis (including carriers of viral hepatitis) or active viral hepatitis, autoimmune liver disease, or other chronic liver diseases, consumed more than 140 g of alcohol per week for males and more than 70 g per week for females, had liver cirrhosis as shown by ultrasound, lacked complete examination data, or had received insulin therapy or taken medications affecting insulin sensitivity or liver function before the first visit.

Definitions and diagnosis

NAFLD is a chronic progressive liver disease caused by excess nutrition and insulin resistance (IR) in genetically susceptible individuals [12]. Utilization of the controlled attenuation parameter (CAP) via vibration-controlled transient elastography (VCTE) is advantageous for identifying individuals with hepatic steatosis [13]. We defined NAFLD as CAP ≥ 258 dB/m [14]. The examination was considered reliable when at least 10 valid measurements were obtained and the interquartile range/median LSM ratio was less than 30%.

Data collection

Data on age, sex, hypertension, diabetes, height, and weight, were obtained from medical records. Participants who smoked fewer than 100 cigarettes in their lifetime were considered non-smokers, whereas the others were considered smokers. All eligible participants fasted for at least 8 h overnight, and blood samples were

collected the next morning between 8:00 AM and 9:00 AM. Observed indices included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), serum gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and fasting insulin. Two researchers inputted and reviewed the data. The FibroScan device simultaneously measures the LSM and CAP using VCTE technology. A FibroScan 502 touch model equipped with M and XL probes was used. The FibroScan examinations were conducted by nurses trained and certified by the manufacturer. All patients fasted for at least 3 h before the examination and were then placed in a supine position with their right arms fully extended. Measurements were obtained by scanning the right lobe of the liver through the intercostal spaces. The formulae used to calculate the indices are as follows:

$$\mathrm{BMI} = \mathrm{weight}\ (\mathrm{kg})/\mathrm{height}^2\left(\mathrm{m}^2\right)$$

$$\mathrm{TyG} = \mathrm{Ln}\left[\mathrm{TG}(\mathrm{mg/dL}) \times \mathrm{FPG}(\mathrm{mg/dL})/2\right],$$

$$\mathrm{TyG-BMI} = \mathrm{Ln}\left[\mathrm{TG}(\mathrm{mg/dL}) \times \mathrm{FPG}(\mathrm{mg/dL})/2\right] \times \mathrm{BMI}\left(\mathrm{kg/m}^2\right)$$

$$\mathrm{TyG-WC} = \mathrm{Ln}\left[\mathrm{TG}(\mathrm{mg/dL}) \times \mathrm{FPG}(\mathrm{mg/dL})/2\right] \times \mathrm{WC(cm)}$$

$$\mathrm{TyG-WHR} = \mathrm{Ln}\left[\mathrm{TG}(\mathrm{mg/dL}) \times \mathrm{FPG}(\mathrm{mg/dL})/2\right] \times [\mathrm{WC(cm)}/\mathrm{height(cm)}],$$

$$\mathrm{HOMA-IR} = \mathrm{FPG\ (mmol/L)} \times \mathrm{FINS}\ (\mu\mathrm{U/mL})\ /22.5.$$

Statistical analysis

Statistical analyses were performed using SPSS (version 26.0 (IBM Corp., Armonk, NY, USA) and MedCalc V.16.2 (MedCalc).Categorical data are presented as proportions (%), and comparisons between two different groups were conducted using the chi-square test. Continuous data are expressed as the median and interquartile range M (Q1–Q3), and an independent samples t-test or Mann–Whitney U test was used to compare these variables between the two groups. Multivariate logistic regression analysis was performed. Furthermore, the targeted parameters were categorized into quartiles to explore their relationships. The diagnostic value of TyG-related indices for NAFLD was evaluated using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). Subgroup analyses were conducted based on sex and BMI, and non-parametric DeLong tests were used to reveal differences in the AUC between TyG-related indices and HOMA-IR. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

General information of the participants

A total of 268 patients were included in the final analyses. The baseline characteristics of the study participants are shown in Table 1. Among the 268 participants, 145 were diagnosed with both T2DM and NAFLD, resulting in a NAFLD prevalence of 54.10% among the T2DM patients. The mean age of the T2DM with NAFLD group was significantly lower than that of the T2DM without NAFLD group ($P < 0.001$), with a higher prevalence in males compared to females (64.1% vs. 57.8%). Moreover, compared with the T2DM without NAFLD group, the T2DM with NAFLD group exhibited elevated levels of ALT, GGT, TG, and HbA1c (all $P < 0.001$). Notably, participants with NAFLD had significantly higher BMI, WC, WHR, CAP, LSM, and TyG-related indices than those in the T2DM without NAFLD group (all $P < 0.001$).

Optimal cut-off analysis of various insulin resistance indices for diagnosing NAFLD

Receiver operating characteristic (ROC) curve analysis was performed to clarify the diagnostic capabilities of TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR for NAFLD in patients with T2DM. The results showed that the AUC values for TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR were 0.710, 0.738, 0.737, 0.730, and 0.598, respectively. The cutoff values for predicting NAFLD in T2DM patients were as follows: TyG: 2.04, TyG-BMI: 39.58, TyG-WC: 211.12, TyG-WHR: 1.52, and HOMA-IR: 2.12. Among these indices, TyG-BMI demonstrated an optimal effect with an AUC of 0.738 (Table 2). The AUC value of HOMA-IR was significantly lower than those of the other parameters ($P < 0.001$) (Fig. 1).

Subgroup analysis of the predict values of different indices for NAFLD

Subgroup analysis based on gender

As shown in Fig. 2, TyG-BMI had the highest AUC for both males and females (0.764 and 0.702, respectively). For males, the optimal predictive value of TyG-BMI was 31.54, with a sensitivity of 90.32% and a specificity of 47.89%. However, the TyG index performed the worst among the parameters for both males and females (AUCs: 0.744 and 0.658, respectively). Notably, the AUC of HOMA-IR in females (0.659) was significantly higher than that in males (0.559), as shown in Table 3.

Subgroup analysis based on BMI

As shown in Table 4, in the lean group (BMI < 23 kg/m^2), TyG-BMI exhibited a particularly strong performance,

Table 1 Participant characteristics

Variables	NAFLD Group (T2DM with NAFLD) (*n* = 145)	T2DMGroup(T2DM without NAFLD) (*n* = 123)	*P* value
Demographic parameters			
Age(years)	49.0(40.0,60.0)	56.0(47.0,61.0)	< 0.001
Sex (%)			
Female	52(35.9)	52(42.2)	0.315
Male	93(64.1)	71(57.8)	
DM duration (years)	4(2,5)	4(3,6)	0.057
Cigarette smoking (%)	77(53.1)	56(45.5)	0.217
SBP	130(119.5,149	133(118,148)	0.730
DBP	80(71,93.5)	80(72,95)	0.654
Anthropometric parameters			
WC (cm)	97.40(88.7,106.0)	89.70(83.0,95.4)	< 0.001
WHR (cm)	0.96(0.91,1.00)	0.91(0.87,0.95)	< 0.001
BMI	28.50(25.70,31.07)	26.0(23.60,27.90)	< 0.001
Serum test			
ALT(U/L)	28.00(18.5,49.50)	20.00(14.00,27.00)	< 0.001
GGT(U/L)	45.00(27.25,69.75)	25.00 (17.75,33.25)	< 0.001
FBG (mmol/L)	7.09(5.47,9.41)	6.82(5.80,7.68)	0.015
TC (mmol/L)	4.62(3.93,5.35)	4.40(3.63,5.02)	0.029
TG (mmol/L)	2.03(1.52,1.85)	0.96(0.96,2.09)	< 0.001
HDL-C(mmol/L)	1.18(1.00,1.35)	1.30(1.08,1.54)	< 0.001
LDL-C(mmol/L)	2.79(2.31,3.36)	2.53(2.04,2.98)	0.003
FINS (pmol/L)	8.50(7.40,10.20)	9.87(5.55,16.06)	0.276
HbA1c (%)	12.11(7.3,16.95)	7.70(6.70,8.80)	< 0.001
Noninvasive indices			
TyG	2.05(1.46,2.41)	1.56(1.04,2.03)	0.001
TyG-BMI	56.98(43.92,74.61)	38.41(26.43,56.39)	< 0.001
TyG-WC	195.67(142.16,249.08)	136.35(88.54,186.62)	< 0.001
TyG-WHR	1.89(1.45,2.44)	1.43(0.93,1.87)	< 0.001
HOMA-IR	3.86(2.27,5.91)	2.71(1.46,5.27)	0.006
VCTE parameters			
CAP (dB/m)	313.00(286.0,336.0)	242(224.0,253.25)	< 0.001
vLSM (kPa)	7.0(5.3,9.82)	4.90(4.0,6.0)	< 0.001

Abbreviations: WC Waist circumference, *WHR* Waist-to-Hip Ratio, *BMI* Body mass index, *ALT* Alanine aminotransferase, *GGT* γ-glutamyltransferase, *FBG* Fasting blood glucose, *TC* Cholesterol, *TG* Triglycerides, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *HbA1c*, Glycosylated hemoglobin, *FINS* Fasting insulin, *TyG* Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circumference, *HOMA-IR* Homeostasis model assessment of insulin resistance index, *CAP* Controlled attenuation parameter, *LSM* Liver Stiffness Measurement

Table 2 Diagnostic efficacy of different indicators for NAFLD in patients with type 2 diabetes mellitus combined with fatty liver disease

Variables	AUC (95% CI)	95%CI	*P* value for AUROC	Cutoff value	*P* Value
TyG	0.710	0.652–0.764	0.001	2.04	< 0.001
TyG-BMI	0.738	0.617–0.778	< 0.001	39.58	< 0.001
TyG-WC	0.737	0.680–0.789	< 0.001	211.12	< 0.001
TyG-WHR	0.730	0.673–0.782	< 0.001	1.52	< 0.001
HOMA-IR	0.598	0.537–0.657	-	2.12	< 0.004

Abbreviations: AUC Area under the receiver operating characteristic curve, *BMI* Body mass index, *WHR* Waist-to-Hip Ratio, *WC* Waist circumference, *TyG* Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circumference, *HOMA-IR* Homeostasis model assessment of insulin resistance index

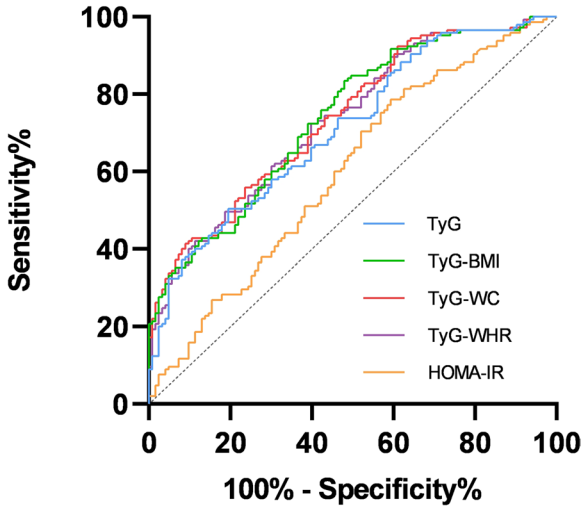

Fig. 1 Receiver operating characteristic curve of each parameter for predicting Non-alcoholic fatty liver disease**.** Abbreviations: AUC Area under the receiver operating characteristic curve, WHR Waist-to-Hip Ratio, TyG Triglyceride glucose, TyG-BMI Triglyceride glucose-body mass index, TyG-WC Triglyceride Glucose-Waist Circumference, HOMA-IR Homeostasis model assessment of insulin resistance index

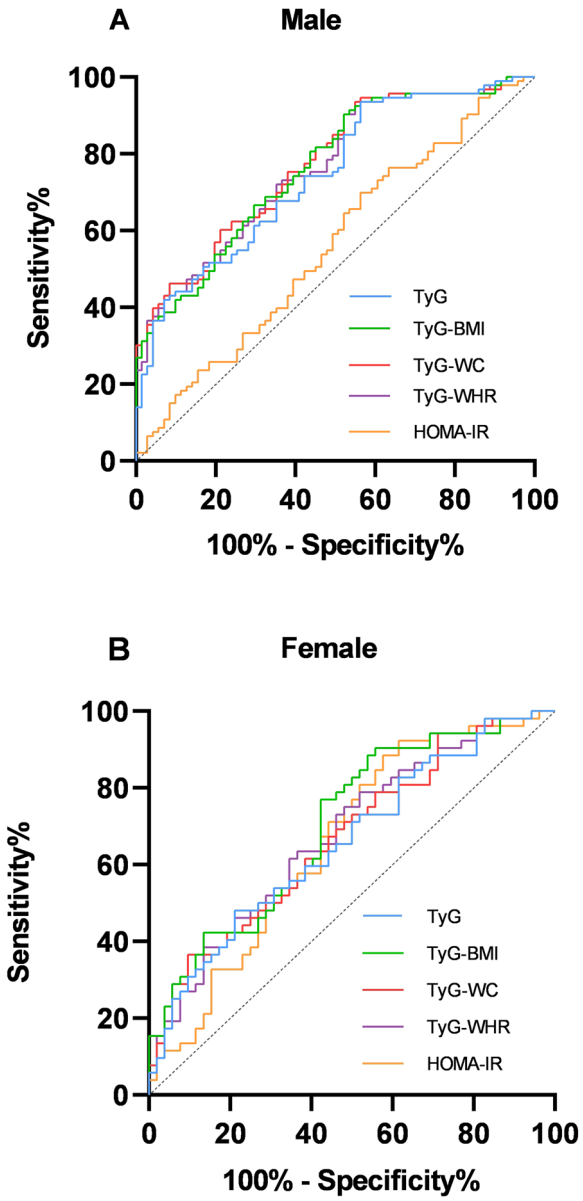

Fig. 2 ROC curve of parameters predicting NAFLD by sex. A:male; B:Female. Abbreviations: AUC Area under the receiver operating characteristic curve, WHR Waist-to-Hip Ratio, WC Waist circumference, TyG Triglyceride glucose, TyG-BMI Triglyceride glucose-body mass index, TyG-WC Triglyceride Glucose-Waist Circumference, HOMA-IR Homeostasis model assessment of insulin resistance index

with an AUC of 0.817, followed closely by TyG-WC and TyG-WHR (AUC of 0.809). When the cutoff value of TyG-BMI was 30.7, the overall performance was optimal, with a sensitivity of 80% and a specificity of 82.61%. HOMA-IR showed the poorest performance among the groups, with AUCs of 0.652, 0.533, and 0.552.

Relationship between different indices and NAFLD

The results showed that Even after adjusting for risk factors, elevations in TyG level, TyG-BMI, TyG-WC, and TyG-WHR remained independent predictors of NAFLD in patients with T2DM ($P<0.05$), as shown in Table 5. The scatter plot showed that for all indicators (TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR), the NAFLD group was significantly higher than the T2DM group (Fig. 3). Furthermore, after stratifying the parameters into quartiles, we observed a dose–response relationship between TyG-related parameters or HOMA-IR and the occurrence of NAFLD ($P<0.05$). The odds ratio (OR) of TyG-BMI increased in the highest parameter quartile. The ORs and 95% confidence intervals (CIs) of NAFLD for TyG-BMI were 0.082 (0.036–0.186), 0.280 (0.129–0.606), and 0.315 (0.145–0.685), respectively (Fig. 4).

Relationships between TyG, TyG-BMI, TyG-WC, TyG-WHR, CAP, and LSM

Generalized linear regression models were used to evaluate the relationships among the controlled attenuation parameter(CAP),Liver Stiffness Measurement(LSM), and the above indices. The results showed that TyG and its combination indexes TyG-BMI,TyG-WC,TyG-WHR were positively correlated with the βs (95% CI) of 21.30 (14.292, 28.323), 0.745 (0.623, 1.047), 0.247 (0.184, 0.310). and 24.40 (17.305–31.505) ($P<0.001$) respectively. HOMA-IR also had a positive relationship with CAP [β = 2.549 (95%CI 1.081,4.017), $P=0.001$]. In

Table 3 Cut-off values and AUCs (95%CI) of each parameter for predicting non-alcoholic fatty liver disease according to sex

	AUC (95%CI)	Cut-off value	Sensitivity (%)	Specificity (%)
Female ($n=104$)				
TyG	0.658(0.558—0.748)	2.04	48.08	78.85
TyG-BMI	0.702(0.605—0.788)	38.40	90.38	44.23
TyG-WC	0.670(0.571—0.759)	211.12	36.54	90.38
TyG-WHR	0.678(0.579—0.766)	1.43	78.85	48.08
HOMA-IR	0.659(0.560—0.749)	1.88	92.31	38.46
Male ($n=164$)				
TyG	0.744(0.670—0.809)	1.19	93.55	43.66
TyG-BMI	0.764(0.691—0.827)	31.54	90.32	47.89
TyG-WC	0.763(0.701—0.822)	186.62	60.22	78.87
TyG-WHR	0.764(0.691—0.826)	1.09	93.55	45.07
HOMA-IR	0.559(0.479—0.636)	2.282	69.89	43.66

Abbreviations: AUC Area under the receiver operating characteristic curve, *BMI* Body mass index, *WHR*Waist-to-Hip Ratio, *WC* Waist circumference, *TyG* Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circumference,*HOMA-IR*Homeostasis model assessment of insulin resistance index

Table 4 Cut-off values and AUCs (95%CI) of each parameter for predicting non-alcoholic fatty liver disease in different BMI subgroups

	AUC(95%CI)	Cut-off value	Sensitivity(%)	Specificity(%)
BMI < 23 ($n=28$)				
TyG	0.800(0.607-0.926)	2.04	60.00	100
TyG-BMI	0.817(0.626-0.937)	30.7	80.00	82.61
TyG-WC	0.809(0.616- 0.932)	108.11	80.00	82.61
TyG-WHR	0.809(0.616-0.932)	1.18	80.00	82.61
HOMA-IR	0.652(0.450- 0.821)	4.75	60.00	91.30
23 ≤ BMI < 25 ($n=47$)				
TyG	0.607(0.454–0.746)	1.82	52.17	79.17
TyG-BMI	0.620(0.466–0.757)	38.95	60.87	70.83
TyG-WC	0.627(0.474—0.763)	157.00	52.17	79.17
TyG-WHR	0.623(0.470—0.760)	1.71	47.83	83.33
HOMA-IR	0.533(0.381—0.680)	2.35	56.52	62.50
BMI ≥ 25 ($n=193$)				
TyG	0.671(0.599—0.736)	2.25	39.32	89.47
TyG-BMI	0.701(0.631—0.764)	68.10	39.3	92.10
TyG-WC	0.698(0.628—0.762)	211.12	47.01	86.84
TyG-WHR	0.690(0.620—0.755)	2.20	36.75	93.42
HOMA-IR	0.552(0.479—0.624)	1.90	85.47	30.26

Abbreviations: AUC Area under the receiver operating characteristic curve, *BMI* Body mass index, *WHR* Waist-to-Hip Ratio, *WC* Waist circumference, *TyG* Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circum ference, *HOMA-IR* Homeostasis model assessment of insulin resistance index

addition, we observed a positive association between TyG, its combination indices, and LSM (Table 6).

Discussion

To the best of our knowledge, this is the first study to explore the potential of insulin-based insulin resistance markers (HOMA-IR) and non-insulin-based insulin resistance markers (TyG, TyG-BMI, TyG-WC, and TyG-WHR) to identify NAFLD in patients with type 2 diabetes. In this study, we evaluated the performance of TyG-related indices and HOMA-IR for the diagnosis of NAFLD in patients with type 2 diabetes. We found that TyG-WC, TyG-BMI, and TyG-WHR, especially TyG-BMI, had better diagnostic values for NAFLD than the

Table 5 Logistic regression modelling of risk factors for NAFLD in patients with type 2 diabetes mellitus combined with fatty liver disease

Variable	Unadjusted		Model 1		Model2	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR (95%CI)	*P* value
TyG	3.415(2.223–5.245)	< 0.001	3.317(2.138–5.145)	< 0.001	2.875(1.521–5.434)	0.001
TyG-BMI	1.047(1.032–1.063)	< 0.001	1.047(1.031–1.062)	< 0.001	1.038(1.014–1.062)	0.002
TyG-WC	1.014(1.010–1.018)	< 0.001	1.014(1.009–1.018)	< 0.001	1.011(1.004–1.017)	0.002
TyG-WHR	4.512(2.631–6.553)	< 0.001	4.041(2.532–6.447)	< 0.001	3.478(1.764–6.861)	< 0.001
HOMA-IR	1.086(1.010–1.168)	0.027	1.080(1.003–1.163)	0.040	0.985(0.899–1.080)	0.75

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, blood pressure,BMI,fasting glucose, blood lipids and liver and kidney function

Abbreviations: TyG Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circumference, *HOMA-IR* Homeostasis model assessment of insulin resistance index

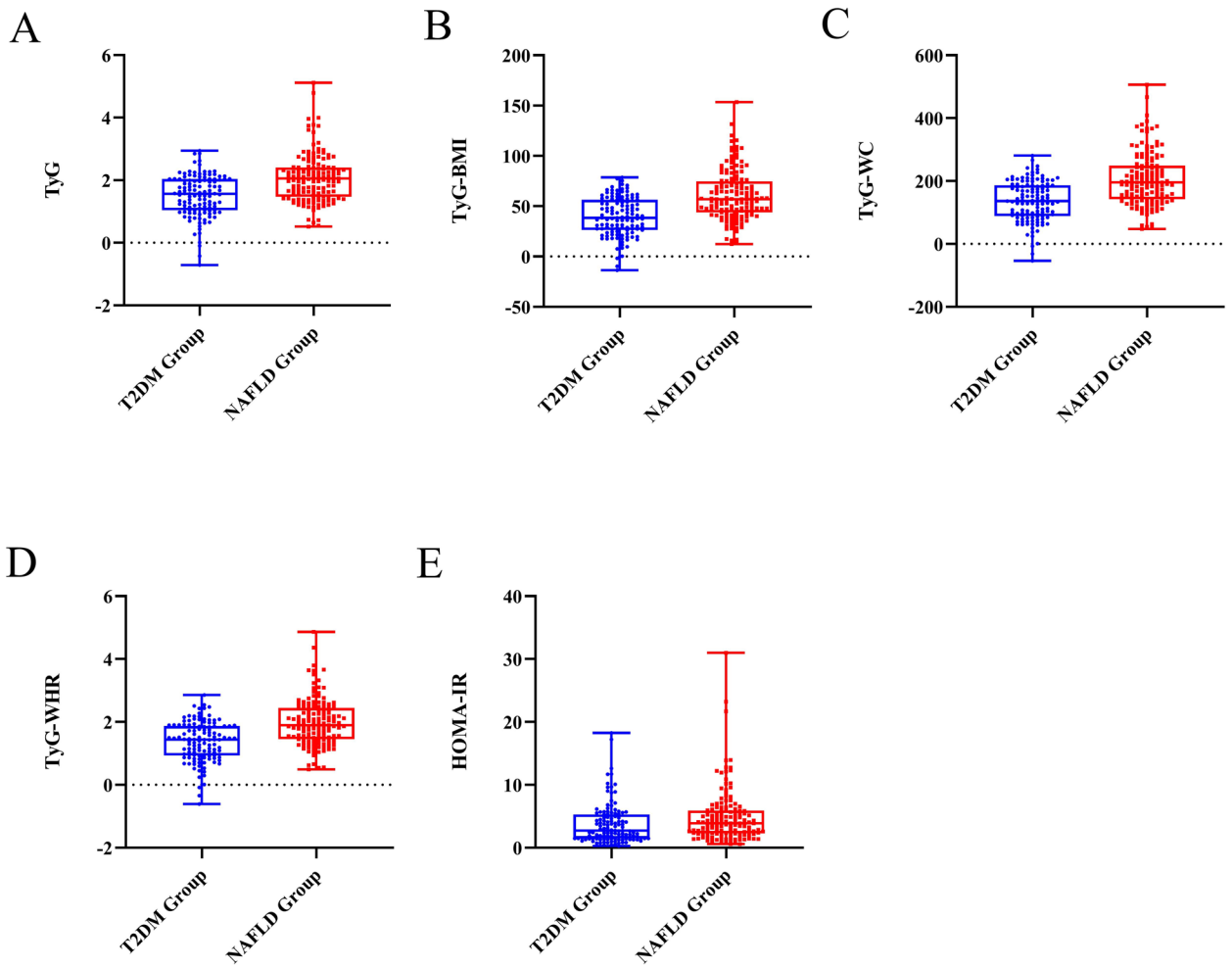

Fig. 3 Comparison of insulin resistance indicators between T2DM Group (T2DM without NAFLD) and NAFLD Group (T2DM with NAFLD)

TyG index and HOMA-IR, consistent with the subgroup analysis (Table 2, Fig. 1) Although the results showed that TyG-WC and TyG-WHR had some predictive potential, they were not as stable as TyG-BMI. To investigate the risk factors of NAFLD, we conducted a binary logistic regression analysis. Findings showed that TyG, TyG-BMI,

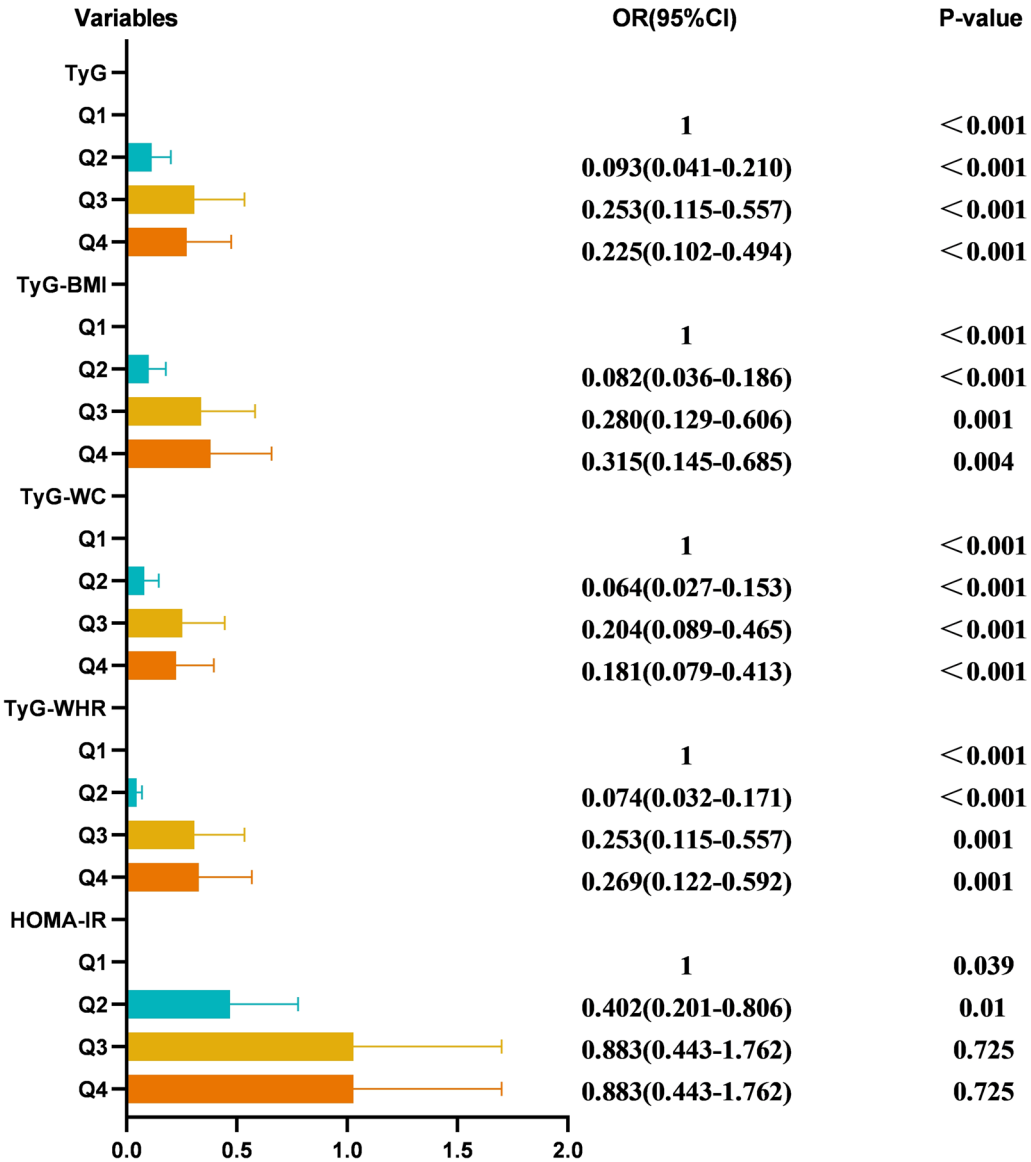

Fig. 4 NAFLD ORs and CIs by quartiles of TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR. Abbreviations: BMI Body mass index, WHR Waist-to-Hip Ratio, WC Waist circumference, TyG Triglyceride glucose, TyG-BMI Triglyceride glucose-body mass index, TyG-WC Triglyceride Glucose-Waist Circumference, HOMA-IR Homeostasis model assessment of insulin resistance index

Table 6 The relationship between TyG, TyG-BMI, TyG-WC, TyG-WHR and CAP, LSM

Exposure	CAP (dB/m) [β(95%CI)]	*p*-value	LSM (kpa) [β(95%CI)]	*p*-value
TyG	21.30(14.292,28.323)	< 0.001	0.872(0.237,1.507)	0.007
TyG-BMI	0.745(0.623,1.047)	< 0.001	0.042(0.022,0.061)	< 0.001
TyG-WC	0.247(0.184,0.310)	< 0.001	0.012(0.006,0.018)	< 0.001
TyG-WHR	24.40(17.305,31.505)	< 0.001	1.122(0.474,1.769)	0.001
HOMA-IR	2.549(1.081,4.017)	0.001	0.330(0.208,0.452)	< 0.001

Abbreviations: BMI Body mass index, *WHR* Waist-to-Hip Ratio, *WC* Waist circumference, *TyG* Triglyceride glucose, *TyG-BMI* Triglyceride glucose-body mass index, *TyG-WC* Triglyceride Glucose-Waist Circumference, *HOMA-IR* Homeostasis model assessment of insulin resistance index, *CAP* Controlled attenuation parameter, *LSM* Liver Stiffness Measurement

TyG-WC, TyG-WHR, and HOMA-IR were independent risk factors of NAFLD in T2DM patients. Additionally, TyG and its related indices, as well as HOMA-IR, were positively correlated with CAP values and LSM. For every unit increase in TyG, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR, the CAP increased by 21.30, 0.745, 0.747, 24.40, and 2.549 dB/m, respectively.

NAFLD is currently one of the most common chronic liver diseases worldwide, with a growing disease burden. However, its pathogenesis and early diagnosis remain unclear. Insulin resistance (IR) plays a critical role in NAFLD development. The hyperinsulinemia-euglycaemic clamp (HEC) method is widely regarded as the gold standard for measuring insulin resistance and sensitivity in humans [15]. However, this method is time-consuming, labor-intensive, and expensive, limiting its widespread application. HOMA-IR, a noninvasive measure based on fasting insulin (FINS), is extensively used in the clinical assessment of IR. Some researchers have considered other indices that do not rely on fasting insulin, such as TyG-related indices. Triglyceride-glucose (TyG) index is considered an ideal surrogate marker for IR in the general population [16], serving as a substitute for HOMA-IR, likely due to the close association between its primary indicators (triglycerides and fasting glucose) and "glucotoxicity" or "lipotoxicity." In addition, the TyG index is derived from fasting measurements, is cost-effective, and can be measured in all clinical laboratories without the need to quantify serum insulin levels. Therefore, the TyG index is a convenient and reliable method for IR detection. Numerous studies have found that the TyG index is an independent predictor of adverse cardiovascular events in patients with diabetes. Zhang et al. conducted a retrospective study of 1,072 patients with diabetes or prediabetes and cardiovascular disease [17] and found that the baseline TyG index showed a U-shaped relationship with all-cause and cardiovascular mortality in these patients. Specifically, the risk of death was lower when the TyG index was below 9.05 (all-cause mortality) and 8.84 (cardiovascular mortality), but increased above these thresholds. Liao et al. found that a higher TyG index was associated with a higher risk of death in critically ill ICU patients, suggesting that it may help identify patients with high-risk ICU and in-hospital mortality, thereby better predicting their prognosis [18]. Parameters related to the TyG index, combining the TyG index with WC, BMI, and WHR, were first reported by Er et al. [10]. As these parameters are essential components of glucose and fat metabolism, they are closely associated with the occurrence of NAFLD and can serve as reliable predictive indicators. Sheng et al. conducted an epidemiological survey of the general population to evaluate the optimal obesity and lipid-related indicators for predicting NAFLD [19]. They found that compared with visceral obesity indicators, lipid parameters, lipid ratios, and fat factors, TyG index-related parameters were good predictors of NAFLD. Subsequently, Li et al. used these parameters to measure the diagnostic rate of NAFLD in non-obese populations in the United States and found that TyG-WC had a better discriminatory power for NAFLD than other indicators, with an AUC of 0.806 [20].

Unlike previous studies that focused on obese populations or the general population, our research focused on the ability of the TyG index, TyG-BMI, TyG-WC, TyG-WHR, and HOMA-IR to diagnose NAFLD in individuals with type 2 diabetes. ROC curve analysis demonstrated that the AUC of TyG and its related parameters were higher than that of HOMA-IR (all $P<0.05$), with TyG-BMI exhibiting the largest AUC (0.738) (Table 2). This indicates that the TyG index is superior to other indicators in identifying NAFLD, a finding consistent with that reported by Chang et al. [21]. This may be due to our study's combination of BMI and TyG index, providing a comprehensive assessment of individuals' metabolic status and insulin resistance risk. Given the close association between NAFLD and systemic metabolic abnormalities, this aspect is particularly important for predicting NAFLD [22]. The BMI offers comprehensive insights, especially in patients with type 2 diabetes. In our study, the AUC of the TyG-WC was second only to that of the TyG-BMI (AUCs:0.737 and 0.738, respectively). However, WC data may vary owing to differences in measurement locations and between self-measurement and technician measurements [23]. Currently, there is no consensus regarding the best method for measuring waist circumference. In contrast, BMI is easy to measure and widely regarded as a key indicator for assessing overall obesity and various metabolic abnormalities. Therefore, TyG-BMI may be the best choice for screening NAFLD risk in patients with type 2 diabetes.

Notably, TyG-BMI performed well in both males and females, our data showed that it was more effective in predicting NAFLD in male type 2 diabetes (Table 3). It is well-known that there are differences in body composition, fat mass, and fat distribution between males and females. Males are more prone to accumulate fat in the trunk and abdominal areas, with this visceral adipose tissue (VAT) located in key organs involved in glucose homeostasis, such as the liver and pancreas, potentially triggering insulin resistance (IR) [24]. In contrast, endogenous estrogen has a protective role by reducing the accumulation of visceral fat and maintaining insulin sensitivity [25]. Therefore, despite the higher global obesity rate in females, their susceptibility to metabolic diseases is lower because of differences in fat storage patterns and hormonal protection.

Interestingly, this study revealed that the predictive potential of TyG and its related indicators varied across the different BMI subgroups. Stratification by BMI showed that TyG and its related parameters, especially TyG-BMI, had better predictive values for lean patients. Lean NAFLD was first reported in an Asian population with a prevalence of 25.2% [26]. Unlike previous studies, an increasing number of studies suggest that compared to obese NAFLD patients, lean NAFLD patients have a higher risk of developing diabetes, cardiovascular diseases, and all-cause mortality, and lean NAFLD is challenging to identify and treat [27]. Due to lifestyle and genetic factors, unlike Western populations, East Asians are more prone to lean NAFLD and more susceptible to insulin resistance (IR). In our study, the positive correlation between Ty-BMI and NAFLD in the lean population suggests that an increase in TyG may outweigh the effect of BMI reduction in individuals with NAFLD. This is consistent with previous findings [21]. This finding implies that insulin resistance caused by excessive visceral fat accumulation may play a significant role in the development of NAFLD in lean patients. Therefore, relying on reduced BMI or increased TyG levels may not be sufficient to accurately predict lean NAFLD. Combining TyG with BMI is crucial for a better diagnosis of lean NAFLD.

HOMA-IR is a simple and validated method that can be used clinically. This is a model of the interaction dynamics between glucose and insulin. In the present study, the diagnostic capability of HOMA-IR for NAFLD was limited. However, Zeng et al. reported an AUC of 0.724 for HOMA-IR, which was much higher than that of other insulin markers [28]. We speculate that this discrepancy may be related to variations in the diagnostic cutoff points, study populations, dietary habits, ultrasound diagnostic expertise, and regional differences. The HOMA-IR formula is based on a mathematical model of the insulin signaling pathway and, therefore, may not be suitable for lean populations, such as Asians, as well as those with lower beta-cell function and insulin secretion defects [29]. Furthermore, in the female subgroup, HOMA-IR outperformed in males, possibly because of differences in body fat, muscle mass, hormone levels, and fat distribution (subcutaneous and visceral fat) between men and women [30].

In this study, we aimed to investigate the predictive value of the insulin resistanc e index for non-alcoholic fatty liver disease in patients with type 2 diabetes. We included groups of T2DM patients with NAFLD and those without NAFLD but did not include a normal control group (with/without NAFLD). This design was chosen to focus specifically on the relationship between insulin resistance and NAFLD in T2DM patients. By comparing these two groups, we were able to directly assess the predictive value of the insulin resistance index for NAFLD in this population. However, this design has certain limitation: the absence of a normal control group means we cannot provide baseline data for comparing insulin resistance and NAFLD in the general population. In future studies, we plan to address this limitation by increasing the sample size and including normal control groups (with/without NAFLD) to obtain more comprehensive and reliable results. Secondly, the cross-sectional design precluded the establishment of causal relationships; only correlations were observed. Additionally, the data were collected from participants at a single institution, Considering the variations in TG levels among different ethnic groups, further research is needed to evaluate the applicability of TyG-BMI across different populations. In the future, we will increase the sample size to obtain more comprehensive and reliable findings. It's worth noting that the significant differences in WHR (cm) and BMI between NAFLD and non-NAFLD patients may have influenced our results. To address this, further research is needed to determine if the TyG index retains its accuracy in a BMI-matched group. In future studies, we aim to increase the sample size to achieve more comprehensive and reliable results.

Conclusion

Our study indicates that TyG-BMI has significant potential for predicting NAFLD among patients with type 2 diabetes, particularly in males and lean individuals. This finding highlights the importance of TyG-BMI as a simple and effective predictive marker in clinical practice and supports existing evidence that IR increases the risk of NAFLD. Additionally, individuals with normal BMI in the general population should undergo more comprehensive assessments to accurately evaluate the risk of NAFLD.

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Authors' contributions

J.T. wrote the manuscript, J.T .and YT.C. worked on data entry and data analysis, and WH.Z .and AY.W. and XY.W. prepared the figures and tables.All authors reviewed the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Jiangsu Province Hospital of Traditional Chinese Medicine, with a waiver of informed consent. All methods were conducted in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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