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Triglyceride glucose-body mass index as a useful predictor for metabolic associated fatty liver disease

Mingxing Chang[1], Zhihao Shao[1], Guifang Shen[1]*

[1]Department of Health Management Center, the Affiliated Hospital of Xuzhou Medical University, 99 west huai-hai road, Xuzhou, Jiangsu 221000 China

First author:

Mingxing Chang,

Department of Health Management Center, the Affiliated Hospital of Xuzhou Medical University, China, Master.

Email address: cmxfenger@163.com

Second author:

Zhihao Shao,

Department of Health Management Center, the Affiliated Hospital of Xuzhou Medical University, China, Bachelor.

Email address: 601515650@qq.com

***Corresponding author:**

Guifang Shen,

Department of Health Management Center, the Affiliated Hospital of Xuzhou Medical University, China, Professor.

Email address: 2294194657@qq.com

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Declarations

Ethical approval and consent to participate

The study was approved and supervised by the Ethics Committee of the Affliated Hospital of Xuzhou Medical University. The need for written informed consent to participate was waived by the Ethics Committee of the Affliated Hospital of Xuzhou Medical University due to retrospective nature of the study. Declaration of Helsinki: All methods were carried out in accordance with the relevant

guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

All authors have declared that they have no conflicts of interest.

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Author Contributions

Mingxing Chang and Guifang Shen conceived and designed the study.

Mingxing Chang and Zhihao Shao coordinated data collection and conducted the analyses.

Mingxing Chang wrote the manuscript.

All authors have read and approved the final manuscript.

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Abstract

Objectives To evaluate the performance of triglyceride glucose (TyG) index and its related markers in identifying metabolic associated fatty liver disease (MAFLD) among Chinese healthy subjects.

Designs Cross-sectional study.

Setting Health management of the Affiliated Hospital of Xuzhou Medical University.

Participants 20,922 asymptomatic participants (56% male).

Measures Hepatic ultrasonography was performed to determine the presence of MAFLD based on the latest diagnostic criteria. The TyG index, TyG-body mass index (TyG-BMI), and TyG-waist circumference (TyG-WC) were subsequently calculated and analyzed.

Results: Compared with the lowest quartile of TyG-BMI, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for MAFLD were 20.76 (14.54-29.65), 92.33 (64.61-131.95) and 380.87 (263.25-551.05) in the 2nd, 3rd and 4th quartiles, respectively. According to the subgroup analysis, TyG-BMI in female group and lean group (BMI<23kg/m^2) showed the most effective predictive value, the optimal cut-off points of TyG-BMI for MAFLD were 162.05 and 156.31 respectively, the areas under the ROC curves (AUCs) were 0.933 (95% CI: 0.927-0.938) and 0.928 (95% CI: 0.914-0.943), with 90.7% sensitivity and 81.2% specificity in female MAFLD and 87.2% sensitivity and 87.1% specificity in lean MAFLD, respectively. The predictability of the TyG-BMI for MAFLD was much better than that other markers.

Conclusions: The TyG-BMI index was effective and convenient for identifying MAFLD, especially in the lean population and female population.

Key Words: Metabolic associated fatty liver disease, The triglyceride glucose-body mass index, The triglyceride glucose

Strengths and limitations of this study

(1) This was a large-scale study on the performance of triglyceride glucose (TyG) index and its related markers in identifying metabolic associated fatty liver disease (MAFLD) among Chinese healthy subjects.

(2) A limitation is that the diagnosis of MAFLD was based on ultrasonography, which may have underestimated the true prevalence of MAFLD.

(3) Another limitation is that liver biopsy data and the controlled attenuation parameter and liver stiffness measurement from the Fibroscan Test were not measured.

1. Introduction

The prevalence of metabolic associated fatty liver disease (MAFLD), formly known as non-alcoholic fatty liver disease (NAFLD), has dramatically increasing up to 25% worldwide[1]. Furthermore, studies have linked MAFLD to a variety of adverse clinical sequelae, including severe liver inflammation and fibrosis, metabolic and cardiovascular diseases that may eventually result in increased mortality[2]. Early identification of MAFLD is therefore the primary step. However, a non-invasive tool for MAFLD screening taking simplicity, efficiency and availability into account is still lacking yet.

MAFLD develops through complex interactions between obesity and insulin resistance (IR)[5]. Traditional obesity indicators including body mass index (BMI) and waist circumference (WC) , these elevated indicators are strongly associated with fatty liver and metabolic disorders[6]. But some studies have shown that 5% to 26% of MAFLD patients have a BMI within the normal range[8]. If some people are pre-MAFLD or have normal weight, they generally tend to be ignored. In addition, single BMI or WC could not make a comprehensive reflection of MAFLD because of the neglection of IR. The triglyceride-glucose (TyG) index is a newly proposed index that is more simple and reliable for IR than the homeostasis model assessment of IR index. Importantly, Gastaldelli et al. found that TyG was well correlated with the amount of hepatic fat in the SAM study[9].

The TyG index combined with obesity markers, including TyG-BMI and TyG-WC, could describe both obesity and IR, thereby better reflecting the complex pathophysiological features. Several studies have shown that TyG-related indices are more successful than those single indicators in identifying metabolic and cardiovascular diseases[10]. Therefore, we speculated that the TyG-related indices were quite potential and promising in predicting MAFLD. Herein, we investigated the performance of TyG-related markers to

distinguish MAFLD from healthy subjects and establish a better prediction model for MAFLD.

2. Methods

2.1 Study design and population

This cross-sectional study used data from an urban population in Eastern China who participated in the health examination at the Affliated Hospital of Xuzhou Medical University from January 2021 to December 2021. The inclusion criteria were as follows: age between 18-80 years; hepatic steatosis discovered by abdominal ultrasound. The exclusion criteria were as follows: incomplete data; age younger than 18 years or older than 80 years; hepatic cirrhosis, hepatocellular carcinoma or history of liver surgery; history of malignant tumors; New York Heart Association class III or IV heart failure; chronic kidney disease with an estimated glomerular filtration rate <60mL/min/1.73m^2; pregnancy or lactation. This study followed TRIPOD reporting guidelines[14].

2.2 Methods

2.2.1 Health survey examinations and laboratory measurements

BMI, WC, and blood pressure were measured by trained examiners, and the following laboratory data were measured at the same time that participants underwent health examinations: fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyltransferase (GGT), blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA). The TyG-related parameters were calculated using the following formulae:

$$\mathbf{TyG} = \mathbf{ln}\,\frac{[\mathbf{TG(mg/dL)} * \mathbf{FPG(mg/dL)}]}{\mathbf{2}}$$

$$\mathbf{TyG{-}BMI} = \mathbf{TyG} \times \mathbf{BMI}\ (\mathbf{kg/m^2})$$

$$\mathbf{TyG{-}WC} = \mathbf{TyG} \times \mathbf{WC}\ (\mathbf{cm})$$

2.2.2 Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

2.2.3 Diagnosis of MAFLD

Herein in our study, we used the novel and positive criteria for the diagnosis of MAFLD regardless of the presence of other concomitant liver diseases or alcohol consumption[14]. The proposed criteria were based on liver steatosis (detected either by medical imaging, blood biomarkers/scores or by liver histology) together with the presence of at least one of the following three criteria that included overweight or obesity, presence of type 2 diabetes mellitus or clinical evidence of metabolic dysfunction. The latter was defined by the presence of at least two metabolic risk abnormalities, listed in Figure 1.

2.3 Statistical Analysis

Statistical analysis was executed in SPSS 22.0 and MedCalc 16.2. Differences between MAFLD and non-MAFLD individuals were assessed using the Student's t test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Binary logistic regression models were constructed to explore correlations between indicators and MAFLD. The predictive value of TyG-related indices for MAFLD was assessed with a receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). The AUC difference of TyG-related indices were compared by the nonparametric Delong test. A two-tailed p value<0.05 was considered statistically significant.

3. Results

3.1 Clinical and biochemical characteristics of the subjects

The flowchart of subjects screening was shown in Table 1. Compared with the non-MAFLD group, significantly higher levels of age, blood pressure, ALT, AST, GGT, BUN, UA, FPG, TC, TG and LDL-C were observed in MAFLD individuals (all P<0.0001). Notably, the BMI, WC and TyG-related indices were significantly higher in MAFLD subjects than those without MAFLD (all P<0.0001).

Table 1 Clinical and biochemical characteristics in MAFLD and non-MAFLD groups

	MAFLD	Non-MAFLD	P-value
N (%)	8099 (38.71%)	12823 (61.29%)	<0.0001
Gender (M)	6152/1947	6191/6632	<0.0001
Age (years)	46.91±12.57	42.16±12.65	<0.0001
SBP (mmHg)	131.97±17.47	120.11±16.60	<0.0001
DBP (mmHg)	81.53±11.90	73.51±10.97	<0.0001
BMI (kg/m^2)	27.14±2.90	22.69±2.65	<0.0001

WC (cm)	90.44±8.46	77.16±9.06	<0.0001
TyG	7.44±0.61	6.77±0.53	<0.0001
TyG-BMI	202.04±28.85	154.16±24.91	<0.0001
TyG-WC	673.57±90.67	524.59±87.49	<0.0001
ALT (U/L)	26 (18,38)	15 (11,21)	<0.0001
AST (U/L)	22 (18,27)	18 (16,22)	<0.0001
GGT (U/L)	32 (22,49)	17 (13,25)	<0.0001
BUN (mmo/l)	5.15±1.24	4.84±1.26	<0.0001
Cr (umo/l)	66.43±13.07	66.49±13.07	0.731
UA (umo/l)	354.36±84.81	290.96±76.54	<0.0001
FPG (mmo/l)	5.29 (4.93,5.78)	4.98 (4.71,5.29)	<0.0001
TG (mmo/l)	4.78±0.96	4.45±0.87	<0.0001
TC (mmo/l)	1.83 (1.31,2.63)	1.03 (0.76,1.43)	<0.0001
HDL-C (mmo/l)	1.19±0.26	1.38±0.30	<0.0001
LDL-C (mmo/l)	3.13±0.73	2.84±0.69	<0.0001

3.2 Relationships between different indicators and MAFLD

Our research indicated that elevated BMI, WC, TyG, TyG-BMI and TyG-WC were all identified as independent predictors of MAFLD even after a full adjustment (all P<0.0001) (Table 2). When categorizing the parameters into quartiles, we observed a dose-response fashion between all the parameters and risk of MAFLD (all p < 0.0001) (Figure 2).

In general, the MAFLD ORs increased in the 2nd, 3rd and 4th quartiles compared to the respective 1st quartile of the parameters. The increase in the risk according to the higher quartiles was most pronounced when the TyG-BMI was applied. The full adjusted ORs and 95% CIs for MAFLD were 20.76 (14.54-29.65), 92.33 (64.61-131.95) and 380.87 (263.25-551.05) in the 2nd, 3rd and 4th quartiles of TyG-BMI, respectively, compared with those in the 1st quartile. The multivariable adjusted ORs (95% CIs) for the 4th quartiles of the BMI, WC, TyG and TyG-WC were 88.86 (69.93-112.91), 62.44 (51.28-76.02), 3.60 (3.02-4.29), 145.91 (112.79-188.76) respectively, compared to the 1st quartile.

Table 2 Binary logistic regression analysis of five markers in predicting MAFLD

Variable	Unadjusted		Model 1		Model 2	
	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value

BMI	1.87(1.84-1.90)	0.000	1.83(1.80-1.87)	0.000	1.67(1.64-1.70)	0.000
WC	1.19(1.18-1.19)	0.000	1.21(1.20-1.22)	0.000	1.17(1.16-1.17)	0.000
TyG	8.23(7.70-8.78)	0.000	6.73(6.29-7.20)	0.000	4.36(3.82-4.99)	0.000
TyG-BMI	1.07(1.07-1.07)	0.000	1.07(1.07-1.08)	0.000	1.07(1.07-1.08)	0.000
TyG-WC	1.02(1.02-1.02)	0.000	1.02(1.02-1.02)	0.000	1.02(1.02-1.02)	0.000

Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, blood pressure, fasting glucose, blood lipid, liver and kidney functions.

3.3 Predictive values of different indicators for MAFLD subgroups

3.3.1 Predictive values of different indicators for gender subgroups

As shown in Table 3 and Figure 3, the highest AUC was demonstrated by the TyG-BMI both in males and females (AUC = 0.870 and 0.933, respectively). The TyG-BMI had significantly higher AUC values than the traditional recommended metabolic parameters (BMI and WC) and the other TyG-related indices (all $p < 0.0001$). A TyG-BMI cutoff of 162.05 in females showed the best overall test performance, with a sensitivity of 90.7% and a specificity of 81.2%. (Table 2 and Figure 3).

Table 3 Cut-off points and AUCs (95% CI) of each parameter for predicting MAFLD in males and females

	AUC (95% CI)	Cut-off values	Sensitivity(%)	Specificity(%)
Male (n=12343)				
BMI	0.844 (0.837-0.851)	25.35	75.4	75.7
WC	0.818 (0.810-0.825)	87.50	73.7	73.5
TyG	0.753 (0.744-0.761)	7.10	73.3	64.4
TyG-BMI	0.870 (0.864-0.876)	181.22	79.9	76.3
TyG-WC	0.847 (0.841-0.854)	625.58	78.0	74.5
Female (n=8579)				
BMI	0.900 (0.893-0.907)	23.05	92.2	73.1
WC	0.890 (0.883-0.897)	76.50	84.9	76.8
TyG	0.830 (0.820-0.841)	6.86	77.6	73.8
TyG-BMI	0.933 (0.927-0.938)	162.05	90.7	81.2
TyG-WC	0.922 (0.915-0.928)	529.41	87.9	80.9

3.3.2 Predictive values of different indicators for BMI subgroups

As shown in Table 4 and Figure 4, for different BMI groups, the TyG-BMI performed especially well in lean group (BMI<23kg/m^2) with an AUC of 0.928. A TyG-BMI cutoff of 156.31 in lean group showed the best overall test performance, with a sensitivity of 87.2% and a specificity of 87.1%. Distinct from the previous result, BMI and WC were the worst performer of all three groups (AUC [BMI], 0.763, 0.600, 0.709; AUC [WC], 0.794, 0.635, 0.695, respectively).

Table 4 Cut-off points and AUCs (95% CI) of each parameter for predicting MAFLD in different BMI subgroups

	AUC (95% CI)	Cut-off values	Sensitivity(%)	Specificity(%)
BMI<23 (n=7377)				
BMI	0.763 (0.739-0.788)	21.65	77.5	64.7
WC	0.794 (0.771-0.817)	74.50	79.8	65.4
TyG	0.924 (0.908-0.940)	7.11	89.1	85.2
TyG-BMI	0.928 (0.914-0.943)	156.31	87.2	87.1
TyG-WC	0.918 (0.905-0.931)	541.99	88.0	83.0
23≤BMI<25 (n=4799)				
BMI	0.600 (0.583-0.616)	24.05	55.3	59.1
WC	0.635 (0.618-0.651)	80.5	70.7	48.0
TyG	0.717 (0.702-0.732)	7.10	63.7	68.3
TyG-BMI	0.730 (0.716-0.745)	169.67	67.7	66.9
TyG-WC	0.724 (0.709-0.739)	572.91	73.1	60.9
BMI≥25 (n=8746)				
BMI	0.709 (0.698-0.720)	27.25	55.7	75.7
WC	0.695 (0.683-0.707)	90.50	58.3	69.8
TyG	0.715 (0.703-0.726)	7.19	65.6	66.0
TyG-BMI	0.778 (0.767-0.788)	194.83	69.2	73.5
TyG-WC	0.756 (0.745-0.767)	652.43	65.4	72.4

4. Disccusion

In this cross-sectional study, we identified the relationships between TyG-related indices and risk of MAFLD. We discovered that people with higher levels of TyG-related indices were more likely to have MAFLD. These parameters followed a dose-response pattern across the quartiles even after a full adjustment. However, TyG-BMI was the the best performer among them, the

participants in the highest TyG-BMI quartile group were 380.87 times more likely to have MAFLD than those in the lowest quartile group. Subgroup analysis further verified the validity of TyG-BMI for the detection of MAFLD in healthy subjects. It was the most reliable indicator for MAFLD among the parameters with a high discrimination power both in different gender and BMI subgroups. Notably, TyG-BMI performed especially well in lean subgroup and the female subgroup. The above findings supported the adoption of TyG-BMI as an alternative screening test for MAFLD.

To date, there have only been a few investigations on the diagnostic effectiveness of the TyG-related indices for MAFLD[15]. Ehsaneh Taheri and colleagues first evaluated the association of TyG index with MAFLD risk in an Iranian population. Among those in the highest relative to the lowest TyG tertiles, the multivariable-adjusted ORs (95% CI) were 12.01 (9.03 - 15.98) and 10.89 (7.66 - 15.48), respectively. The results demonstrated that a TyG index cutoff of 8.62 had 81.66% sensitivity and 75.36% specificity[15]. However, that study used the fatty liver index to define MAFLD rather than ultrasonography or liver biopsies, and it did not assess the performance of TyG-BMI or TyG-WC. In contrast, another Chinese study reported results that were consistent with Ehsaneh Taheri's. Besides, the study also found that a combination of TyG, BMI and ALT improved the diagnostic capability for MAFLD. The combined model demonstrated an AUC of 0.985 (95% CI, 0.973-0.998) compared to TyG alone (AUC=0.943; 95% CI, 0.912-0.973) and TyG-BMI (AUC=0.956; 95% CI, 0.933-0.980). This study exhibited a higher diagnostic accuracy than that found in our study, but it only included a small sample size of 229 patients[16]. Furthermore, Yan Xue et al. provided evidence for TyG-related indices as better predictive indicators for MAFLD than NAFLD. The top performer was TyG-WC, with an AUC (95% CI) of 0.815 (0.796–0.833) to predict NAFLD and 0.832 (0.814–0.850) to predict MAFLD[17]. However, different from previous studies, our study made a comprehensive assessment of the performance of TyG-related indices, including TyG, TyG-BMI and TyG-WC, to screen and identify MAFLD in a large-scale population.

Of note, the present study revealed that the predictive accuracies of TyG-related indices have varied in different subgroups. When we stratified MAFLD individuals by BMI profile, we found that TyG-BMI performed especially well in lean population. Although MAFLD has been increasing in parallel with the rising prevalence of obesity, it should be noted that lean individuals may also suffered from MAFLD. A recent study in China found that among the nonobese population, the prevalence of MAFLD was 11.5% (males: 16.4%, females: 6.9%), consistent with Vilarinho's[18]. Importantly, lean MAFLD is not a benign or stable state as expected. A number of studies even suggested that lean individuals with MAFLD have an increased risk of diabetes mellitus, cardiovascular and all-cause mortality, compared to those with obese MAFLD[20]. BMI is widely used to

evaluate obesity, but not to describe regional fat distribution. The contribution of visceral fat to MAFLD was more important than total body fat[22]. Though Asians have a lower absolute BMI than Westerners, yet asians were more vulnerable to visceral fat accumulation and IR[23]. Thus, the reduced BMI levels were not capable of representing a metabolically healthy state. IR caused by excessive accumulation of visceral fat may be more pronounced in the development of lean MAFLD[24]. Yu ling et al. revealed that metabolic disorders in nonobese individuals with MAFLD were all significantly higher than those in nonobese individuals without MAFLD[18]. These findings imply that IR may be the leading cause in the development of lean MAFLD.

On other hand, the predict value of TyG-related indices also differed after a gender classification. Significantly, TyG-BMI was the top performer both in males and females, but more accurate in predicting female MAFLD. The current study and one of the previous study came to the same conclusion that MAFLD is much more common in men than women (P<0.0001). In addition, Yu ling et al. further described the age-related prevalence of MAFLD. Males were more susceptible to MAFLD at younger ages and then rose slowly until middle ages, but for females, the prevalence rose slowly during younger ages but suddenly accelerated after the age of 45[18]. This epidemic trend difference indicated that the decrease in estrogen may be the primary cause in aging female MAFLD. Low estrogen levels during the postmenopausal periods may be an important risk factor for MAFLD in females[25]. A number of studies have found that the decreased estrogen levels were associated with many metabolic disorders, including dyslipidemia and IR. The lack of estrogen availability also decreased hepatic insulin clearance and allowed the development of diet-induced IR[26]. Therefore, the increased TyG-BMI levels were closely relevant to the risk of MAFLD for female individuals. However, the concret and precise mechanisms remained to be clarified.

Our study had several limitations. First, the diagnosis of MAFLD was based on ultrasonography, which might be partially insensitive when liver steatosis is below 30%[28]. Therefore, using ultrasound to screen for MAFLD may have underestimated the true prevalence of MAFLD. Second, some information was not available from the current health examination data, such as the liver biopsy data or the controlled attenuation parameter and liver stiffness measurement from the Fibroscan Test. Further studies on the relationships between TyG-related indices and the severity of MAFLD are yet to be achieved. Third, we included asymptomatic individuals attending a single center, thus certain selection bias was inevitable. Multi-center and prospective studies will be needed to evaluate broader populations to validate our findings.

The main strength of our study lied in the large sample size and the fresh evidence for the use of TyG-BMI to identify lean MAFLD and female MAFLD. We enrolled a large-scale population with a wide range of clinical data to ensure

statistical reliability and enabled us to validate our main findings from multiple angles and levels. Besides, our study may provide some clinical implications. Vitally, our study first demonstrated that the assessment of TyG-BMI could be helpful in identifying high-risk MAFLD population, especially for the lean population and female population.

In conclusion, the present study suggested that TyG-BMI was a useful predictor for MAFLD. Individuals with normal BMI levels but high TyG-BMI levels should also then undergo a more detailed assessment for MAFLD. And our findings extended previous investigations by demonstrating that TyG-BMI might be ideal for the prediction of lean MAFLD and female MAFLD.

Figure legends

Figure 1 The flowchart of diagnositic criteria for MAFLD

Figure 2 The MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, TyG-WC in the total population

Figure 3 ROC curve of each parameter for predicting MAFLD in males and females

Figure 4 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

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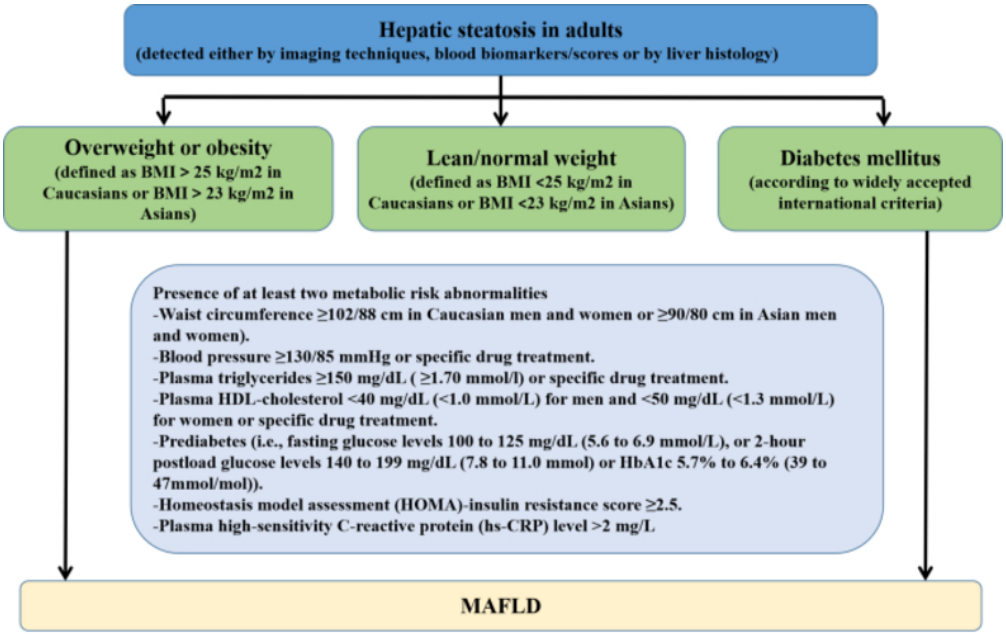

Figure 1 The flowchart of diagnositic criteria for MAFLD

169x106mm (118 x 118 DPI)

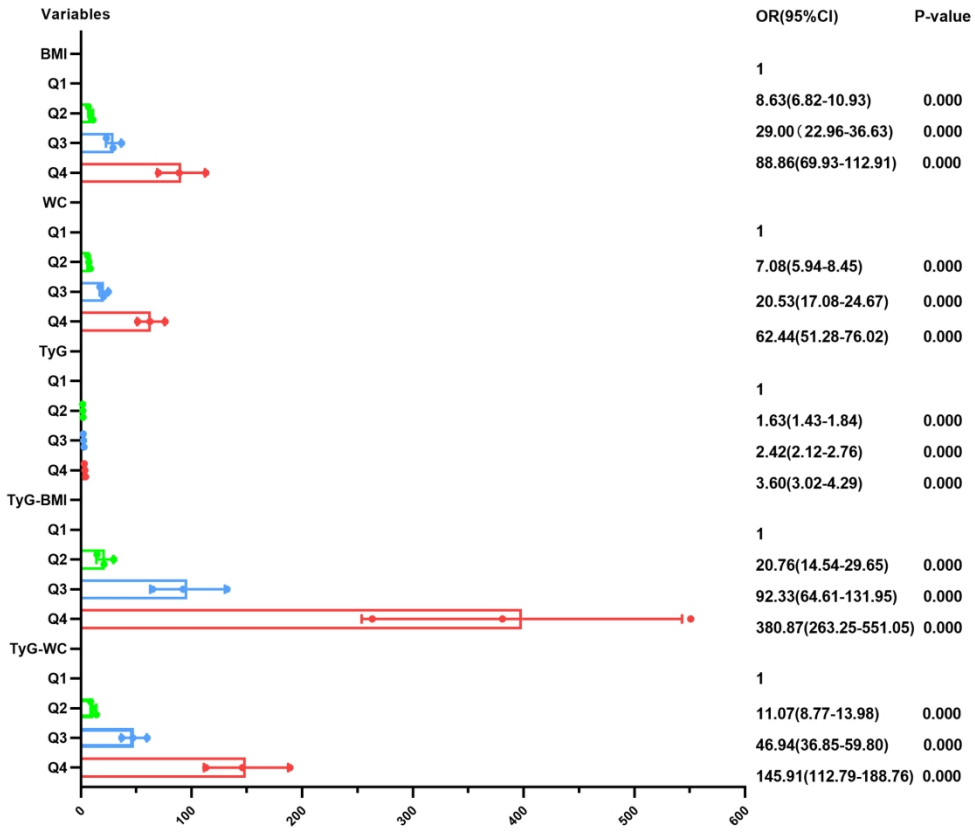

Figure 2 The MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, TyG-WC in the total population

190x163mm (300 x 300 DPI)

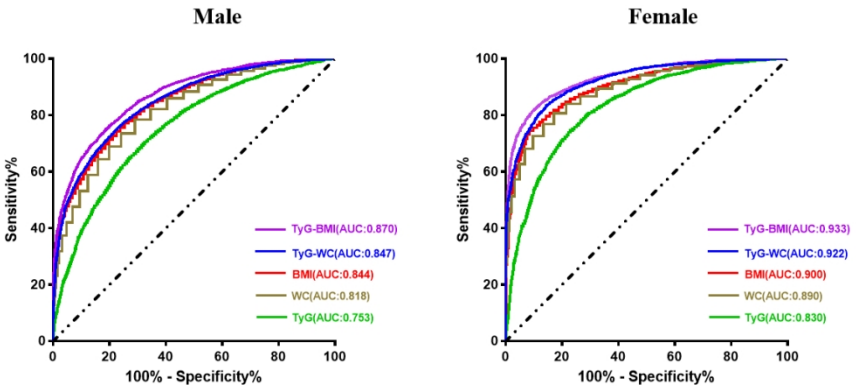

Figure 3 ROC curve of each parameter for predicting MAFLD in males and females

288x115mm (118 x 118 DPI)

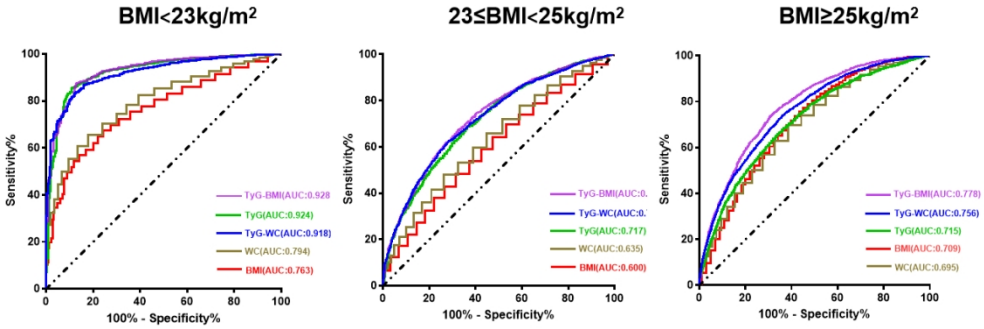

Figure 4 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

286x97mm (118 x 118 DPI)

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	3
Abstract			
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction			
	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4

	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
Participants	#5b	Describe eligibility criteria for participants.	5
Participants	#5c	Give details of treatments received, if relevant	NA not relevant
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	5
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	#8	Explain how the study size was arrived at.	NA this is a large scale study
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	6
Statistical	#10b	If you are developing a prediction model, specify type of	6

analysis methods		model, all model-building procedures (including any predictor selection), and method for internal validation.	
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	NA without a validating model
Statistical analysis methods	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	NA without a validating model
Risk groups	#11	Provide details on how risk groups were created, if done.	5
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA without a validating model
Results			
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
Participants	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA without a validating model
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	7-9
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	7-9

Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	7-9
Model specification	#15b	If developing a prediction model, explain how to the use it.	9
Model performance	#16	Report performance measures (with CIs) for the prediction model.	7-9
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	NA without a validating model
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	NA without a validating model
Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-11
Implications	#20	Discuss the potential clinical use of the model and implications for future research	10-12
Other information			
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	2
Funding	#22	Give the source of funding and the role of the funders for the present study.	2

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Associations between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease : a cross-sectional study in healthy Chinese subjects.

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Keywords:	Other metabolic, e.g. iron, porphyria < DIABETES & ENDOCRINOLOGY, Adult gastroenterology < GASTROENTEROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Associations between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease : a cross-sectional study in healthy Chinese subjects

Mingxing Chang[1], Zhihao Shao[1], Guifang Shen[1]*

[1]Department of Health Management Center, the Affiliated Hospital of Xuzhou Medical University, 99 West Huai-Hai Road, Xuzhou, Jiangsu 221000 China

First author:

Mingxing Chang,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, China, Master.

Email address: cmxfenger@163.com

Second author:

Zhihao Shao,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, China, Bachelor.

Email address: 601515650@qq.com

***Corresponding author:**

Guifang Shen,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, China, Professor.

Email address: 2294194657@qq.com

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Associations between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease : a cross-sectional study in healthy Chinese subjects

Abstract

Objectives The aim of this study was to evaluate the performance of the triglyceride glucose (TyG) index and its related markers in predicting metabolic-associated fatty liver disease (MAFLD) in healthy Chinese subjects.

Design This was a cross-sectional study.

Setting The study was conducted at Health Management Department of the Affiliated Hospital of Xuzhou Medical University.

Participants A total of 20922 asymptomatic participants (56% male) were enrolled.

Measures Hepatic ultrasonography was performed to determine the presence of MAFLD based on the latest diagnostic criteria. The TyG index, TyG-body mass index (TyG-BMI), and TyG-waist circumference (TyG-WC) index were calculated and analysed.

Results Compared with the lowest quartile of the TyG-BMI, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for MAFLD were 20.76 (14.54-29.65), 92.33 (64.61-131.95) and 380.87 (263.25-551.05) in the 2nd, 3rd and 4th quartiles, respectively. According to the subgroup analysis, the TyG-BMI in the female group and the lean group (BMI<23 kg/m^2) showed the most effective predictive value, with optimal cut-off points for MAFLD of 162.05 and 156.31, respectively. The areas under the receiver operating characteristic (ROC) curves (AUCs) were 0.933 (95% CI: 0.927-0.938) and 0.928 (95% CI: 0.914-0.943), respectively, with 90.7% sensitivity and 81.2% specificity in female subjects with MAFLD and 87.2% sensitivity and 87.1% specificity in lean subjects with MAFLD. The ability of the TyG-BMI to predict MAFLD was much better than that of other markers.

Conclusions The TyG-BMI may be effective and convenient for predicting MAFLD, especially in lean subjects and in female subjects.

Key Words: Metabolic-associated fatty liver disease, the triglyceride glucose-body mass index, the triglyceride glucose

Strengths and limitations of this study

⇒ This was the first study involved comprehensive assessment of the performance of the triglyceride glucose (TyG) index and its related markers in predicting metabolic-associated fatty liver disease (MAFLD) in healthy Chinese subjects.

⇒ A limitation was that the diagnosis of MAFLD was based on ultrasonography, which may have underestimated the true prevalence of MAFLD.

⇒ Another limitation was that liver biopsy data and the controlled attenuation parameter and liver stiffness measurement from the FibroScan Test were not obtained.

⇒ Results should be interpreted carefully due to the observational design and further studies would be needed to validate our findings in broader populations.

1. Introduction

The prevalence of metabolic-associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has dramatically increased up to 25% worldwide[1]. Furthermore, studies have linked MAFLD to a variety of adverse clinical sequelae, including severe liver inflammation and fibrosis and metabolic and cardiovascular diseases and even extra-hepatic cancer such as bladder cancer that may eventually result in increased mortality[2]. Early identification of MAFLD is therefore critical. However, a non-invasive tool for MAFLD screening that is simple to use, efficient, and available is lacking.

MAFLD develops through complex interactions between obesity and insulin resistance (IR)[6]. Traditional obesity indicators, including body mass index (BMI) and waist circumference (WC) are strongly associated with fatty liver and metabolic disorders[7]. However, some studies have shown that 5% to 26% of MAFLD patients have a BMI within the normal range[9]. If some people are pre-MAFLD or have normal weight, they generally tend to be ignored. In addition, BMI or WC alone cannot provide a comprehensive reflection of MAFLD because of the neglect of IR. The triglyceride-glucose (TyG) index is a newly proposed index that is simpler and more reliable for evaluating IR than the homeostasis model assessment of IR index. Importantly, Gastaldelli et al. found that the TyG index was well correlated with the amount of hepatic fat in the San Antonio Metabolism (SAM) study[10].

The TyG index combined with obesity markers, including the TyG-BMI and TyG-WC index, could be used to describe both obesity and IR, thereby better

reflecting these complex pathophysiological features. Several studies have shown that TyG-related indices are more successful than single indicators in identifying metabolic and cardiovascular diseases[11]. Therefore, we speculated that the TyG-related indices were quite promising in predicting MAFLD. Herein, we investigated the performance of TyG-related markers in distinguishing MAFLD in healthy subjects and established a better prediction model for MAFLD.

2. Methods

2.1 Study design and population

This cross-sectional study used data from an urban population in eastern China who participated in a health examination at the Affiliated Hospital of Xuzhou Medical University from January 2021 to December 2021. The inclusion criteria were as follows: age between 18 and 80 years and hepatic steatosis discovered by abdominal ultrasound. The exclusion criteria were as follows: incomplete data; age younger than 18 years or older than 80 years; hepatic cirrhosis, hepatocellular carcinoma or history of liver surgery; history of malignant tumours; New York Heart Association class III or IV heart failure; chronic kidney disease with an estimated glomerular filtration rate of <60mL/min/1.73m^2; and pregnancy or lactation. Subjects with missing outcome measures and lost clinical and biochemical records were also excluded. Finally, 20922 subjects (8099 MAFLD cases and 12823 non-MAFLD controls) were included in the final analysis (Figure 1). This study followed the TRIPOD reporting guidelines[17] and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. To avoid duplication of information, we only use the first physical examination data of participants who underwent multiple physical examinations throughout the year.

2.2 Methods

2.2.1 Health survey examinations and laboratory measurements

BMI, WC, and blood pressure were measured by trained examiners, and the following laboratory data were measured at the same time that participants underwent health examinations: fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyltransferase (GGT), blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA). The TyG-related parameters were calculated using the following formulae[17]:

$$\mathbf{TyG} = \mathbf{ln}\frac{[\mathbf{TG(mg/dL)} * \mathbf{FPG(mg/dL)}]}{\mathbf{2}}$$

$$\mathbf{TyG{-}BMI} = \mathbf{TyG} \times \mathbf{BMI}\ (\mathbf{kg/m^2})$$

$$\mathbf{TyG{-}WC} = \mathbf{TyG} \times \mathbf{WC}\ (\mathbf{cm})$$

2.2.2 Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination of the study findings.

2.2.3 Diagnosis of MAFLD

We used novel and positive criteria for the diagnosis of MAFLD regardless of the presence of other concomitant liver diseases or alcohol consumption[17]. The diagnosis of MAFLD was based on the ultrasonically diagnosed hepatic steatosis together with the presence of at least one of the following three criteria: overweight or obesity, presence of type 2 diabetes mellitus or clinical evidence of metabolic dysfunction. The latter was defined by the presence of at least two metabolic risk abnormalities, listed in Figure 2[17]. The diagnosis of steatosis was based on the following ultrasonographic patterns: liver parenchymal brightness, increased echo contrast between hepatic and renal parenchyma, vascular blurring or poor visualization of diaphragm[17].

2.3 Statistical analysis

Statistical analysis was performed with SPSS 22.0 and MedCalc 16.2. The descriptive statistics included mean ± SD or medians interquartile ranges (IQRs) for continuous variables and frequencies percent (%) for categorical variables. Differences between MAFLD and non-MAFLD individuals were assessed using the Student's t test or the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Based on sociademographic data and laboratory testing from this study, age, sex, blood pressure, fasting glucose, blood lipids, and liver and kidney function were further adjusted in the multiple logistic regression analyses. Multiple logistic regression models were constructed to explore correlations between indicators and MAFLD. We also categorized the targeted parameters into quartiles to further explore these relationships. The predictive value of TyG-related indices for MAFLD was assessed with a receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) in subgroup analysis were performed according to sex and BMI, respectively. The AUC differences of TyG-related indices were compared with the nonparametric DeLong test. A two-tailed P value<0.05 was considered statistically significant.

3. Results

3.1 Clinical and biochemical characteristics of the subjects

The baseline characteristics of the study subjects is shown in Table 1. Among the 20922 included subjects, 8099 (38.71%) were diagnosed with MAFLD. The prevalence of MAFLD was significantly higher in males (n=6152, 75.96%) than in females (n=1947, 24.04%) (P<0.0001). In all three BMI subgroups, the incidence of MAFLD gradually increased with BMI increases of 3.5%, 33.3% and 71.4%, respectively. Compared with those in the non-MAFLD group, individuals in the MAFLD group were significantly older, and had higher blood pressures, and levels of ALT, AST, GGT, BUN, UA, FPG, TC, TG and LDL-C (all P<0.0001). Notably, the BMI, WC and TyG-related indices were significantly higher in the MAFLD subjects than in the non-MAFLD subjects (all P<0.0001). In addition, we also found that males had significantly higher WC and TyG-WC levels than females in both MAFLD and non-MAFLD groups (all P<0.0001).

Table 1 Clinical and biochemical characteristics of the MAFLD and non-MAFLD groups

	MAFLD	Non-MAFLD	P value
N (%)	8099 (38.71%)	12823 (61.29%)	<0.0001
Male (%)	6152 (75.96%)	6191 (48.29%)	<0.0001
Age (years)	46.91±12.57	42.16±12.65	<0.0001
SBP (mmHg)	131.97±17.47	120.11±16.60	<0.0001
DBP (mmHg)	81.53±11.90	73.51±10.97	<0.0001
BMI (kg/m^2)	27.14±2.90	22.69±2.65	<0.0001
BMI<23 (%)	258 (3.50%)	7119 (96.50%)	<0.0001
23≤BMI<25 (%)	1598 (33.30%)	3201 (66.70%)	<0.0001
BMI≥25 (%)	6244 (71.40%)	2502 (28.60%)	<0.0001
WC (cm)	90.44±8.46	77.16±9.06	<0.0001
WC_{male}	92.38±7.73	82.84±7.46	<0.0001
WC_{female}	84.06±7.62	71.85±6.98	<0.0001
TyG	7.44±0.61	6.77±0.53	<0.0001
TyG-BMI	202.04±28.85	154.16±24.91	<0.0001
TyG-WC	673.57±90.67	524.59±87.49	<0.0001
$TyG\text{-}WC_{male}$	692.52±86.67	577.04±77.69	<0.0001
$TyG\text{-}WC_{female}$	612.49±76.61	475.47±64.79	<0.0001

ALT (U/L)	26 (18,38)	15 (11,21)	<0.0001
AST (U/L)	22 (18,27)	18 (16,22)	<0.0001
GGT (U/L)	32 (22,49)	17 (13,25)	<0.0001
BUN (mmol/l)	5.15±1.24	4.84±1.26	<0.0001
Cr (μmol/l)	66.43±13.07	66.49±13.07	0.731
UA (μmol/l)	354.36±84.81	290.96±76.54	<0.0001
FPG (mmol/l)	5.29 (4.93,5.78)	4.98 (4.71,5.29)	<0.0001
TG (mmol/l)	4.78±0.96	4.45±0.87	<0.0001
TC (mmol/l)	1.83 (1.31,2.63)	1.03 (0.76,1.43)	<0.0001
HDL-C (mmol/l)	1.19±0.26	1.38±0.30	<0.0001
LDL-C (mmol/l)	3.13±0.73	2.84±0.69	<0.0001

Data are expressed as mean±SD or medians (IQRs) for skewed variables or numbers (proportions) for categorical variables.
MAFLD, metabolic-associated fatty liver disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, γ-glutamyltransferase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

3.2 Relationships between different indicators and MAFLD

Our research indicated that elevated BMI, WC, TyG, TyG-BMI and TyG-WC were all independent predictors of MAFLD even after full adjustment (all P<0.0001) (Table 2). When categorizing the parameters into quartiles, we observed a dose-response relationship between all the parameters and the risk of MAFLD (all P < 0.0001) (Figure 3).

In general, the MAFLD ORs increased in the 2nd, 3rd and 4th quartiles compared to the 1st quartile of the parameters. The increase in the risk according to the higher quartiles was most pronounced for the TyG-BMI. The full adjusted ORs and 95% CIs for MAFLD were 20.76 (14.54-29.65), 92.33 (64.61-131.95) and 380.87 (263.25-551.05) in the 2nd, 3rd and 4th quartiles of the TyG-BMI, respectively, compared with those in the 1st quartile. The multivariable-adjusted ORs (95% CIs) for the 4th quartiles compared to the 1st quartiles of the BMI, WC, TyG and TyG-WC were 88.86 (69.93-112.91), 62.44 (51.28-76.02), 3.60 (3.02-4.29), and 145.91 (112.79-188.76), respectively.

Table 2 Binary logistic regression analysis of five markers for predicting MAFLD

Variable	Unadjusted		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
BMI	1.87(1.84-1.90)	<0.0001	1.83(1.80-1.87)	<0.0001	1.67(1.64-1.70)	<0.0001

WC	1.19(1.18-1.19)	<0.0001	1.21(1.20-1.22)	<0.0001	1.17(1.16-1.17)	<0.0001
TyG	8.23(7.70-8.78)	<0.0001	6.73(6.29-7.20)	<0.0001	4.36(3.82-4.99)	<0.0001
TyG-BMI	1.07(1.07-1.07)	<0.0001	1.07(1.07-1.08)	<0.0001	1.07(1.07-1.08)	<0.0001
TyG-WC	1.02(1.02-1.02)	<0.0001	1.02(1.02-1.02)	<0.0001	1.02(1.02-1.02)	<0.0001

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, blood pressure, fasting glucose, blood lipids, and liver and kidney function.
CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

3.3 Predictive values of different indicators for MAFLD according to subgroup analyses

3.3.1 Predictive values of different indicators for MAFLD according to sex

As shown in Table 3 and Figure 4, the highest AUC was demonstrated by the TyG-BMI in both males and females (AUC = 0.870 and 0.933, respectively). The TyG-BMI had significantly higher AUC values than the traditional recommended metabolic parameters (BMI and WC) and the other TyG-related indices (all P < 0.0001). A TyG-BMI cut-off of 162.05 in females showed the best overall test performance, with a sensitivity of 90.7% and a specificity of 81.2%. However, TyG showed the worst performance both in males and females among different indicators (AUC=0.753 and 0.830, respectively) (Table 2 and Figure 4).

Table 3 Cut-off points and AUCs (95% CI) of each parameter for predicting MAFLD in males and females

	AUC (95% CI)	Cut-off value	Sensitivity(%)	Specificity(%)
Male (n=12343)				
BMI	0.844 (0.837-0.851)	25.35	75.4	75.7
WC	0.818 (0.810-0.825)	87.50	73.7	73.5
TyG	0.753 (0.744-0.761)	7.10	73.3	64.4
TyG-BMI	0.870 (0.864-0.876)	181.22	79.9	76.3
TyG-WC	0.847 (0.841-0.854)	625.58	78.0	74.5
Female (n=8579)				
BMI	0.900 (0.893-0.907)	23.05	92.2	73.1
WC	0.890 (0.883-0.897)	76.50	84.9	76.8
TyG	0.830 (0.820-0.841)	6.86	77.6	73.8
TyG-BMI	0.933 (0.927-0.938)	162.05	90.7	81.2
TyG-WC	0.922 (0.915-0.928)	529.41	87.9	80.9

AUC, area under the ROC curve; CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

3.3.2 Predictive values of different indicators for MAFLD according to BMI

As shown in Table 4 and Figure 5, for different BMI groups, the TyG-BMI performed especially well in the lean group (BMI<23 kg/m^2) with an AUC of 0.928, followed by TyG with an AUC of 0.924 and TyG-WC with an AUC of 0.918. A TyG-BMI cut-off of 156.31 in the lean group showed the best overall performance, with a sensitivity of 87.2% and a specificity of 87.1%. Distinct from the previous result, BMI and WC exhibited the worst performances in all three groups (AUC [BMI], 0.763, 0.600, 0.709; AUC [WC], 0.794, 0.635, 0.695, respectively).

Table 4 Cut-off points and AUCs (95% CI) of each parameter for predicting MAFLD in different BMI subgroups

	AUC (95% CI)	Cut-off value	Sensitivity(%)	Specificity(%)
BMI<23 (n=7377)				
BMI	0.763 (0.739-0.788)	21.65	77.5	64.7
WC	0.794 (0.771-0.817)	74.50	79.8	65.4
TyG	0.924 (0.908-0.940)	7.11	89.1	85.2
TyG-BMI	0.928 (0.914-0.943)	156.31	87.2	87.1
TyG-WC	0.918 (0.905-0.931)	541.99	88.0	83.0
23≤BMI<25 (n=4799)				
BMI	0.600 (0.583-0.616)	24.05	55.3	59.1
WC	0.635 (0.618-0.651)	80.50	70.7	48.0
TyG	0.717 (0.702-0.732)	7.10	63.7	68.3
TyG-BMI	0.730 (0.716-0.745)	169.67	67.7	66.9
TyG-WC	0.724 (0.709-0.739)	572.91	73.1	60.9
BMI≥25 (n=8746)				
BMI	0.709 (0.698-0.720)	27.25	55.7	75.7
WC	0.695 (0.683-0.707)	90.50	58.3	69.8
TyG	0.715 (0.703-0.726)	7.19	65.6	66.0
TyG-BMI	0.778 (0.767-0.788)	194.83	69.2	73.5
TyG-WC	0.756 (0.745-0.767)	652.43	65.4	72.4

AUC, area under the ROC curve; CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

4. Discussion

In this cross-sectional study, we identified the relationships between TyG-related indices and the risk of MAFLD. We discovered that people with higher levels of TyG-related indices were more likely to have MAFLD. These parameters followed a dose-response relationship across the quartiles even after a full adjustment. However, the TyG-BMI exhibited the best performance among

them, and the participants in the highest TyG-BMI quartile group were 380.87 times more likely to have MAFLD than those in the lowest quartile group. Subgroup analysis further verified the validity of the TyG-BMI for detecting MAFLD in healthy subjects. It was potential to be the most reliable indicator for MAFLD among the parameters with high discrimination power in both sex and BMI subgroups. Notably, the TyG-BMI performed especially well in the lean subgroup and the female subgroup. Although TyG and the TyG-WC index also presented some predictive value for MAFLD, we observed that they were not quite stable and fluctuated in different subgroups. The above findings supported the adoption of the TyG-BMI as an alternative screening test for MAFLD.

To date, there have only been a few investigations on the diagnostic effectiveness of TyG-related indices for MAFLD[20]. Ehsaneh Taheri and colleagues first evaluated the association of the TyG index with MAFLD risk in an Iranian population. Among those in the highest relative to the lowest TyG tertiles, the multivariable-adjusted ORs (95% CI) were 12.01 (9.03-15.98) and 10.89 (7.66-15.48), respectively. The results demonstrated that a TyG index cut-off of 8.62 had 81.66% sensitivity and 75.36% specificity[20]. However, that study used the fatty liver index to define MAFLD rather than ultrasonography or liver biopsies, and it did not assess the performance of the TyG-BMI or the TyG-WC index. In contrast, another Chinese study reported results that were consistent with those in Ehsaneh Taheri. In addition, the study found that a combination of TyG, BMI and ALT improved the diagnostic capability for MAFLD. The combined model demonstrated an AUC of 0.985 (95% CI, 0.973-0.998) compared to TyG alone (AUC=0.943; 95% CI, 0.912-0.973) and the TyG-BMI (AUC=0.956; 95% CI, 0.933-0.980). This study exhibited a higher diagnostic accuracy than that found in our study, but it only included a small sample size of 229 patients[21]. Furthermore, Yan Xue et al. provided evidence for TyG-related indices as better predictive indicators for MAFLD than NAFLD. The TyG-WC index had the top performance, with an AUC (95% CI) of 0.815 (0.796–0.833) for predicting NAFLD and 0.832 (0.814–0.850) for predicting MAFLD[22]. However, unlike previous studies, our study involved a comprehensive assessment of the performance of TyG-related indices, including TyG, TyG-BMI and TyG-WC, to screen for and identify MAFLD in healthy Chinese subjects.

Of note, the present study revealed that the predictive accuracies of TyG-related indices varied in different subgroups. When we stratified MAFLD individuals by BMI profile, we found that the TyG-BMI performed especially well in the lean population. Although MAFLD has been increasing in parallel with the rising prevalence of obesity, it should be noted that lean individuals may also suffer from MAFLD. A recent study in China found that among the nonobese population, the prevalence of MAFLD was 11.5% (males: 16.4%, females: 6.9%), consistent with Vilarinho's findings[23]. Importantly, MAFLD in lean subjects is not a benign or stable state as expected. A number of studies have even

suggested that compared to those with obese MAFLD, lean individuals with MAFLD have an increased risk of diabetes mellitus and cardiovascular and all-cause mortality[25]. BMI is widely used to evaluate obesity, but not to describe regional fat distribution. The contribution of visceral fat to MAFLD has been found to be more important than that of total body fat[27]. Although Asians have a lower absolute BMI than Westerners, Asians are more vulnerable to visceral fat accumulation and IR[28]. Thus, reduced BMI levels are not necessarily representative of a metabolically healthy state. Based on the formula of TyG-BMI[27], we could reasonably infer that the higher the subject´s BMI, the higher the TyG-BMI index. From this perspective alone, TyG-BMI does not appear to be an ideal predictor for MAFLD. However, our study observed that increased TyG-BMI levels were positively correlated with the risk of MAFLD in lean individuals. Perhaps this is why the role of "TyG" has not been addressed, we may ignore its dynamic changes of various metabolic states. The effect of "TyG" increase might be far greater than BMI decrease in lean individuals with MAFLD. That is to say, IR caused by excessive accumulation of visceral fat may be more pronounced in the development of MAFLD in lean individuals**Error! Reference source not found.**. Yu ling et al. revealed that metabolic disorders in nonobese individuals with MAFLD were all significantly higher than those in nonobese individuals without MAFLD[23]. Therefore, simply focusing on decreased BMI or increased TyG does not seem to be suitable for the prediction of lean MAFLD. Only by considering the TyG-BMI index as a whole can we better understand its predictive value in lean MAFLD.

On the other hand, the predictive value of TyG-related indices also differed after sex classification. Significantly, the TyG-BMI had the top performance in both males and females but was more accurate in predicting MAFLD in females. The current study and a previous study came to the same conclusion that MAFLD is much more common in men than in women (P<0.0001). In addition, Yu ling et al. further described the age-related prevalence of MAFLD. Males were more susceptible to MAFLD at younger ages, and then this susceptibility rose slowly through middle age, whereas for females, the prevalence rose slowly at younger ages but suddenly accelerated after the age of 45[23]. This finding suggests that a decrease in oestrogen may be the primary cause of the sharp increase in MAFLD in older females. Low oestrogen levels during the postmenopausal period may be an important risk factor for MAFLD in females[29]. A number of studies have found that decreased oestrogen levels are associated with many metabolic disorders, including dyslipidaemia and IR. The lack of oestrogen availability also decreases hepatic insulin clearance and allows the development of diet-induced IR[30]. Notably, in the current study, we observed that increased TyG-BMI levels were closely related to the risk of MAFLD in female individuals. However, the concrete and precise mechanisms remain to be clarified.

Our study had several limitations. First, the diagnosis of MAFLD was based on ultrasonography, which might be partially insensitive when liver steatosis is below 30%[32]. Therefore, using ultrasound to screen for MAFLD may have underestimated the true prevalence of MAFLD. Second, some information was not available from the current health examination data, such as the liver biopsy data or the controlled attenuation parameter and liver stiffness measurement from the FibroScan Test. Further studies on the relationships between TyG-related indices and the severity of MAFLD are needed. Third, we included asymptomatic individuals attending a single centre, thus certain selection bias was inevitable. In addition, we noticed that the 95% CIs of the quartile analysis were relatively wide, especially the 4th quartile of the TyG-BMI (263.25-551.05), which may be related to the insufficient sample size. Therefore, multicentre and prospective studies would be needed to evaluate broader populations to validate our findings. The main strength of our study lies in the new evidence of the use of the TyG-BMI in predicting MAFLD in lean individuals and in women. We enrolled participants from diverse occupations and backgrounds with a wide range of clinical data to ensure statistical reliability and to validate our main findings from multiple perspectives. In addition, our study may provide some clinical implications, namely, our study is the first to demonstrate that the assessment of the TyG-BMI could be helpful in identifying individuals with high-risk of MAFLD, especially among those who are lean and female.

In conclusion, the present study suggested that the TyG-BMI was an promising predictor for MAFLD. Individuals with normal BMI levels but high TyG-BMI levels should undergo a more detailed assessment for MAFLD. Our findings extended previous investigations by demonstrating that the TyG-BMI might be ideal for the prediction of MAFLD in lean individuals and in females.

Figure legends

Figure 1 Flowchart of the study design

Figure 2 Flowchart of diagnostic criteria for MAFLD

Figure 3 MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

Figure 4 ROC curve of each parameter for predicting MAFLD in males and females

Figure 5 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

Declarations

Ethical approval and consent to participate

This study was approved and supervised by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. The need for written informed consent to participate was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have declared that they have no conflicts of interest.

Funding

Not applicable.

Author Contributions

Mingxing Chang and Guifang Shen conceived of and designed the study.

Mingxing Chang and Zhihao Shao coordinated data collection and conducted the analyses.

Mingxing Chang wrote the manuscript.

All authors have read and approved the final manuscript.

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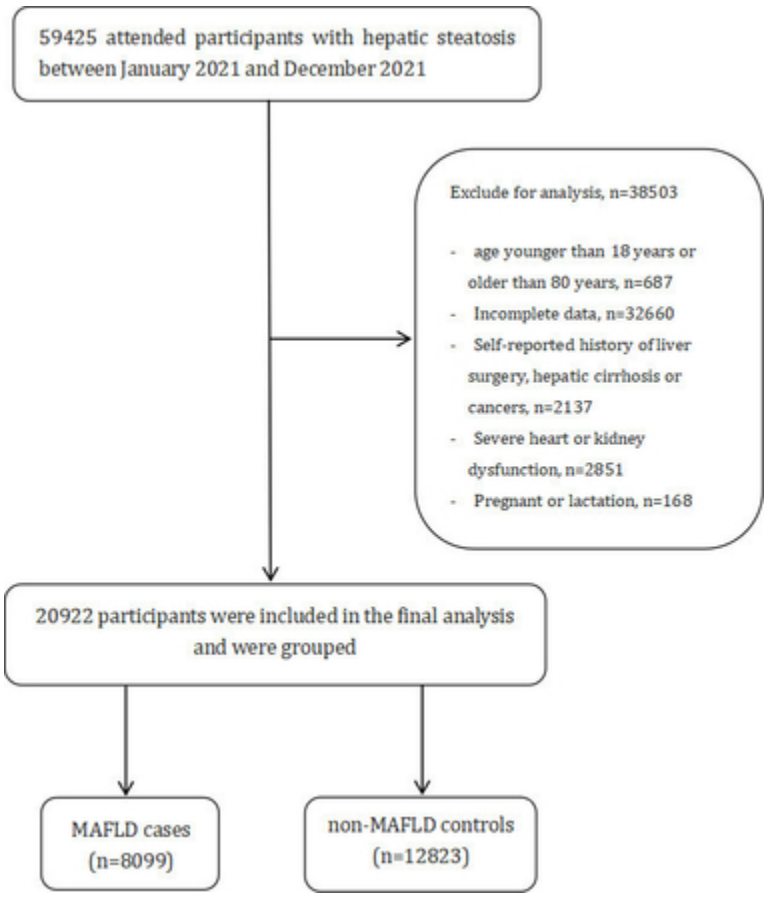

Flowchart of the study design

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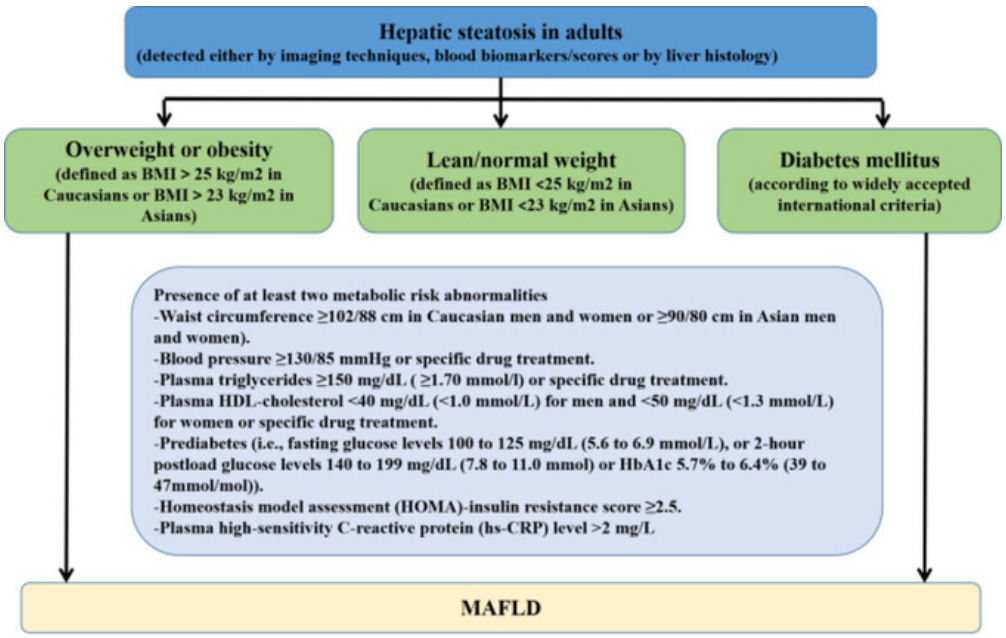

Flowchart of diagnostic criteria for MAFLD

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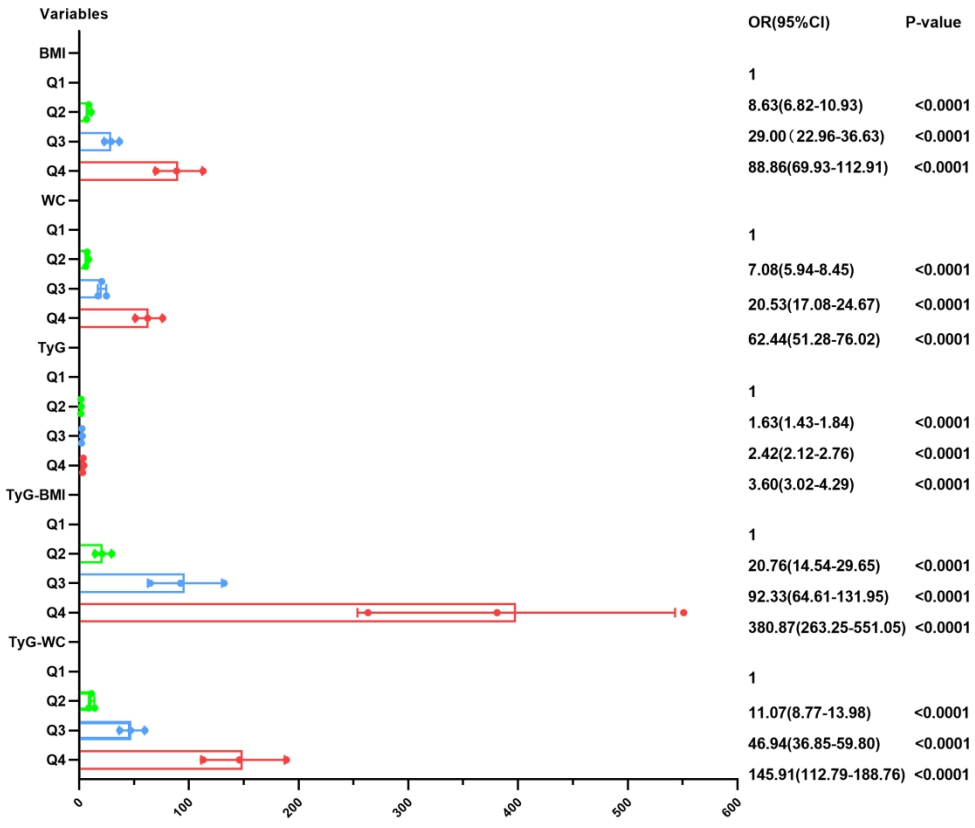

MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

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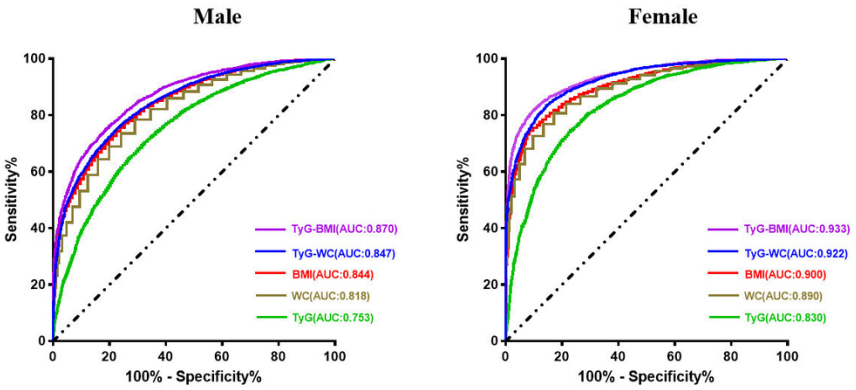
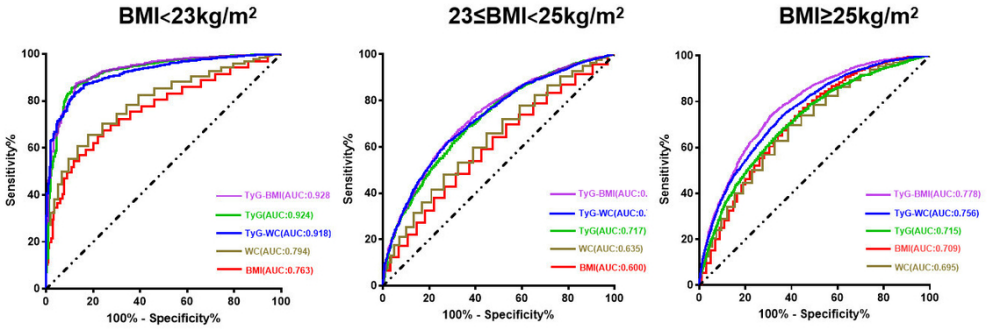


ROC curve of each parameter for predicting MAFLD in males and females

97x38mm (300 x 300 DPI)



ROC curve of each parameter for predicting MAFLD in different BMI subgroups

96x32mm (300 x 300 DPI)

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	2
Abstract			
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3

	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	3-4
Methods			
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
Participants	#5b	Describe eligibility criteria for participants.	4
Participants	#5c	Give details of treatments received, if relevant	NA. This study was not relevant to treatment.
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	NA. This study did not involve blind assessment.
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	4
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA. This study did not involve blind assessment.
Sample size	#8	Explain how the study size was arrived at.	4
Missing data	#9	Describe how missing data were handled (e.g., complete-	4

		case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	5
Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	NA. This study did not involve a validating model.
Statistical analysis methods	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	NA. This study did not involve a validating model.
Risk groups	#11	Provide details on how risk groups were created, if done.	5
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA. This study did not involve a validating model.
Results			
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
Participants	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6

Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA. This study did not involve a validating model.
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	7-9
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	7-8
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	7-9
Model specification	#15b	If developing a prediction model, explain how to the use it.	9
Model performance	#16	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	NA. This study did not involve a validating model.
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	NA. This study did not involve a validating model.
Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and	10

		other relevant evidence.	
Implications	#20	Discuss the potential clinical use of the model and implications for future research	12
Other information			
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	13
Funding	#22	Give the source of funding and the role of the funders for the present study.	NA. This study did not involve any fundings.

BMJ Open

Association between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease: a cross-sectional study in healthy Chinese participants

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Complete List of Authors:	chang, mingxing; The Affiliated Hospital of Xuzhou Medical University, Health management center Shao, Zhihao; The Affiliated Hospital of Xuzhou Medical University Shen, Guifang; The Affiliated Hospital of Xuzhou Medical University
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Association between triglyceride glucose-related markers and the risk of metabolic-associated fatty liver disease: a cross-sectional study in healthy Chinese participants

Mingxing Chang[1], Zhihao Shao[1], Guifang Shen[1]*

[1]Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, 99 West Huai-Hai Road, Xuzhou, Jiangsu 221000 China

First author:

Mingxing Chang,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

Email address: cmxfenger@163.com

Second author:

Zhihao Shao,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

Email address: 601515650@qq.com

***Corresponding author:**

Guifang Shen,

Department of Health Management Centre, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China

Email address: 2294194657@qq.com

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ABSTRACT

Objectives This study aimed to evaluate the performance of the triglyceride glucose (TyG) index and its related markers in predicting metabolic-associated fatty liver disease (MAFLD) in healthy Chinese participants.

Design This was a cross-sectional study.

Setting The study was conducted at Health Management Department of the Affiliated Hospital of Xuzhou Medical University.

Participants A total of 20922 asymptomatic Chinese participants (56% male) were enrolled.

Outcome measures Hepatic ultrasonography was performed to diagnose MAFLD based on the latest diagnostic criteria. The TyG, TyG-body mass (TyG-BMI), and TyG-waist circumference (TyG-WC) indices were calculated and analysed.

Results Compared with the lowest quartile of the TyG-BMI index, the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for MAFLD were 20.76 (14.54–29.65), 92.33 (64.61–131.95) and 380.87 (263.25–551.05) in the 2nd, 3rd and 4th quartiles, respectively. According to the subgroup analysis, the TyG-BMI index in the female and the lean groups (BMI<23 kg/m^2) showed the strongest predictive value, with optimal cut-off values for MAFLD of 162.05 and 156.31, respectively. The areas under the receiver operating characteristic curves in female and lean groups were 0.933 (95% CI: 0.927–0.938) and 0.928 (95% CI: 0.914–0.943), respectively, with 90.7% sensitivity and 81.2% specificity in female participants with MAFLD and 87.2% sensitivity and 87.1% specificity in lean participants with MAFLD. The TyG-BMI index demonstrated superior predictive ability for MAFLD compared to other markers.

Conclusions The TyG-BMI index is an effective, simple, and promising tool for predicting MAFLD, especially in lean and female participants.

Key Words: Metabolic-associated fatty liver disease, triglyceride glucose-body mass index, triglyceride glucose

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this is the first study to comprehensively evaluate the predictive performance of the triglyceride glucose (TyG) index and its related markers for metabolic-associated fatty liver disease (MAFLD) in healthy Chinese participants.

⇒ A limitation was that the diagnosis of MAFLD was based primarily on ultrasonography, which may have underestimated the true prevalence of MAFLD.

⇒ Another limitation was the lack of liver biopsy data and the controlled attenuation parameter and liver stiffness measurement from the FibroScan Test.

⇒ Results should be interpreted carefully due to the study's observational design and further studies are warranted to validate our findings in larger and more diverse populations.

INTRODUCTION

The global prevalence of metabolic-associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has dramatically increased to up to 25%. [1] Furthermore, studies have associated MAFLD with a variety of adverse clinical sequelae that may eventually result in increased mortality, including severe liver inflammation and fibrosis, metabolic and cardiovascular diseases and extra-hepatic cancer such as bladder cancer. [2-5] Early identification of MAFLD is therefore critical. However, a simple, effective, non-invasive tool for MAFLD screening is unavailable.

MAFLD develops through complex interactions between obesity and insulin resistance (IR). [6] Traditional obesity indicators, including body mass index (BMI) and waist circumference (WC) are strongly associated with fatty liver and metabolic disorders. [7,8] However, some studies have shown that 5–26% of patients with MAFLD have a BMI within the normal range. [9] Thus, these individuals and those who exhibit pre-MAFLD are often disregarded during MALFD screening. Moreover, relying solely on BMI and WC as a comprehensive reflection of MAFLD is unreliable due to their omission of IR. The triglyceride-glucose (TyG) index is a newly proposed index that is simpler and more reliable for evaluating IR than the homeostasis model assessment of IR index. Furthermore, Gastaldelli et al. found that the TyG index was well correlated with hepatic fat content in the San Antonio Metabolism (SAM) study, indicating the potential significance of this index. [10]

The TyG index, combined with obesity markers such as the TyG-BMI and TyG-WC index, captures both obesity and IR, thereby more accurately reflecting these complex pathophysiological features. Several studies have demonstrated that TyG-related indices outperform single indicators in identifying metabolic and cardiovascular diseases. [11-13] Therefore, we speculated that the TyG-related indices were promising markers in predicting MAFLD. In the present study, we investigated the effectiveness of TyG-related markers in distinguishing MAFLD in healthy participants and established a better prediction model for MAFLD.

PARTICIPANTS AND METHODS

Study design and populations

This cross-sectional study utilized data obtained from an urban population in eastern China who underwent a health examination at the Affiliated Hospital of Xuzhou Medical University between January 2021 to December 2021. The inclusion criteria were as follows: age between 18–80 years; and hepatic steatosis diagnosed through abdominal ultrasound. The exclusion criteria were as follows: incomplete data; age <18 years or >80 years; cirrhosis, hepatocellular carcinoma or history of liver surgery; history of malignant tumours; New York Heart Association class III or IV heart failure; chronic kidney disease with an estimated

glomerular filtration rate of <60mL/min/1.73m^2; and pregnancy or lactation. Participants with missing outcome measures or lost clinical and biochemical records were also excluded. Figure 1 provides the flowchart of the study design. This study followed the TRIPOD reporting guidelines [14] and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval number: XYFY2023-KL086-01). To avoid duplication of information, we included only the initial physical examination data of participants who underwent multiple physical examinations throughout the year, thereby ensuring that each participant contributed only one set of data to the study.

Health survey examinations and laboratory measurements

BMI, WC, and blood pressure were measured by trained examiners, and the following laboratory data were obtained during the health examinations: fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyltransferase (GGT), blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA) levels. The TyG-related parameters were calculated using the following formulae [15,16]:

$$\mathbf{TyG} = \mathbf{ln}\frac{[\mathbf{TG(mg/dL)} * \mathbf{FPG(mg/dL)}]}{\mathbf{2}}$$

$$\mathbf{TyG{-}BMI} = \mathbf{TyG} \times \mathbf{BMI\ (kg/m^2)}$$

$$\mathbf{TyG{-}WC} = \mathbf{TyG} \times \mathbf{WC\ (cm)}$$

Patient and public involvement

The research question, design, and outcome measures of the study were determined without patient involvement, and patient contribution was limited to study participation. Furthermore, there are no plans to involve patients in the dissemination of study findings.

Diagnosis of MAFLD

In this study, we used novel and positive criteria to diagnose MAFLD irrespective of other concomitant liver diseases or alcohol consumption. [17] The diagnosis of MAFLD was based on ultrasonically diagnosed hepatic steatosis with the presence of at least one of the following three criteria: overweight or obesity, type 2 diabetes mellitus or clinical evidence of metabolic dysfunction. The latter was defined by the presence of at least two metabolic risk abnormalities, listed in Figure 2. [18] The diagnosis of steatosis was based on the following ultrasonographic patterns: liver parenchymal brightness, increased echo contrast between hepatic and renal parenchyma and vascular blurring or poor visualization of diaphragm**Error! Reference source not found.**.

Statistical analysis

Statistical analysis was conducted using SPSS 22.0 (IBM Corp, Armonk, NY, USA) and MedCalc 16.2 (MedCalc Software Ltd, Ostend, Belgium). Descriptive statistics are presented as mean±SD or medians interquartile ranges (IQRs) for continuous variables and frequencies or percentage (%) for categorical variables. The differences between individuals with MAFLD and non-MAFLD were assessed using the Student's t test or the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression models were constructed to explore correlations between indicators and MAFLD after adjusting for sociodemographic and laboratory data, including age, sex, blood pressure, fasting glucose serum lipid levels, and liver and kidney function. The targeted parameters were categorized into quartiles to further explore these relationships. The predictive value of TyG-related indices for MAFLD was assessed using a receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). The subgroup analyses were performed according to sex and BMI, and the AUC differences of TyG-related indices were compared with the nonparametric DeLong test. A two-tailed P value<0.05 was considered statistically significant.

RESULTS

Clinical and biochemical characteristics of the participants

In total, 20922 participants were included in the final analysis. The baseline characteristics of the study participants are shown in Table 1. Among the 20922 participants, 8099 (38.71%) were diagnosed with MAFLD while were 12823 non-MAFLD controls. The prevalence of MAFLD was significantly higher in males (n=6152, 75.96%) than in females (n=1947, 24.04%) (P<0.0001). In all three BMI subgroups, the incidence of MAFLD gradually increased with BMI, with increases of 3.5%, 33.3% and 71.4%, respectively. Compared with those in the non-MAFLD group, individuals in the MAFLD group were significantly older, and had higher blood pressure, and levels of ALT, AST, GGT, BUN, UA, FPG, TC, TG and LDL-C (all P<0.0001). Notably, the BMI, WC and TyG-related indices were significantly higher in the MAFLD participants than in the non-MAFLD participants (all P<0.0001). In addition, we also found that males had significantly higher WC and TyG-WC values than females in both the MAFLD and non-MAFLD groups (P<0.0001).

Table 1 Clinical and biochemical characteristics of the MAFLD and non-MAFLD groups

	MAFLD	Non-MAFLD	P value
N (%)	8099 (38.71%)	12823 (61.29%)	<0.0001
Male (%)	6152 (75.96%)	6191 (48.29%)	<0.0001
Age (years)	46.91±12.57	42.16±12.65	<0.0001
SBP (mmHg)	131.97±17.47	120.11±16.60	<0.0001

DBP (mmHg)	81.53±11.90	73.51±10.97	<0.0001
BMI (kg/m^2)	27.14±2.90	22.69±2.65	<0.0001
BMI<23 (%)	258 (3.50%)	7119 (96.50%)	<0.0001
23≤BMI<25 (%)	1598 (33.30%)	3201 (66.70%)	<0.0001
BMI≥25 (%)	6244 (71.40%)	2502 (28.60%)	<0.0001
WC (cm)	90.44±8.46	77.16±9.06	<0.0001
WC_{male}	92.38±7.73	82.84±7.46	<0.0001
WC_{female}	84.06±7.62	71.85±6.98	<0.0001
TyG	7.44±0.61	6.77±0.53	<0.0001
TyG-BMI	202.04±28.85	154.16±24.91	<0.0001
TyG-WC	673.57±90.67	524.59±87.49	<0.0001
TyG-WC_{male}	692.52±86.67	577.04±77.69	<0.0001
TyG-WC_{female}	612.49±76.61	475.47±64.79	<0.0001
ALT (U/L)	26 (18,38)	15 (11,21)	<0.0001
AST (U/L)	22 (18,27)	18 (16,22)	<0.0001
GGT (U/L)	32 (22,49)	17 (13,25)	<0.0001
BUN (mmol/l)	5.15±1.24	4.84±1.26	<0.0001
Cr (μmol/l)	66.43±13.07	66.49±13.07	0.731
UA (μmol/l)	354.36±84.81	290.96±76.54	<0.0001
FPG (mmol/l)	5.29 (4.93,5.78)	4.98 (4.71,5.29)	<0.0001
TG (mmol/l)	4.78±0.96	4.45±0.87	<0.0001
TC (mmol/l)	1.83 (1.31,2.63)	1.03 (0.76,1.43)	<0.0001
HDL-C (mmol/l)	1.19±0.26	1.38±0.30	<0.0001
LDL-C (mmol/l)	3.13±0.73	2.84±0.69	<0.0001

Data are expressed as mean±SD or medians (IQRs) for skewed variables or numbers (proportions) for categorical variables.
MAFLD, metabolic-associated fatty liver disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, γ-glutamyltransferase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Relationships between different indicators and MAFLD

Our findings indicated that elevated BMI, WC, TyG, TyG-BMI and TyG-WC were all independent predictors of MAFLD even after adjustment (all P<0.0001) (Table 2). Furthermore, after categorizing the parameters into quartiles, we observed a dose-response relationship between all the parameters and the risk of MAFLD (all P < 0.0001) (Figure 3).

The ORs for MAFLD increased with higher quartiles of the parameters and was particularly more pronounced for the TyG-BMI index. The adjusted ORs and 95% CIs for MAFLD were 20.76 (14.54–29.65), 92.33 (64.61–131.95) and 380.87 (263.25–551.05) in the 2nd, 3rd and 4th quartiles of the TyG-BMI index, respectively, compared with that in the 1st quartile. The multivariable-adjusted ORs (95% CIs) for the 4th quartile compared to the 1st quartile of the BMI, WC, TyG and TyG-WC were 88.86 (69.93–112.91), 62.44 (51.28–76.02), 3.60 (3.02–4.29), and 145.91 (112.79–188.76), respectively.

Table 2 Binary logistic regression analysis of five markers for predicting MAFLD

Variable	Unadjusted		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
BMI	1.867 (1.835-1.899)	<0.0001	1.831 (1.799-1.864)	<0.0001	1.668 (1.636-1.700)	<0.0001
WC	1.184 (1.178-1.189)	<0.0001	1.209 (1.202-1.216)	<0.0001	1.164 (1.156-1.171)	<0.0001
TyG	8.270 (7.750-8.826)	<0.0001	6.789 (6.349-7.261)	<0.0001	4.366 (3.827-4.981)	<0.0001
TyG-BMI	1.074 (1.072-1.076)	<0.0001	1.074 (1.072-1.076)	<0.0001	1.073 (1.070-1.075)	<0.0001
TyG-WC	1.019 (1.018-1.019)	<0.0001	1.021 (1.021-1.022)	<0.0001	1.020 (1.020-1.021)	<0.0001

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, blood pressure, fasting glucose, blood lipids, and liver and kidney function.
CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

Predictive values of different indicators for MAFLD according to subgroup analyses

Predictive values of different indicators for MAFLD according to sex

As shown in Table 3 and Figure 4, the highest AUC was demonstrated by the TyG-BMI index in both males and females (AUC = 0.870 and 0.933, respectively). The TyG-BMI index had significantly higher AUC values than the traditional metabolic parameters (BMI and WC) and other TyG-related indices (all P < 0.0001). A TyG-BMI cut-off of 162.05 in females showed the best overall test performance, with a sensitivity of 90.7% and a specificity of 81.2%. However, the TyG index showed the worst performance both in males and females among different indicators (AUC=0.753 and 0.830, respectively) (Table 2 and Figure 4).

Table 3 Cut-off values and AUCs (95% CI) of each parameter for predicting MAFLD according to sex

	AUC (95% CI)	Cut-off value	Sensitivity(%)	Specificity(%)
Male (n=12343)				
BMI	0.844 (0.837-0.851)	25.35	75.4	75.7
WC	0.818 (0.810-0.825)	87.50	73.7	73.5

TyG	0.753 (0.744-0.761)	7.10	73.3	64.4
TyG-BMI	0.870 (0.864-0.876)	181.22	79.9	76.3
TyG-WC	0.847 (0.841-0.854)	625.58	78.0	74.5
Female (n=8579)				
BMI	0.900 (0.893-0.907)	23.05	92.2	73.1
WC	0.890 (0.883-0.897)	76.50	84.9	76.8
TyG	0.830 (0.820-0.841)	6.86	77.6	73.8
TyG-BMI	0.933 (0.927-0.938)	162.05	90.7	81.2
TyG-WC	0.922 (0.915-0.928)	529.41	87.9	80.9

AUC, area under the ROC curve; CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

Predictive values of different indicators for MAFLD according to BMI

As shown in Table 4 and Figure 5, the performance of the TyG-BMI index was particularly noteworthy in the lean group (BMI<23 kg/m^2; AUC of 0.928), followed by the performance of TyG (AUC of 0.924) and TyG-WC (AUC of 0.918) indices. A TyG-BMI cut-off value of 156.31 in the lean group showed the best overall performance, with a sensitivity of 87.2% and a specificity of 87.1%. In contrast to the previous analyses, BMI and WC exhibited the worst performances across all three groups (AUC [BMI], 0.763, 0.600, 0.709; AUC [WC], 0.794, 0.635, 0.695, respectively).

Table 4 Cut-off values and AUCs (95% CI) of each parameter for predicting MAFLD in different BMI subgroups

	AUC (95% CI)	Cut-off value	Sensitivity(%)	Specificity(%)
BMI<23 (n=7377)				
BMI	0.763 (0.739-0.788)	21.65	77.5	64.7
WC	0.794 (0.771-0.817)	74.50	79.8	65.4
TyG	0.924 (0.908-0.940)	7.11	89.1	85.2
TyG-BMI	0.928 (0.914-0.943)	156.31	87.2	87.1
TyG-WC	0.918 (0.905-0.931)	541.99	88.0	83.0
23≤BMI<25 (n=4799)				
BMI	0.600 (0.583-0.616)	24.05	55.3	59.1
WC	0.635 (0.618-0.651)	80.50	70.7	48.0
TyG	0.717 (0.702-0.732)	7.10	63.7	68.3
TyG-BMI	0.730 (0.716-0.745)	169.67	67.7	66.9
TyG-WC	0.724 (0.709-0.739)	572.91	73.1	60.9
BMI≥25 (n=8746)				
BMI	0.709 (0.698-0.720)	27.25	55.7	75.7
WC	0.695 (0.683-0.707)	90.50	58.3	69.8

TyG	0.715 (0.703-0.726)	7.19	65.6	66.0
TyG-BMI	0.778 (0.767-0.788)	194.83	69.2	73.5
TyG-WC	0.756 (0.745-0.767)	652.43	65.4	72.4

AUC, area under the ROC curve; CI, confidence interval; BMI, body mass index; WC, waist circumference; TyG, triglyceride glucose.

DISCUSSION

In this cross-sectional study, we identified the relationships between TyG-related indices and the risk of MAFLD. We discovered that individuals with higher values of TyG-related indices were more likely to have MAFLD. Furthermore, these parameters followed a dose-response relationship across the quartiles even after adjustment. In particular, the TyG-BMI index exhibited the strongest predictive performance among the indices, and participants in the highest TyG-BMI quartile group were 380.87 times more likely to have MAFLD than those in the lowest quartile group. Subgroup analysis further verified the validity of the TyG-BMI index for detecting MAFLD in healthy participants. Therefore, the TyG-BMI index may be the most reliable indicator for MAFLD among other traditional parameters, as evidenced by its high discriminatory power in both the sex and BMI subgroups. Notably, this index performed exceptionally in the lean and female subgroups. Although the TyG and TyG-WC indices also presented some predictive value for MAFLD, we observed that they were not quite stable and fluctuated in different subgroups. The abovementioned study findings support the adoption of the TyG-BMI index as an alternative screening instrument for MAFLD.

To date, there have only been a few investigations on the diagnostic effectiveness of TyG-related indices for MAFLD. [20-22] Taheri et al. first evaluated the association between the TyG index and MAFLD risk in an Iranian population. Among those in the highest, relative to the lowest TyG tertile, the multivariable-adjusted ORs (95% CI) were 12.01 (9.03–15.98) and 10.89 (7.66–15.48), respectively. Their results demonstrated that a TyG index cut-off of 8.62 had 81.66% sensitivity and 75.36% specificity. [20] However, that study used the fatty liver index to define MAFLD rather than ultrasonography or liver biopsies, and it did not assess the performance of the TyG-BMI or the TyG-WC index. Similarly, a Chinese study, while reporting results consistent with Taheri's findings, found that a combination of TyG, BMI and ALT improved the diagnostic capability for MAFLD. The combined model demonstrated an AUC of 0.985 (95% CI, 0.973-0.998) which outperformed the TyG alone (AUC=0.943; 95% CI, 0.912-0.973) and TyG-BMI indices (AUC=0.956; 95% CI, 0.933-0.980). This study exhibited a higher diagnostic accuracy than that of the present study; however, it included a small sample size of 229 patients. [21] Xue et al. provided evidence for TyG-related indices as better predictive indicators for MAFLD than NAFLD. The TyG-WC index had the strongest performance, with an AUC (95% CI) of 0.815 (0.796–0.833) for predicting NAFLD and 0.832 (0.814–0.850) for predicting MAFLD. [22] However, unlike previous studies, our study provided a comprehensive assessment of the TyG-related indices, including TyG, TyG-BMI and TyG-WC, for their ability to screen for and identify MAFLD in healthy Chinese participants.

Interestingly, the present study revealed that the predictive accuracies of TyG-related indices varied among different subgroups. When we stratified MAFLD individuals by BMI profile, we found that the TyG-BMI index performed the strongest in the lean population. It is noteworthy that the incidence of metabolic-associated fatty liver disease (MAFLD) has been observed to increase in tandem with the escalating prevalence of obesity. However, it should be emphasized that individuals with a lean body composition may also be susceptible to the condition. A recent study in China found that among the non-obese population, the prevalence of MAFLD was 11.5% (males: 16.4%, females: 6.9%), which was consistent with Vilarinho's findings. [23,24] Importantly, MAFLD in lean participants was not benign or stable, contrary to what was initially believe. Numerous studies have even suggested that compared to those with obese MAFLD, lean individuals with MAFLD have an increased risk of diabetes mellitus and cardiovascular and all-cause mortality. [25,26] BMI is widely used to evaluate obesity, but fails to evaluate regional fat distribution. The contribution of visceral fat to MAFLD has been found to be more important than that of total body fat. [27] Although Asians have a lower absolute BMI than Westerners, Asians are more vulnerable to visceral fat accumulation and IR. [28] Thus, reduced BMI levels are not necessarily representative of a metabolically healthy state. Based on the formula of the TyG-BMI index, [16] we could reasonably infer that the higher an individual's BMI, the higher the TyG-BMI index. From this perspective alone, the TyG-BMI index does not appear to be an ideal predictor for MAFLD. However, our study observed that increased TyG-BMI values were positively correlated with the risk of MAFLD in lean individuals. Thus, the lack of attention to the dynamic changes of various metabolic states may be a reason why the predictive ability of TyG has often been overlooked. In lean individuals with MAFLD, the impact of TyG increase may outweigh that of BMI decrease. That is to say, IR induced by excessive accumulation of visceral fat may have a more pronounced role in MAFLD development in lean individuals. [9] Chen et al. revealed that incidence of metabolic disorders in non-obese individuals with MAFLD were significantly higher than that in non-obese individuals without MAFLD. [23] Therefore, relying solely on decreased BMI or increased TyG may not be adequate for predicting lean MAFLD. A comprehensive consideration of the TyG-BMI index is essential for a better understanding of its predictive value in lean MAFLD.

The predictive value of TyG-related indices differed depending on sex classification. Significantly, while the TyG-BMI index demonstrated superior performance in both males and females, it was more accurate in predicting MAFLD in females in the present study. Moreover, the current study and a previous study [23] came to the same conclusion that MAFLD has a higher prevalence in men than in women ($P<0.0001$). In addition, Chen et al. further described the age-related prevalence of MAFLD, with males being more susceptible at younger ages and after which it increased only gradually through middle age, while females showed a slow rise in susceptibility until the age of 45, after which it accelerated sharply. [23] This finding suggests that a decrease in oestrogen may be the primary cause of the sudden increase in MAFLD prevalence in older females and thus low oestrogen levels during the postmenopausal period may be an important risk factor for MAFLD in females. [29] Several studies have found that decreased oestrogen levels are associated with many

metabolic disorders, including dyslipidaemia and IR. The lack of oestrogen availability also decreases hepatic insulin clearance and allows the development of diet-induced IR. [30,31] Notably, in the current study, we observed that increased TyG-BMI values were closely related to the risk of MAFLD in female individuals. However, the specific mechanisms underlying this phenomenon remain to be elucidated.

Our study had several limitations. First, the diagnosis of MAFLD was based on ultrasonography, which may have showed decreased sensitivity when liver steatosis is below 30%. [32] Therefore, using ultrasound to screen for MAFLD may have underestimated the true prevalence of MAFLD. Second, certain data were not available from the health examination, such as the liver biopsy data or the controlled attenuation parameter and liver stiffness measurement from the FibroScan Test. Hence, further studies on the relationships between TyG-related indices and the severity of MAFLD are needed. Third, we included asymptomatic individuals from a single centre; thus, selection bias to a certain extent was inevitable. In addition, we noticed that the 95% CIs of the quartile analysis were relatively wide, especially the 4th quartile of the TyG-BMI (263.25–551.05) index, which may be related to the insufficient sample size. Therefore, multicentre and prospective studies with larger and more diverse populations are required to validate our findings. Our study had several notable strengths. First and foremost, we provide novel evidence regarding the utility of the TyG-BMI index in predicting MAFLD in lean and female individuals. Moreover, we enrolled participants from diverse occupations and backgrounds and collected extensive clinical data to ensure statistical reliability and to validate our findings from multiple perspectives. In addition, our study has important clinical implications, as it is the first to demonstrate that the assessment of the TyG-BMI index could be helpful in identifying individuals with high-risk of MAFLD, especially among those who are lean and female.

In conclusion, the present study suggested that the TyG-BMI index was a promising predictor for MAFLD. Individuals with BMI values within the normal range but high TyG-BMI levels should undergo a more detailed assessment for MAFLD. Our findings extended previous investigations by demonstrating that the TyG-BMI index may be an ideal predictor for the presence of MAFLD in lean and female individuals.

DECLARATIONS

Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Approval number: XYFY2023-KL086-01). The requirement for written informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflicts of interest.

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Author Contributions

Mingxing Chang and Guifang Shen conceived of and designed the study.

Mingxing Chang and Zhihao Shao coordinated data collection and performed the analyses.

Mingxing Chang wrote the manuscript.

All authors have read and approved the final version of the manuscript.

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Not applicable.

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FIGURE LEGENDS

Figure 1 Flowchart of the study design

Figure 2 Flowchart of diagnostic criteria for MAFLD

Figure 3 MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

Figure 4 ROC curve of each parameter for predicting MAFLD according to sex

Figure 5 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

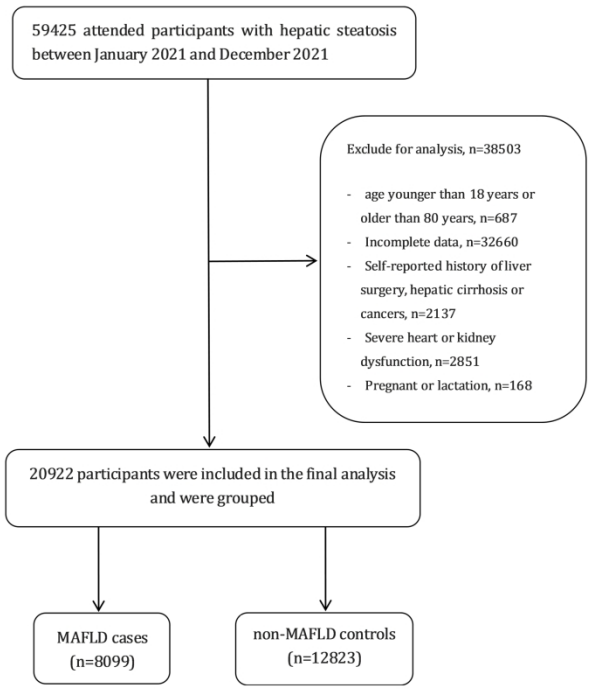

Figure 1 Flowchart of the study design

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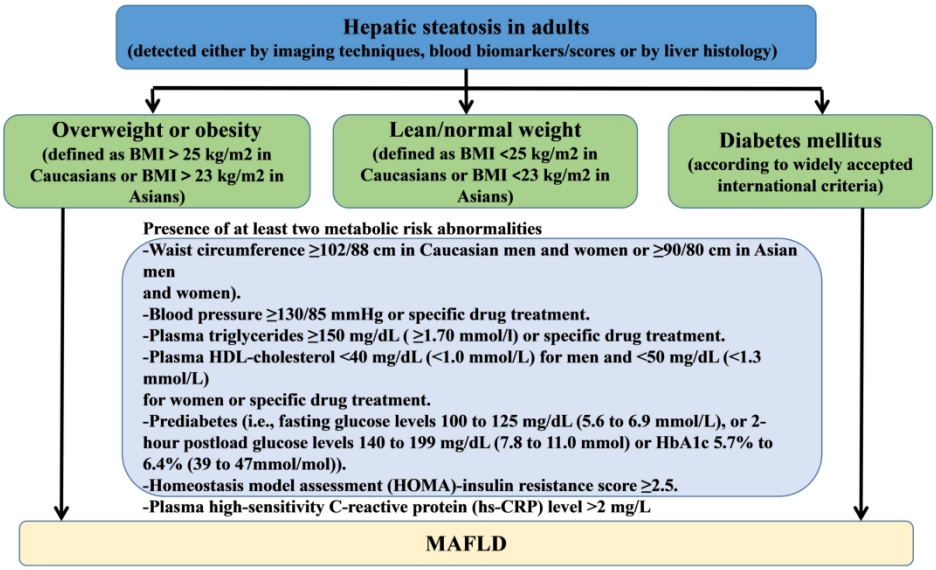

Figure 2 Flowchart of diagnostic criteria for MAFLD

267x195mm (300 x 300 DPI)

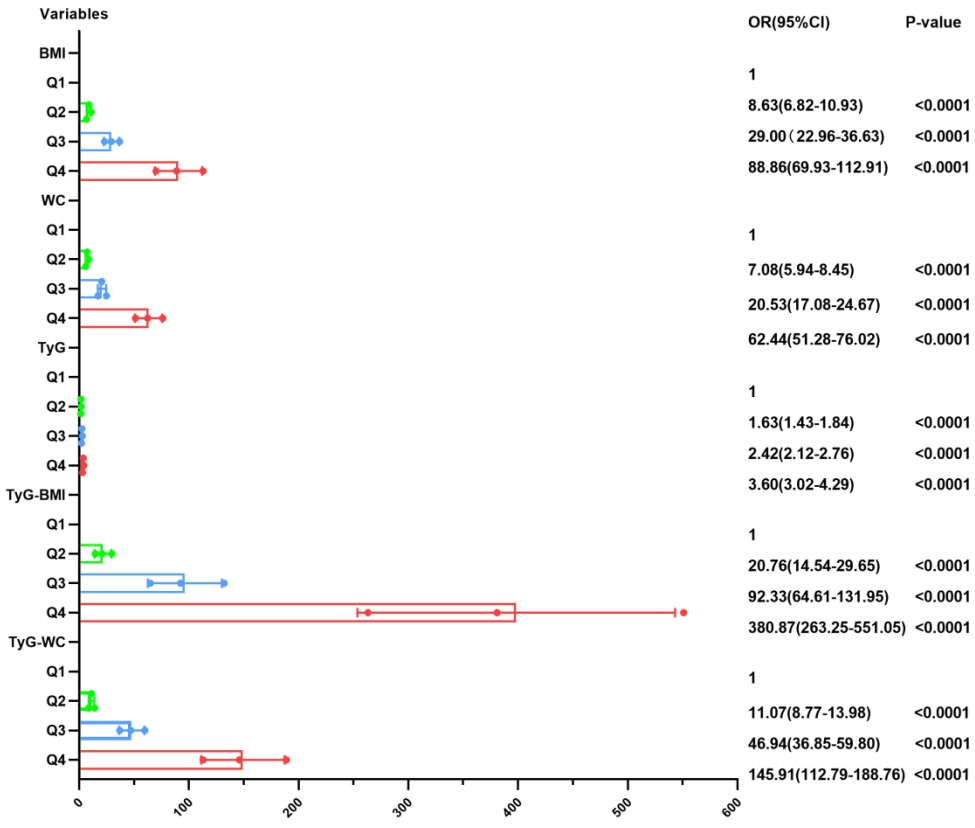

Figure 3 MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

197x166mm (300 x 300 DPI)

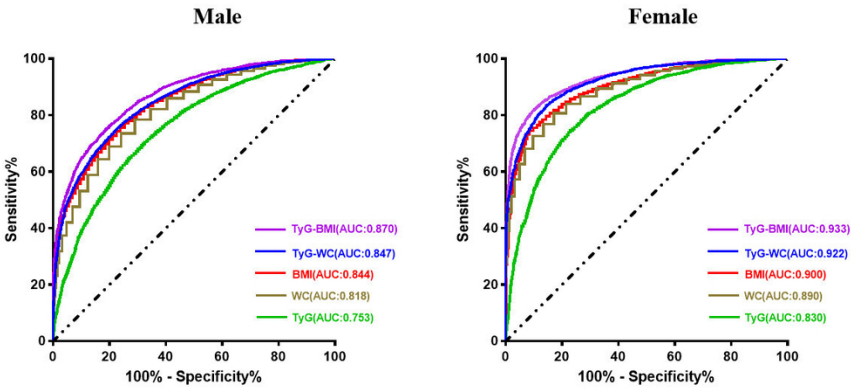

Figure 4 ROC curve of each parameter for predicting MAFLD according to sex

97x38mm (300 x 300 DPI)

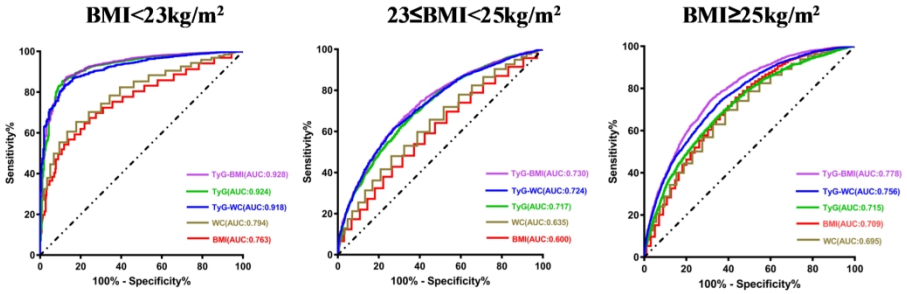

Figure 5 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

262x195mm (300 x 300 DPI)

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

		Reporting Item	Page Number
Title			
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract			
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
	#3a	Explain the medical context (including whether diagnostic	4

		or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4-5
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
Participants	#5b	Describe eligibility criteria for participants.	4-5
Participants	#5c	Give details of treatments received, if relevant	NA. This study was not relevant to treatment.
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	NA. This study did not involve blind assessment.
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how	5

		and when they were measured	
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA. This study did not involve blind assessment.
Sample size	#8	Explain how the study size was arrived at.	4
Missing data	#9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	6
Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	NA. This study did not involve a validating model.
Statistical analysis methods	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	NA. This study did not involve a validating model.
Risk groups	#11	Provide details on how risk groups were created, if done.	6
Development vs.	#12	For validation, identify any differences from the	NA. This

validation		development data in setting, eligibility criteria, outcome, and predictors.	study did not involve a validating model.
Results			
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
Participants	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA. This study did not involve a validating model.
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	7-10
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	7-9
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	7-10
Model specification	#15b	If developing a prediction model, explain how to the use it.	8-9

Model performance	#16	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	NA. This study did not involve a validating model.
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	NA. This study did not involve a validating model.
Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	10
Implications	#20	Discuss the potential clinical use of the model and implications for future research	12
Other information			
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	13
Funding	#22	Give the source of funding and the role of the funders for the present study.	NA. This study did not involve any

fundings.