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# BMJ Open

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

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

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43 fatty liver disease  
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46 **Declarations**

47  
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49 **Ethical approval and consent to participate**

50  
51 The study was approved and supervised by the Ethics Committee of the Affiliated  
52 Hospital of Xuzhou Medical University. The need for written informed consent to  
53 participate was waived by the Ethics Committee of the Affiliated Hospital of  
54 Xuzhou Medical University due to retrospective nature of the study. Declaration  
55 of Helsinki: All methods were carried out in accordance with the relevant  
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4 guidelines and regulations.

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6 **Consent for publication**

7  
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11 **Availability of data and materials**

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

15  
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18  
19 All authors have declared that they have no conflicts of interest.

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27 **Author Contributions**

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

29  
30 Mingxing Chang and Zhihao Shao coordinated data collection and conducted the  
31 analyses.

32  
33 Mingxing Chang wrote the manuscript.

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35 All authors have read and approved the final manuscript.

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

### 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<sup>2</sup>) 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**

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3 (1) This was a large-scale study on the performance of triglyceride glucose  
4 (TyG) index and its related markers in identifying metabolic associated fatty  
5 liver disease (MAFLD) among Chinese healthy subjects.  
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8 (2) A limitation is that the diagnosis of MAFLD was based on ultrasonography,  
9 which may have underestimated the true prevalence of MAFLD.  
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12 (3) Another limitation is that liver biopsy data and the controlled attenuation  
13 parameter and liver stiffness measurement from the Fibroscan Test were not  
14 measured.  
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## 17 18 19 **1. Introduction**

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21 The prevalence of metabolic associated fatty liver disease (MAFLD), formerly  
22 known as non-alcoholic fatty liver disease (NAFLD), has dramatically increasing  
23 up to 25% worldwide<sup>[1]</sup>. Furthermore, studies have linked MAFLD to a variety of  
24 adverse clinical sequelae, including severe liver inflammation and fibrosis,  
25 metabolic and cardiovascular diseases that may eventually result in increased  
26 mortality<sup>[2]</sup>. Early identification of MAFLD is therefore the primary step.  
27 However, a non-invasive tool for MAFLD screening taking simplicity, efficiency  
28 and availability into account is still lacking yet.  
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33 MAFLD develops through complex interactions between obesity and insulin  
34 resistance (IR)<sup>[5]</sup>. Traditional obesity indicators including body mass index (BMI)  
35 and waist circumference (WC), these elevated indicators are strongly  
36 associated with fatty liver and metabolic disorders<sup>[6]</sup>. But some studies have  
37 shown that 5% to 26% of MAFLD patients have a BMI within the normal  
38 range<sup>[8]</sup>. If some people are pre-MAFLD or have normal weight, they generally  
39 tend to be ignored. In addition, single BMI or WC could not make a  
40 comprehensive reflection of MAFLD because of the neglect of IR. The  
41 triglyceride-glucose (TyG) index is a newly proposed index that is more simple  
42 and reliable for IR than the homeostasis model assessment of IR index.  
43 Importantly, Gastaldelli et al. found that TyG was well correlated with the  
44 amount of hepatic fat in the SAM study<sup>[9]</sup>.  
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50 The TyG index combined with obesity markers, including TyG-BMI and  
51 TyG-WC, could describe both obesity and IR, thereby better reflecting the  
52 complex pathophysiological features. Several studies have shown that  
53 TyG-related indices are more successful than those single indicators in  
54 identifying metabolic and cardiovascular diseases<sup>[10]</sup>. Therefore, we speculated  
55 that the TyG-related indices were quite potential and promising in predicting  
56 MAFLD. Herein, we investigated the performance of TyG-related markers to  
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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 Affiliated 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<sup>2</sup>; pregnancy or lactation. This study followed TRIPOD reporting guidelines<sup>[14]</sup>.

### 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),  $\gamma$ -glutamyltransferase (GGT), blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA). The TyG-related parameters were calculated using the following formulae:

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

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

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

#### 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<sup>[14]</sup>. 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 <sup>2</sup> )	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(%)
<b>Male (n=12343)</b>				
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
<b>Female (n=8579)</b>				
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<sup>2</sup>) 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(%)
<b>BMI&lt;23 (n=7377)</b>				
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
<b>23≤BMI&lt;25 (n=4799)</b>				
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
<b>BMI≥25 (n=8746)</b>				
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. Discussion

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

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3 participants in the highest TyG-BMI quartile group were 380.87 times more  
4 likely to have MAFLD than those in the lowest quartile group. Subgroup analysis  
5 further verified the validity of TyG-BMI for the detection of MAFLD in healthy  
6 subjects. It was the most reliable indicator for MAFLD among the parameters  
7 with a high discrimination power both in different gender and BMI subgroups.  
8 Notably, TyG-BMI performed especially well in lean subgroup and the female  
9 subgroup. The above findings supported the adoption of TyG-BMI as an  
10 alternative screening test for MAFLD.  
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15 To date, there have only been a few investigations on the diagnostic  
16 effectiveness of the TyG-related indices for MAFLD<sup>[15]</sup>. Ehsaneh Taheri and  
17 colleagues first evaluated the association of TyG index with MAFLD risk in an  
18 Iranian population. Among those in the highest relative to the lowest TyG  
19 tertiles, the multivariable-adjusted ORs (95% CI) were 12.01 (9.03 - 15.98) and  
20 10.89 (7.66 - 15.48), respectively. The results demonstrated that a TyG index  
21 cutoff of 8.62 had 81.66% sensitivity and 75.36% specificity<sup>[15]</sup>. However, that  
22 study used the fatty liver index to define MAFLD rather than ultrasonography or  
23 liver biopsies, and it did not assess the performance of TyG-BMI or TyG-WC. In  
24 contrast, another Chinese study reported results that were consistent with  
25 Ehsaneh Taheri's. Besides, the study also found that a combination of TyG, BMI  
26 and ALT improved the diagnostic capability for MAFLD. The combined model  
27 demonstrated an AUC of 0.985 (95% CI, 0.973-0.998) compared to TyG alone  
28 (AUC=0.943; 95% CI, 0.912-0.973) and TyG-BMI (AUC=0.956; 95% CI,  
29 0.933-0.980). This study exhibited a higher diagnostic accuracy than that found  
30 in our study, but it only included a small sample size of 229 patients<sup>[16]</sup>.  
31 Furthermore, Yan Xue et al. provided evidence for TyG-related indices as better  
32 predictive indicators for MAFLD than NAFLD. The top performer was TyG-WC,  
33 with an AUC (95% CI) of 0.815 (0.796–0.833) to predict NAFLD and 0.832  
34 (0.814–0.850) to predict MAFLD<sup>[17]</sup>. However, different from previous studies,  
35 our study made a comprehensive assessment of the performance of TyG-related  
36 indices, including TyG, TyG-BMI and TyG-WC, to screen and identify MAFLD in a  
37 large-scale population.  
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46 Of note, the present study revealed that the predictive accuracies of  
47 TyG-related indices have varied in different subgroups. When we stratified  
48 MAFLD individuals by BMI profile, we found that TyG-BMI performed especially  
49 well in lean population. Although MAFLD has been increasing in parallel with the  
50 rising prevalence of obesity, it should be noted that lean individuals may also  
51 suffered from MAFLD. A recent study in China found that among the nonobese  
52 population, the prevalence of MAFLD was 11.5% (males: 16.4%, females: 6.9%),  
53 consistent with Vilarinho's<sup>[18]</sup>. Importantly, lean MAFLD is not a benign or stable  
54 state as expected. A number of studies even suggested that lean individuals with  
55 MAFLD have an increased risk of diabetes mellitus, cardiovascular and all-cause  
56 mortality, compared to those with obese MAFLD<sup>[20]</sup>. BMI is widely used to  
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3 evaluate obesity, but not to describe regional fat distribution. The contribution of  
4 visceral fat to MAFLD was more important than total body fat<sup>[22]</sup>. Though Asians  
5 have a lower absolute BMI than Westerners, yet Asians were more vulnerable to  
6 visceral fat accumulation and IR<sup>[23]</sup>. Thus, the reduced BMI levels were not  
7 capable of representing a metabolically healthy state. IR caused by excessive  
8 accumulation of visceral fat may be more pronounced in the development of lean  
9 MAFLD<sup>[24]</sup>. Yu ling et al. revealed that metabolic disorders in nonobese  
10 individuals with MAFLD were all significantly higher than those in nonobese  
11 individuals without MAFLD<sup>[18]</sup>. These findings imply that IR may be the leading  
12 cause in the development of lean MAFLD.  
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17 On other hand, the predict value of TyG-related indices also differed after a  
18 gender classification. Significantly, TyG-BMI was the top performer both in males  
19 and females, but more accurate in predicting female MAFLD. The current study  
20 and one of the previous study came to the same conclusion that MAFLD is much  
21 more common in men than women ( $P < 0.0001$ ). In addition, Yu ling et al. further  
22 described the age-related prevalence of MAFLD. Males were more susceptible to  
23 MAFLD at younger ages and then rose slowly until middle ages, but for females,  
24 the prevalence rose slowly during younger ages but suddenly accelerated after  
25 the age of 45<sup>[18]</sup>. This epidemic trend difference indicated that the decrease in  
26 estrogen may be the primary cause in aging female MAFLD. Low estrogen levels  
27 during the postmenopausal periods may be an important risk factor for MAFLD  
28 in females<sup>[25]</sup>. A number of studies have found that the decreased estrogen levels  
29 were associated with many metabolic disorders, including dyslipidemia and IR.  
30 The lack of estrogen availability also decreased hepatic insulin clearance and  
31 allowed the development of diet-induced IR<sup>[26]</sup>. Therefore, the increased  
32 TyG-BMI levels were closely relevant to the risk of MAFLD for female individuals.  
33 However, the concret and precise mechanisms remained to be clarified.  
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41 Our study had several limitations. First, the diagnosis of MAFLD was based  
42 on ultrasonography, which might be partially insensitive when liver steatosis is  
43 below 30%<sup>[28]</sup>. Therefore, using ultrasound to screen for MAFLD may have  
44 underestimated the true prevalence of MAFLD. Second, some information was  
45 not available from the current health examination data, such as the liver biopsy  
46 data or the controlled attenuation parameter and liver stiffness measurement  
47 from the Fibroscan Test. Further studies on the relationships between  
48 TyG-related indices and the severity of MAFLD are yet to be achieved. Third, we  
49 included asymptomatic individuals attending a single center, thus certain  
50 selection bias was inevitable. Multi-center and prospective studies will be  
51 needed to evaluate broader populations to validate our findings.  
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57 The main strength of our study lied in the large sample size and the fresh  
58 evidence for the use of TyG-BMI to identify lean MAFLD and female MAFLD. We  
59 enrolled a large-scale population with a wide range of clinical data to ensure  
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3 statistical reliability and enabled us to validate our main findings from multiple  
4 angles and levels. Besides, our study may provide some clinical implications.  
5 Vitally, our study first demonstrated that the assessment of TyG-BMI could be  
6 helpful in identifying high-risk MAFLD population, especially for the lean  
7 population and female population.  
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11 In conclusion, the present study suggested that TyG-BMI was a useful  
12 predictor for MAFLD. Individuals with normal BMI levels but high TyG-BMI  
13 levels should also then undergo a more detailed assessment for MAFLD. And our  
14 findings extended previous investigations by demonstrating that TyG-BMI might  
15 be ideal for the prediction of lean MAFLD and female MAFLD.  
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### 18 19 **Figure legends**

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21 **Figure 1** The flowchart of diagnostic criteria for MAFLD

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

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

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

### 33 34 **5. Reference**

- 35  
36  
37  
38 [1]. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J,  
39 Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk  
40 factors and prevention. *Nat Rev Gastroenterol Hepatol.* 2018;15:11-20.  
41  
42  
43 [2]. Huang SC, Su HJ, Kao JH, Tseng TC, Yang HC, Su TH, Chen PJ, Liu CJ. Clinical  
44 and Histologic Features of Patients with Biopsy-Proven Metabolic  
45 Dysfunction-Associated Fatty Liver Disease. *Gut Liver.* 2021;15:451-58.  
46  
47  
48 [3]. Guerreiro GTS, Longo L, Fonseca MA, de Souza VEG, Álvares-da-Silva MR.  
49 Does the risk of cardiovascular events differ between biopsy-proven NAFLD  
50 and MAFLD? *Hepatol Int.* 2021;15:380-391.  
51  
52  
53  
54 [4]. Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic  
55 dysfunction-associated fatty liver disease is associated with increased  
56 all-cause mortality in the United States. *J Hepatol.* 2021;75:1284-91.  
57  
58  
59  
60

- 1  
2  
3 [5]. Xian YX, Weng JP, Xu F. MAFLD vs. NAFLD: shared features and potential  
4 changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy.  
5 *Chin Med J (Engl)*. 2020;134:8-19.  
6  
7  
8  
9 [6]. Abe M, Fujii H, Funakoshi S, Satoh A, Kawazoe M, Maeda T, Tada K, Yokota S,  
10 Yamanokuchi T, Yoshimura C, Mimata R, Takahashi K, Ito K, Yasuno T, Kuga  
11 T, Mukoubara S, Akiyoshi K, Kawanami D, Masutani K, Arima H. Comparison  
12 of Body Mass Index and Waist Circumference in the Prediction of Diabetes: A  
13 Retrospective Longitudinal Study. *Diabetes Ther*. 2021;12:2663-76.  
14  
15  
16  
17 [7]. Aizawa M, Inagaki S, Moriyama M, Asano K, Kakehashi M. Modeling the  
18 natural history of fatty liver using lifestyle-related risk factors: Effects of  
19 body mass index (BMI) on the life-course of fatty liver. *PLoS One*.  
20 2019;14:e0223683.  
21  
22  
23  
24 [8]. Eslam M, El-Serag HB, Francque S, Sarin SK, Wei L, Bugianesi E, George J.  
25 Metabolic (dysfunction)-associated fatty liver disease in individuals of  
26 normal weight. *Nat Rev Gastroenterol Hepatol*. 2022;19:638-51.  
27  
28  
29  
30 [9]. Gastaldelli A, Folli F, Defronzo R A. The Product of Triglycerides and  
31 Glucose as index of insulin resistance. Validation in the SAM study. *Journal of*  
32 *Clinical Endocrinology & Metabolism*. 2010;95.  
33  
34  
35 [10]. Khamseh ME, Malek M, Abbasi R, Taheri H, Lahouti M, Alaei-Shahmiri F.  
36 Triglyceride Glucose Index and Related Parameters (Triglyceride  
37 Glucose-Body Mass Index and Triglyceride Glucose-Waist Circumference)  
38 Identify Nonalcoholic Fatty Liver and Liver Fibrosis in Individuals with  
39 Overweight/Obesity. *Metab Syndr Relat Disord*. 2021;19:167-73.  
40  
41  
42  
43 [11]. Cho YK, Lee J, Kim HS, Kim EH, Lee MJ, Yang DH, Kang JW, Jung CH, Park  
44 JY, Kim HK, Lee WJ. Triglyceride Glucose-Waist Circumference Better  
45 Predicts Coronary Calcium Progression Compared with Other Indices of  
46 Insulin Resistance: A Longitudinal Observational Study. *J Clin Med*.  
47 2020;10:92.  
48  
49  
50  
51 [12]. Raimi TH, Dele-Ojo BF, Dada SA, Fadare JO, Ajayi DD, Ajayi EA, Ajayi OA.  
52 Triglyceride-Glucose Index and Related Parameters Predicted Metabolic  
53 Syndrome in Nigerians. *Metab Syndr Relat Disord*. 2021;19:76-82.  
54  
55  
56 [13]. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a  
57 multivariable prediction model for individual prognosis or diagnosis  
58 (TRIPOD): The TRIPOD statement. *Circulation*. 2015;131:211-19.  
59  
60



- 1  
2  
3  
4 [14]. Eslam M, Sanyal AJ, George J. International Consensus Panel. MAFLD: A  
5 Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty  
6 Liver Disease. *Gastroenterology*.2020;158:1999-2014.e1.  
7
- 8  
9 [15]. Taheri E, Pourhoseingholi MA, Moslem A, Hassani AH, Mousavi Jarrahi A,  
10 Asadzadeh Aghdaei H, Zali MR, Hatami B. The triglyceride-glucose index as a  
11 clinical useful marker for metabolic associated fatty liver disease (MAFLD): a  
12 population-based study among Iranian adults. *J Diabetes Metab Disord*.  
13 2022;21:97-107.  
14
- 15  
16 [16]. Liu Z, He H, Dai Y, Yang L, Liao S, An Z, Li S. Comparison of the diagnostic  
17 value between triglyceride-glucose index and triglyceride to high-density  
18 lipoprotein cholesterol ratio in metabolic-associated fatty liver disease  
19 patients: a retrospective cross-sectional study. *Lipids Health Dis*.  
20 2022;21:55.  
21
- 22  
23 [17]. Xue Y, Xu J, Li M, Gao Y. Potential screening indicators for early diagnosis  
24 of NAFLD/MAFLD and liver fibrosis: Triglyceride glucose index-related  
25 parameters. *Front Endocrinol (Lausanne)*. 2022;13:951689.  
26
- 27  
28 [18]. Chen YL, Li H, Li S, Xu Z, Tian S, Wu J, Liang XY, Li X, Liu ZL, Xiao J, Wei JY,  
29 Ma CY, Wu KN, Ran L, Kong LQ. Prevalence of and risk factors for metabolic  
30 associated fatty liver disease in an urban population in China: a  
31 cross-sectional comparative study. *BMC Gastroenterol*. 2021;21:212.  
32
- 33  
34 [19]. Vilarinho S, Ajmera V, Zheng M, Loomba R. Emerging Role of Genomic  
35 Analysis in Clinical Evaluation of Lean Individuals With NAFLD. *Hepatology*.  
36 2021;74:2241-50.  
37
- 38  
39 [20]. Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, Sun CH.  
40 Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders  
41 in a normal weight Chinese population. *World J Gastroenterol*.  
42 2014;20:17932-40.  
43
- 44  
45 [21]. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, Yang H, Liu C, Kam LY, Tan  
46 XXE, Chien N, Trinh S, Henry L, Stave CD, Hosaka T, Cheung RC, Nguyen MH.  
47 Global prevalence, incidence, and outcomes of non-obese or lean  
48 non-alcoholic fatty liver disease: a systematic review and meta-analysis.  
49 *Lancet Gastroenterol Hepatol*. 2020;5:739-52.  
50
- 51  
52 [22]. Gutiérrez-Cuevas J, Santos A, Armendariz-Borunda J. Pathophysiological  
53 Molecular Mechanisms of Obesity: A Link between MAFLD and NASH with  
54 Cardiovascular Diseases. *Int J Mol Sci*. 2021;22:11629.  
55
- 56  
57  
58  
59  
60

- 1  
2  
3  
4 [23]. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes  
5 in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*.  
6 2009;301:2129-40.  
7  
8  
9 [24]. Eslam M, El-Serag HB, Francque S, Sarin SK, Wei L, Bugianesi E, George J.  
10 Metabolic (dysfunction)-associated fatty liver disease in individuals of  
11 normal weight. *Nat Rev Gastroenterol Hepatol*. 2022;19:638-51.  
12  
13  
14 [25]. Della Torre S. Non-alcoholic Fatty Liver Disease as a Canonical Example  
15 of Metabolic Inflammatory-Based Liver Disease Showing a Sex-Specific  
16 Prevalence: Relevance of Estrogen Signaling. *Front Endocrinol (Lausanne)*.  
17 2020;11:572490.  
18  
19  
20 [26]. Alemany M. Estrogens and the regulation of glucose metabolism. *World J*  
21 *Diabetes*. 2021 Oct 15;12:1622-54.  
22  
23  
24 [27]. Palmisano BT, Zhu L, Stafford JM. Role of Estrogens in the Regulation of  
25 Liver Lipid Metabolism. *Adv Exp Med Biol*. 2017;1043:227-56.  
26  
27  
28 [28]. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark  
29 JM. Diagnostic accuracy and reliability of ultrasonography for the detection  
30 of fatty liver: a meta-analysis. *Hepatology*. 2011;54:1082-90.  
31  
32  
33  
34  
35  
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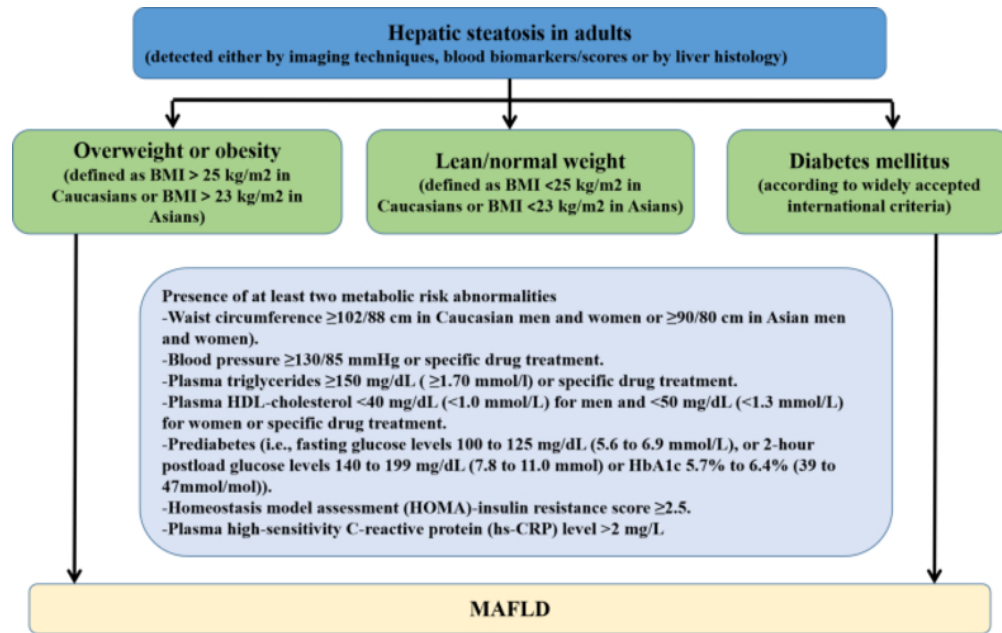


Figure 1 The flowchart of diagnostic criteria for MAFLD

169x106mm (118 x 118 DPI)

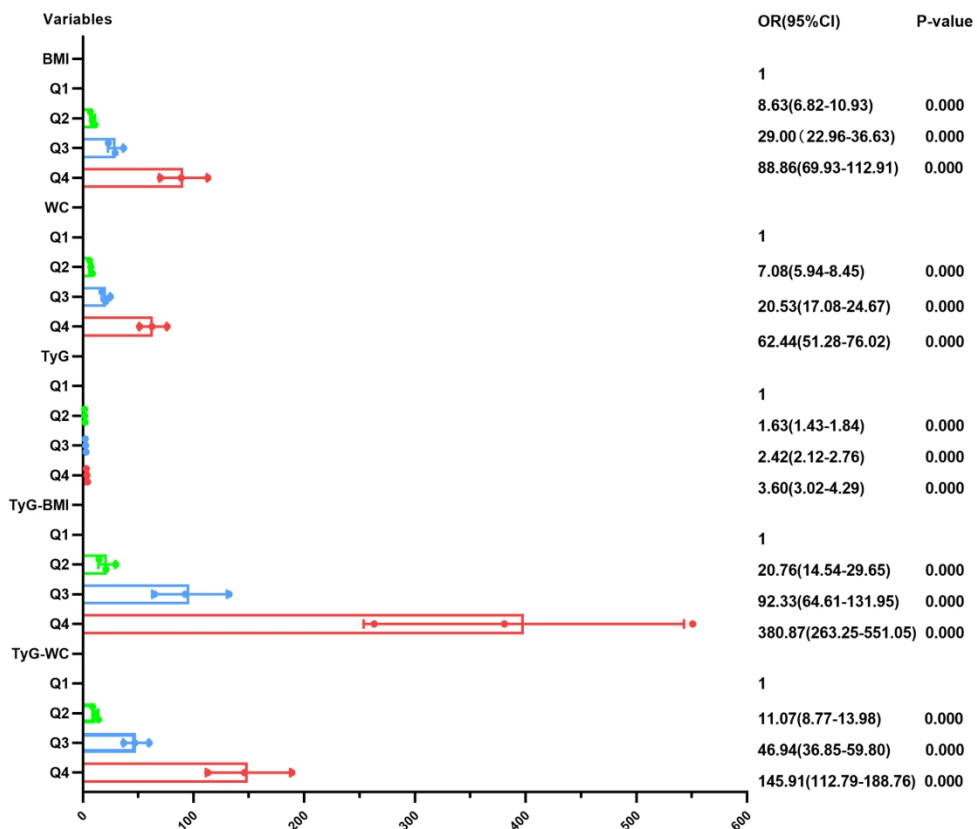


Figure 2 The MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, TyG-WC in the total population

190x163mm (300 x 300 DPI)

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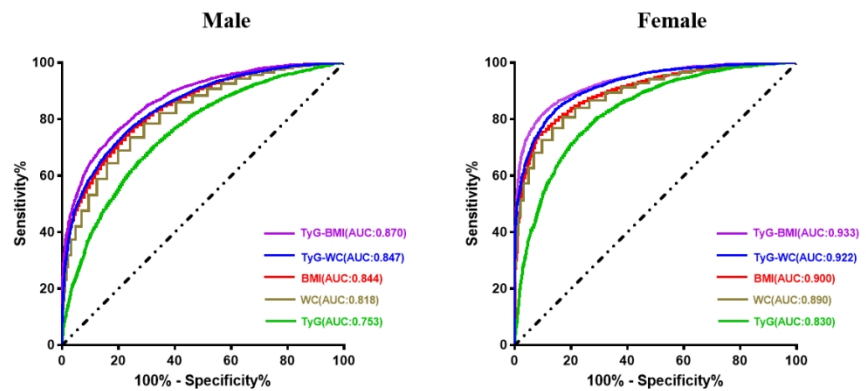


Figure 3 ROC curve of each parameter for predicting MAFLD in males and females

288x115mm (118 x 118 DPI)

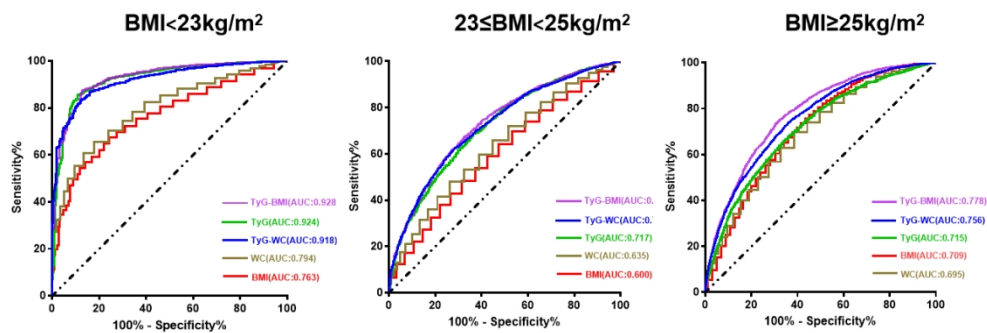


Figure 4 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

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.

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 TRIPOD reporting 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
<b>Title</b>		
	<a href="#">#1</a> Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	3
<b>Abstract</b>		
	<a href="#">#2</a> Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
<b>Introduction</b>		
	<a href="#">#3a</a> 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

1		<a href="#">#3b</a>	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
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5	<b>Methods</b>			
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7	Source of data	<a href="#">#4a</a>	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
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12	Source of data	<a href="#">#4b</a>	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
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16	Participants	<a href="#">#5a</a>	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
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21	Participants	<a href="#">#5b</a>	Describe eligibility criteria for participants.	5
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24	Participants	<a href="#">#5c</a>	Give details of treatments received, if relevant	NA not relevant
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28	Outcome	<a href="#">#6a</a>	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
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31	Outcome	<a href="#">#6b</a>	Report any actions to blind assessment of the outcome to be predicted.	5
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35	Predictors	<a href="#">#7a</a>	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	5
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41	Predictors	<a href="#">#7b</a>	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
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45	Sample size	<a href="#">#8</a>	Explain how the study size was arrived at.	NA this is a large scale study
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49	Missing data	<a href="#">#9</a>	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
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55	Statistical analysis methods	<a href="#">#10a</a>	If you are developing a prediction model describe how predictors were handled in the analyses.	6
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59	Statistical	<a href="#">#10b</a>	If you are developing a prediction model, specify type of	6
60			For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	



1	analysis methods		model, all model-building procedures (including any predictor selection), and method for internal validation.	
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4	Statistical	<a href="#">#10c</a>	If you are validating a prediction model, describe how the predictions were calculated.	NA
5	analysis methods			without a
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10	Statistical	<a href="#">#10d</a>	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
11	analysis methods			
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14	Statistical	<a href="#">#10e</a>	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	NA
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21	Risk groups	<a href="#">#11</a>	Provide details on how risk groups were created, if done.	5
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24	Development vs.	<a href="#">#12</a>	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
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30	<b>Results</b>			
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33	Participants	<a href="#">#13a</a>	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
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40	Participants	<a href="#">#13b</a>	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
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47	Participants	<a href="#">#13c</a>	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
48				without a
49				validating
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53	Model	<a href="#">#14a</a>	If developing a model, specify the number of participants and outcome events in each analysis.	7-9
54	development			
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57	Model	<a href="#">#14b</a>	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	7-9
58	development			
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1	Model	<a href="#">#15a</a>	If developing a model, present the full prediction model to	7-9
2	specification		allow predictions for individuals (i.e., all regression	
3			coefficients, and model intercept or baseline survival at a	
4			given time point).	
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8	Model	<a href="#">#15b</a>	If developing a prediction model, explain how to the use it.	9
9	specification			
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11	Model	<a href="#">#16</a>	Report performance measures (with CIs) for the prediction	7-9
12	performance		model.	
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15	Model-updating	<a href="#">#17</a>	If validating a model, report the results from any model	NA
16			updating, if done (i.e., model specification, model	without a
17			performance).	validating
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22	<b>Discussion</b>			
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24	Limitations	<a href="#">#18</a>	Discuss any limitations of the study (such as	11
25			nonrepresentative sample, few events per predictor, missing	
26			data).	
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30	Interpretation	<a href="#">#19a</a>	For validation, discuss the results with reference to	NA
31			performance in the development data, and any other	without a
32			validation data	validating
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36	Interpretation	<a href="#">#19b</a>	Give an overall interpretation of the results, considering	9-11
37			objectives, limitations, results from similar studies, and other	
38			relevant evidence.	
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42	Implications	<a href="#">#20</a>	Discuss the potential clinical use of the model and	10-12
43			implications for future research	
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46	<b>Other</b>			
47	<b>information</b>			
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49	Supplementary	<a href="#">#21</a>	Provide information about the availability of supplementary	2
50	information		resources, such as study protocol, Web calculator, and data	
51			sets.	
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55	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	2
56			present study.	
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-070189.R1
Article Type:	Original research
Date Submitted by the Author:	07-Mar-2023
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<b>Primary Subject Heading</b>:	Health services research
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Other metabolic, e.g. iron, porphyria < DIABETES & ENDOCRINOLOGY, Adult gastroenterology < GASTROENTEROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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4 1 **Associations between triglyceride glucose-related markers and the risk of**  
5 2 **metabolic-associated fatty liver disease : a cross-sectional study in healthy**  
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7 3 **Chinese subjects**

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44 22 **Running Title:** Triglyceride glucose-related markers and metabolic-associated  
45 23 fatty liver disease

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47 24 **Word count** 3684

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4 1 **Associations between triglyceride glucose-related markers and the**  
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6 2 **risk of metabolic-associated fatty liver disease : a cross-sectional**  
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9 3 **study in healthy Chinese subjects**  
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12 5 **Abstract**  
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15 7 **Objectives** The aim of this study was to evaluate the performance of the  
16 8 triglyceride glucose (TyG) index and its related markers in predicting  
17 9 metabolic-associated fatty liver disease (MAFLD) in healthy Chinese subjects.  
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20 11 **Design** This was a cross-sectional study.  
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23 13 **Setting** The study was conducted at Health Management Department of the  
24 14 Affiliated Hospital of Xuzhou Medical University.  
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27 16 **Participants** A total of 20922 asymptomatic participants (56% male) were  
28 17 enrolled.  
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31 19 **Measures** Hepatic ultrasonography was performed to determine the presence of  
32 20 MAFLD based on the latest diagnostic criteria. The TyG index, TyG-body mass  
33 21 index (TyG-BMI), and TyG-waist circumference (TyG-WC) index were calculated  
34 22 and analysed.  
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36 23  
37 24 **Results** Compared with the lowest quartile of the TyG-BMI, the adjusted odds  
38 25 ratios (ORs) and 95% confidence intervals (CIs) for MAFLD were 20.76  
39 26 (14.54-29.65), 92.33 (64.61-131.95) and 380.87 (263.25-551.05) in the 2nd, 3rd  
40 27 and 4th quartiles, respectively. According to the subgroup analysis, the TyG-BMI  
41 28 in the female group and the lean group (BMI<23 kg/m<sup>2</sup>) showed the most  
42 29 effective predictive value, with optimal cut-off points for MAFLD of 162.05 and  
43 30 156.31, respectively. The areas under the receiver operating characteristic (ROC)  
44 31 curves (AUCs) were 0.933 (95% CI: 0.927-0.938) and 0.928 (95% CI:  
45 32 0.914-0.943), respectively, with 90.7% sensitivity and 81.2% specificity in  
46 33 female subjects with MAFLD and 87.2% sensitivity and 87.1% specificity in lean  
47 34 subjects with MAFLD. The ability of the TyG-BMI to predict MAFLD was much  
48 35 better than that of other markers.  
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51 37 **Conclusions** The TyG-BMI may be effective and convenient for predicting  
52 38 MAFLD, especially in lean subjects and in female subjects.  
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55 40 **Key Words:** Metabolic-associated fatty liver disease, the triglyceride  
56 41 glucose-body mass index, the triglyceride glucose  
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## 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<sup>[1]</sup>. 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<sup>[2]</sup>. 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)<sup>[6]</sup>. Traditional obesity indicators, including body mass index (BMI) and waist circumference (WC) are strongly associated with fatty liver and metabolic disorders<sup>[7]</sup>. However, some studies have shown that 5% to 26% of MAFLD patients have a BMI within the normal range<sup>[9]</sup>. 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<sup>[10]</sup>.

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



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

## 7 8 9 **2. Methods**

### 10 11 **2.1 Study design and population**

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13 This cross-sectional study used data from an urban population in eastern  
14 China who participated in a health examination at the Affiliated Hospital of  
15 Xuzhou Medical University from January 2021 to December 2021. The inclusion  
16 criteria were as follows: age between 18 and 80 years and hepatic steatosis  
17 discovered by abdominal ultrasound. The exclusion criteria were as follows:  
18 incomplete data; age younger than 18 years or older than 80 years; hepatic  
19 cirrhosis, hepatocellular carcinoma or history of liver surgery; history of  
20 malignant tumours; New York Heart Association class III or IV heart failure;  
21 chronic kidney disease with an estimated glomerular filtration rate of  
22 <60mL/min/1.73m<sup>2</sup>; and pregnancy or lactation. Subjects with missing outcome  
23 measures and lost clinical and biochemical records were also excluded. Finally,  
24 20922 subjects (8099 MAFLD cases and 12823 non-MAFLD controls) were  
25 included in the final analysis (Figure 1). This study followed the TRIPOD  
26 reporting guidelines<sup>[17]</sup> and was approved by the Ethics Committee of the  
27 Affiliated Hospital of Xuzhou Medical University. To avoid duplication of  
28 information, we only use the first physical examination data of participants who  
29 underwent multiple physical examinations throughout the year.

### 30 31 **2.2 Methods**

#### 32 33 **2.2.1 Health survey examinations and laboratory measurements**

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

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

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

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

### 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<sup>[17]</sup>. 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<sup>[17]</sup>. 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<sup>[17]</sup>.

### 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 sociodemographic 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 <sup>2</sup> )	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 <sub>male</sub>	92.38±7.73	82.84±7.46	<0.0001
WC <sub>female</sub>	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 <sub>male</sub>	692.52±86.67	577.04±77.69	<0.0001
TyG-WC <sub>female</sub>	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.						

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

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#### 3.3.1 Predictive values of different indicators for MAFLD according to sex

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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).

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**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(%)
<b>Male (n=12343)</b>				
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
<b>Female (n=8579)</b>				
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.				

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#### 3.3.2 Predictive values of different indicators for MAFLD according to BMI

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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<sup>2</sup>) 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(%)
<b>BMI&lt;23 (n=7377)</b>				
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
<b>23≤BMI&lt;25 (n=4799)</b>				
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
<b>BMI≥25 (n=8746)</b>				
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



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3 1 them, and the participants in the highest TyG-BMI quartile group were 380.87  
4 2 times more likely to have MAFLD than those in the lowest quartile group.  
5 3 Subgroup analysis further verified the validity of the TyG-BMI for detecting  
6 4 MAFLD in healthy subjects. It was potential to be the most reliable indicator for  
7 5 MAFLD among the parameters with high discrimination power in both sex and  
8 6 BMI subgroups. Notably, the TyG-BMI performed especially well in the lean  
9 7 subgroup and the female subgroup. Although TyG and the TyG-WC index also  
10 8 presented some predictive value for MAFLD, we observed that they were not  
11 9 quite stable and fluctuated in different subgroups. The above findings supported  
12 10 the adoption of the TyG-BMI as an alternative screening test for MAFLD.

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14 To date, there have only been a few investigations on the diagnostic  
15 13 effectiveness of TyG-related indices for MAFLD<sup>[20]</sup>. Ehsaneh Taheri and  
16 14 colleagues first evaluated the association of the TyG index with MAFLD risk in an  
17 15 Iranian population. Among those in the highest relative to the lowest TyG  
18 16 tertiles, the multivariable-adjusted ORs (95% CI) were 12.01 (9.03-15.98) and  
19 17 10.89 (7.66-15.48), respectively. The results demonstrated that a TyG index  
20 18 cut-off of 8.62 had 81.66% sensitivity and 75.36% specificity<sup>[20]</sup>. However, that  
21 19 study used the fatty liver index to define MAFLD rather than ultrasonography or  
22 20 liver biopsies, and it did not assess the performance of the TyG-BMI or the  
23 21 TyG-WC index. In contrast, another Chinese study reported results that were  
24 22 consistent with those in Ehsaneh Taheri. In addition, the study found that a  
25 23 combination of TyG, BMI and ALT improved the diagnostic capability for MAFLD.  
26 24 The combined model demonstrated an AUC of 0.985 (95% CI, 0.973-0.998)  
27 25 compared to TyG alone (AUC=0.943; 95% CI, 0.912-0.973) and the TyG-BMI  
28 26 (AUC=0.956; 95% CI, 0.933-0.980). This study exhibited a higher diagnostic  
29 27 accuracy than that found in our study, but it only included a small sample size of  
30 28 229 patients<sup>[21]</sup>. Furthermore, Yan Xue et al. provided evidence for TyG-related  
31 29 indices as better predictive indicators for MAFLD than NAFLD. The TyG-WC  
32 30 index had the top performance, with an AUC (95% CI) of 0.815 (0.796–0.833) for  
33 31 predicting NAFLD and 0.832 (0.814–0.850) for predicting MAFLD<sup>[22]</sup>. However,  
34 32 unlike previous studies, our study involved a comprehensive assessment of the  
35 33 performance of TyG-related indices, including TyG, TyG-BMI and TyG-WC, to  
36 34 screen for and identify MAFLD in healthy Chinese subjects.

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38 Of note, the present study revealed that the predictive accuracies of  
39 36 TyG-related indices varied in different subgroups. When we stratified MAFLD  
40 37 individuals by BMI profile, we found that the TyG-BMI performed especially well  
41 38 in the lean population. Although MAFLD has been increasing in parallel with the  
42 39 rising prevalence of obesity, it should be noted that lean individuals may also  
43 40 suffer from MAFLD. A recent study in China found that among the nonobese  
44 41 population, the prevalence of MAFLD was 11.5% (males: 16.4%, females: 6.9%),  
45 42 consistent with Vilarinho's findings<sup>[23]</sup>. Importantly, MAFLD in lean subjects is  
46 43 not a benign or stable state as expected. A number of studies have even  
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1 suggested that compared to those with obese MAFLD, lean individuals with  
2 MAFLD have an increased risk of diabetes mellitus and cardiovascular and  
3 all-cause mortality<sup>[25]</sup>. BMI is widely used to evaluate obesity, but not to describe  
4 regional fat distribution. The contribution of visceral fat to MAFLD has been  
5 found to be more important than that of total body fat<sup>[27]</sup>. Although Asians have a  
6 lower absolute BMI than Westerners, Asians are more vulnerable to visceral fat  
7 accumulation and IR<sup>[28]</sup>. Thus, reduced BMI levels are not necessarily  
8 representative of a metabolically healthy state. Based on the formula of  
9 TyG-BMI<sup>[27]</sup>, we could reasonably infer that the higher the subject's BMI, the  
10 higher the TyG-BMI index. From this perspective alone, TyG-BMI does not appear  
11 to be an ideal predictor for MAFLD. However, our study observed that increased  
12 TyG-BMI levels were positively correlated with the risk of MAFLD in lean  
13 individuals. Perhaps this is why the role of "TyG" has not been addressed, we  
14 may ignore its dynamic changes of various metabolic states. The effect of "TyG"  
15 increase might be far greater than BMI decrease in lean individuals with MAFLD.  
16 That is to say, IR caused by excessive accumulation of visceral fat may be more  
17 pronounced in the development of MAFLD in lean individuals<sup>Error! Reference source  
18 not found.</sup> Yu ling et al. revealed that metabolic disorders in nonobese individuals  
19 with MAFLD were all significantly higher than those in nonobese individuals  
20 without MAFLD<sup>[23]</sup>. Therefore, simply focusing on decreased BMI or increased  
21 TyG does not seem to be suitable for the prediction of lean MAFLD. Only by  
22 considering the TyG-BMI index as a whole can we better understand its  
23 predictive value in lean MAFLD.

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

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

22  
23 In conclusion, the present study suggested that the TyG-BMI was an  
24 promising predictor for MAFLD. Individuals with normal BMI levels but high  
25 TyG-BMI levels should undergo a more detailed assessment for MAFLD. Our  
26 findings extended previous investigations by demonstrating that the TyG-BMI  
27 might be ideal for the prediction of MAFLD in lean individuals and in females.

## 28 29 **Figure legends**

30 **Figure 1** Flowchart of the study design

31 **Figure 2** Flowchart of diagnostic criteria for MAFLD

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

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

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

## 38 39 **Declarations**

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4 **1 Ethical approval and consent to participate**  
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6 2 This study was approved and supervised by the Ethics Committee of the  
7  
8 3 Affiliated Hospital of Xuzhou Medical University. The need for written informed  
9  
10 4 consent to participate was waived due to the retrospective nature of the study.  
11

12 **5 Consent for publication**  
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15 6 Not applicable.  
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17 **7 Availability of data and materials**  
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20 8 The datasets used and/or analysed during the current study are available from  
21  
22 9 the corresponding author on reasonable request.  
23

24 **10 Competing interests**  
25

26 11 All authors have declared that they have no conflicts of interest.  
27

28 **12 Funding**  
29

30  
31 13 Not applicable.  
32

33 **14 Author Contributions**  
34

35 15 Mingxing Chang and Guifang Shen conceived of and designed the study.  
36

37 16 Mingxing Chang and Zhihao Shao coordinated data collection and conducted the  
38  
39 17 analyses.  
40

41 18 Mingxing Chang wrote the manuscript.  
42

43 19 All authors have read and approved the final manuscript.  
44

45 **20 Acknowledgements**  
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47 21 Not applicable.  
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50 **23 5. References**  
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52  
53 25 [1]. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH:  
54 26 trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol*  
55 27 *Hepatol* 2018;15:11-20.  
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- [2]. Huang SC, Su HJ, Kao JH, et al. Clinical and Histologic Features of Patients with Biopsy-Proven Metabolic Dysfunction-Associated Fatty Liver Disease. *Gut Liver* 2021;15:451-58.
- [3]. Guerreiro GTS, Longo L, Fonseca MA, et al. Does the risk of cardiovascular events differ between biopsy-proven NAFLD and MAFLD? *Hepatol Int* 2021;15:380-91.
- [4]. Kim D, Konyn P, Sandhu KK, et al. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *J Hepatol* 2021;75:1284-91.
- [5]. Tarantino G, Crocetto F, Di Vito C, et al. Association of NAFLD and Insulin Resistance with Non Metastatic Bladder Cancer Patients: A Cross-Sectional Retrospective Study. *J Clin Med* 2021;10:346.
- [6]. Xian YX, Weng JP, Xu F. MAFLD vs. NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. *Chin Med J (Engl)* 2020;134:8-19.
- [7]. Abe M, Fujii H, Funakoshi S, et al. Comparison of Body Mass Index and Waist Circumference in the Prediction of Diabetes: A Retrospective Longitudinal Study. *Diabetes Ther* 2021;12:2663-76.
- [8]. Aizawa M, Inagaki S, Moriyama M, et al. Modeling the natural history of fatty liver using lifestyle-related risk factors: Effects of body mass index (BMI) on the life-course of fatty liver. *PLoS One* 2019;14:e0223683.
- [9]. Eslam M, El-Serag HB, Francque S, et al. Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight. *Nat Rev Gastroenterol Hepatol* 2022;19:638-51.
- [10]. Gastaldelli A, Folli F, DeFronzo R A. The Product of Triglycerides and Glucose as index of insulin resistance. Validation in the SAM study. *Journal of Clinical Endocrinology & Metabolism* 2010;95.
- [11]. Khamseh ME, Malek M, Abbasi R, et al. Triglyceride Glucose Index and Related Parameters (Triglyceride Glucose-Body Mass Index and Triglyceride Glucose-Waist Circumference) Identify Nonalcoholic Fatty Liver and Liver Fibrosis in Individuals with Overweight/Obesity. *Metab Syndr Relat Disord* 2021;19:167-73.

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- 1 [12]. Cho YK, Lee J, Kim HS, et al. Triglyceride Glucose-Waist Circumference  
2 Better Predicts Coronary Calcium Progression Compared with Other Indices  
3 of Insulin Resistance: A Longitudinal Observational Study. *J Clin Med*  
4 2020;10:92.  
5  
6 [13]. Raimi TH, Dele-Ojo BF, Dada SA, et al. Triglyceride-Glucose Index and  
7 Related Parameters Predicted Metabolic Syndrome in Nigerians. *Metab*  
8 *Syndr Relat Disord* 2021;19:76-82.  
9  
10 [14]. Simental-Mend í a LE, Rodr í guez-Mor á n M, Guerrero-Romero F. The  
11 product of fasting glucose and triglycerides as surrogate for identifying  
12 insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord*  
13 2008;6:299-304.  
14  
15 [15]. Er LK, Wu S, Chou HH, et al. Triglyceride Glucose-Body Mass Index Is a  
16 Simple and Clinically Useful Surrogate Marker for Insulin Resistance in  
17 Nondiabetic Individuals. *PLoS One* 2016;11:e0149731.  
18  
19 [16]. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a  
20 multivariable prediction model for individual prognosis or diagnosis  
21 (TRIPOD): The TRIPOD statement. *Circulation* 2015;131:211-19.  
22  
23 [17]. Eslam M, Sanyal AJ, George J. International Consensus Panel. MAFLD: A  
24 Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty  
25 Liver Disease. *Gastroenterology* 2020;158:1999-2014.e1.  
26  
27 [18]. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic  
28 dysfunction-associated fatty liver disease: An international expert consensus  
29 statement. *J Hepatol* 2020;73:202-9.  
30  
31 [19]. Fan JG, Farrell GC. Epidemiology of non-alcoholic fatty liver disease in  
32 China. *J Hepatol* 2009;50:204-10.  
33  
34 [20]. Taheri E, Pourhoseingholi MA, Moslem A, et al. The triglyceride-glucose  
35 index as a clinical useful marker for metabolic associated fatty liver disease  
36 (MAFLD): a population-based study among Iranian adults. *J Diabetes Metab*  
37 *Disord* 2022;21:97-107.  
38  
39 [21]. Liu Z, He H, Dai Y, et al. Comparison of the diagnostic value between  
40 triglyceride-glucose index and triglyceride to high-density lipoprotein  
41 cholesterol ratio in metabolic-associated fatty liver disease patients: a  
42 retrospective cross-sectional study. *Lipids Health Dis* 2022;21:55.  
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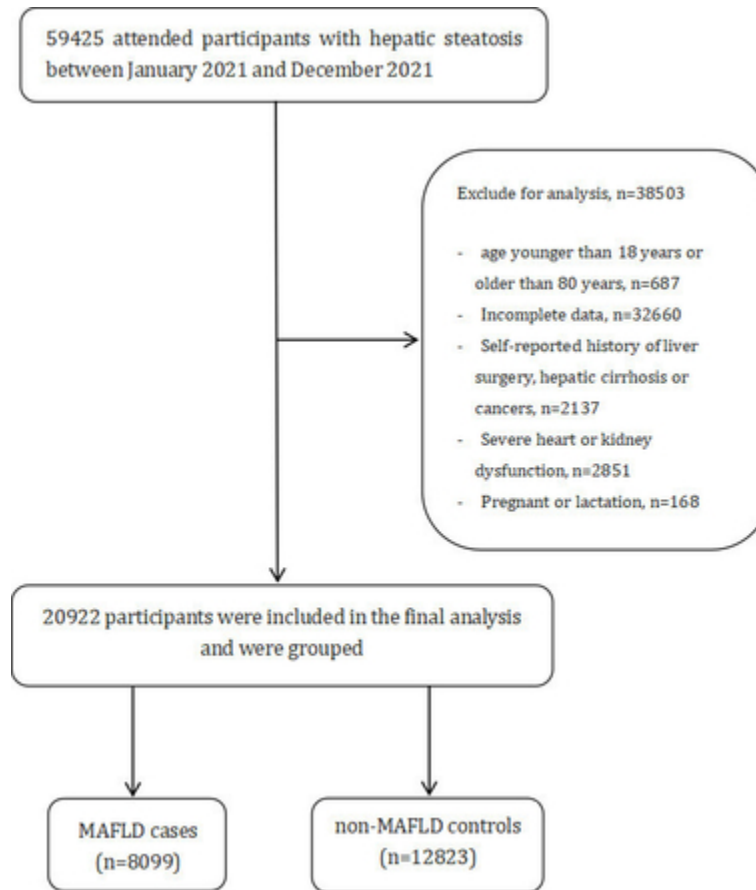
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- [22]. Xue Y, Xu J, Li M, et al. Potential screening indicators for early diagnosis of NAFLD/MAFLD and liver fibrosis: Triglyceride glucose index-related parameters. *Front Endocrinol (Lausanne)* 2022;13:951689.
- [23]. Chen YL, Li H, Li S, et al. Prevalence of and risk factors for metabolic associated fatty liver disease in an urban population in China: a cross-sectional comparative study. *BMC Gastroenterol* 2021;21:212.
- [24]. Vilarinho S, Ajmera V, Zheng M, et al. Emerging Role of Genomic Analysis in Clinical Evaluation of Lean Individuals With NAFLD. *Hepatology* 2021;74:2241-50.
- [25]. Feng RN, Du SS, Wang C, et al. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. *World J Gastroenterol* 2014;20:17932-40.
- [26]. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020;5:739-52.
- [27]. Gutiérrez-Cuevas J, Santos A, Armendariz-Borunda J. Pathophysiological Molecular Mechanisms of Obesity: A Link between MAFLD and NASH with Cardiovascular Diseases. *Int J Mol Sci* 2021;22:11629.
- [28]. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129-40.
- [29]. Della Torre S. Non-alcoholic Fatty Liver Disease as a Canonical Example of Metabolic Inflammatory-Based Liver Disease Showing a Sex-Specific Prevalence: Relevance of Estrogen Signaling. *Front Endocrinol (Lausanne)* 2020;11:572490.
- [30]. Alemany M. Estrogens and the regulation of glucose metabolism. *World J Diabetes* 2021;12:1622-54.
- [31]. Palmisano BT, Zhu L, Stafford JM. Role of Estrogens in the Regulation of Liver Lipid Metabolism. *Adv Exp Med Biol* 2017;1043:227-56.
- [32]. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 2011;54:1082-90.

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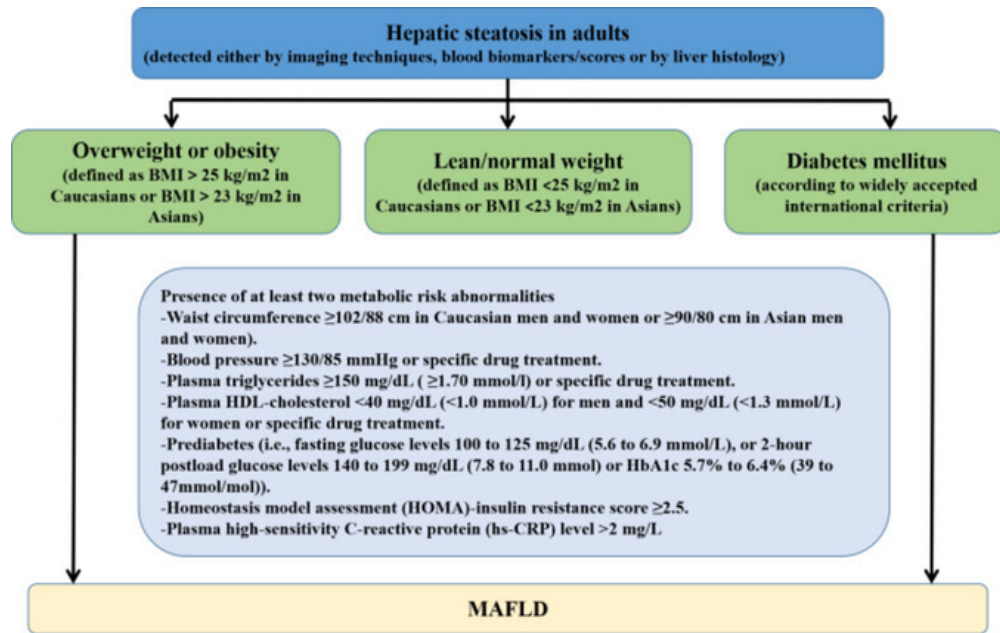
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Flowchart of the study design

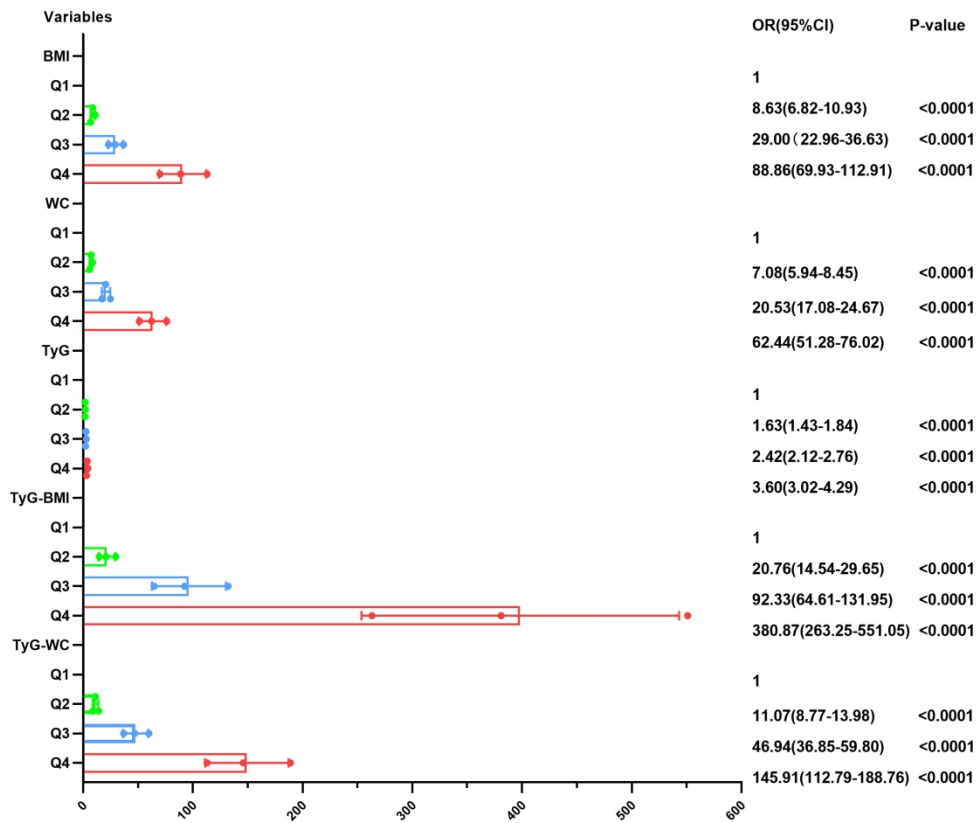
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Flowchart of diagnostic criteria for MAFLD

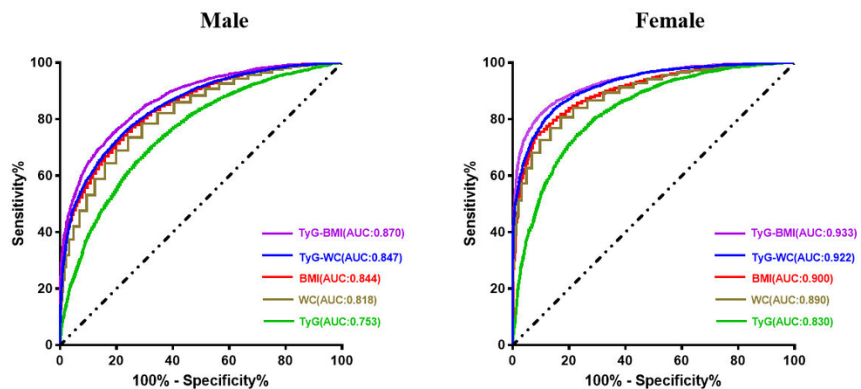
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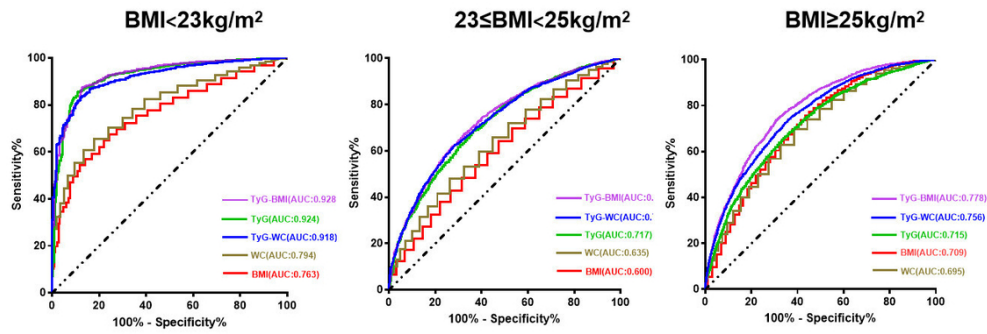
MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

197x166mm (300 x 300 DPI)



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.

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

In your methods section, say that you used the TRIPOD reporting 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
<b>Title</b>		
	<a href="#">#1</a> Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	2
<b>Abstract</b>		
	<a href="#">#2</a> Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
<b>Introduction</b>		
	<a href="#">#3a</a> 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

1		<a href="#">#3b</a>	Specify the objectives, including whether the study describes the development or validation of the model or both.	3-4
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6	<b>Methods</b>			
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9	Source of data	<a href="#">#4a</a>	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
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14	Source of data	<a href="#">#4b</a>	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
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18	Participants	<a href="#">#5a</a>	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
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23	Participants	<a href="#">#5b</a>	Describe eligibility criteria for participants.	4
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25	Participants	<a href="#">#5c</a>	Give details of treatments received, if relevant	NA. This study was not relevant to treatment.
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32	Outcome	<a href="#">#6a</a>	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
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36	Outcome	<a href="#">#6b</a>	Report any actions to blind assessment of the outcome to be predicted.	NA. This study did not involve blind assessment.
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43	Predictors	<a href="#">#7a</a>	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	4
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48	Predictors	<a href="#">#7b</a>	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA. This study did not involve blind assessment.
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55	Sample size	<a href="#">#8</a>	Explain how the study size was arrived at.	4
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57	Missing data	<a href="#">#9</a>	Describe how missing data were handled (e.g., complete-	4
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case analysis, single imputation, multiple imputation) with details of any imputation method.

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4	Statistical	<a href="#">#10a</a>	If you are developing a prediction model describe how
5	analysis methods		predictors were handled in the analyses.
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8	Statistical	<a href="#">#10b</a>	If you are developing a prediction model, specify type of
9	analysis methods		model, all model-building procedures (including any
10			predictor selection), and method for internal validation.
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13	Statistical	<a href="#">#10c</a>	If you are validating a prediction model, describe how the
14	analysis methods		predictions were calculated.
15			NA. This
16			study did not
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21	Statistical	<a href="#">#10d</a>	Specify all measures used to assess model performance
22	analysis methods		and, if relevant, to compare multiple models.
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25	Statistical	<a href="#">#10e</a>	If you are validating a prediction model, describe any
26	analysis methods		model updating (e.g., recalibration) arising from the
27			validation, if done
28			NA. This
29			study did not
30			involve a
31			validating
32			model.
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34	Risk groups	<a href="#">#11</a>	Provide details on how risk groups were created, if done.
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36	Development vs.	<a href="#">#12</a>	For validation, identify any differences from the
37	validation		development data in setting, eligibility criteria, outcome,
38			and predictors.
39			NA. This
40			study did not
41			involve a
42			validating
43			model.
44	<b>Results</b>		
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46	Participants	<a href="#">#13a</a>	Describe the flow of participants through the study,
47			including the number of participants with and without the
48			outcome and, if applicable, a summary of the follow-up
49			time. A diagram may be helpful.
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53	Participants	<a href="#">#13b</a>	Describe the characteristics of the participants (basic
54			demographics, clinical features, available predictors),
55			including the number of participants with missing data for
56			predictors and outcome.
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1	Participants	<a href="#">#13c</a>	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.
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9	Model	<a href="#">#14a</a>	If developing a model, specify the number of participants and outcome events in each analysis.	7-9
10	development			
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13	Model	<a href="#">#14b</a>	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	7-8
14	development			
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18	Model	<a href="#">#15a</a>	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
19	specification			
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25	Model	<a href="#">#15b</a>	If developing a prediction model, explain how to the use it.	9
26	specification			
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29	Model	<a href="#">#16</a>	Report performance measures (with CIs) for the prediction model.	8-9
30	performance			
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33	Model-updating	<a href="#">#17</a>	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.
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41	<b>Discussion</b>			
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43	Limitations	<a href="#">#18</a>	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
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49	Interpretation	<a href="#">#19a</a>	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.
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57	Interpretation	<a href="#">#19b</a>	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and	10
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other relevant evidence.

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3 Implications [#20](#) Discuss the potential clinical use of the model and 12  
4 implications for future research  
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6 **Other**  
7 **information**  
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10 Supplementary [#21](#) Provide information about the availability of supplementary 13  
11 information resources, such as study protocol, Web calculator, and  
12 data sets.  
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15 Funding [#22](#) Give the source of funding and the role of the funders for NA. This  
16 the present study. study did not  
17 involve any  
18 fundings.  
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22 None The TRIPOD checklist is distributed under the terms of the Creative Commons Attribution  
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24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-070189.R2
Article Type:	Original research
Date Submitted by the Author:	18-Apr-2023
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
<b>Primary Subject Heading</b>:	Health services research
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Other metabolic, e.g. iron, porphyria < DIABETES & ENDOCRINOLOGY, Adult gastroenterology < GASTROENTEROLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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4 1 **Association between triglyceride glucose-related markers and the risk of**  
5 **metabolic-associated fatty liver disease: a cross-sectional study in healthy Chinese**  
6 **participants**  
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11 5 Mingxing Chang<sup>1</sup>, Zhihao Shao<sup>1</sup>, Guifang Shen<sup>1\*</sup>  
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## 1 ABSTRACT

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6 **Objectives** This study aimed to evaluate the performance of the triglyceride glucose (TyG)  
7 index and its related markers in predicting metabolic-associated fatty liver disease (MAFLD)  
8 in healthy Chinese participants.  
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11 **Design** This was a cross-sectional study.  
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14 **Setting** The study was conducted at Health Management Department of the Affiliated  
15 Hospital of Xuzhou Medical University.  
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18 **Participants** A total of 20922 asymptomatic Chinese participants (56% male) were enrolled.  
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21 **Outcome measures** Hepatic ultrasonography was performed to diagnose MAFLD based on  
22 the latest diagnostic criteria. The TyG, TyG-body mass (TyG-BMI), and TyG-waist  
23 circumference (TyG-WC) indices were calculated and analysed.  
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26 **Results** Compared with the lowest quartile of the TyG-BMI index, the adjusted odds ratios  
27 (ORs) and 95% confidence intervals (CIs) for MAFLD were 20.76 (14.54–29.65), 92.33  
28 (64.61–131.95) and 380.87 (263.25–551.05) in the 2nd, 3rd and 4th quartiles, respectively.  
29 According to the subgroup analysis, the TyG-BMI index in the female and the lean groups  
30 (BMI<23 kg/m<sup>2</sup>) showed the strongest predictive value, with optimal cut-off values for  
31 MAFLD of 162.05 and 156.31, respectively. The areas under the receiver operating  
32 characteristic curves in female and lean groups were 0.933 (95% CI: 0.927–0.938) and 0.928  
33 (95% CI: 0.914–0.943), respectively, with 90.7% sensitivity and 81.2% specificity in female  
34 participants with MAFLD and 87.2% sensitivity and 87.1% specificity in lean participants  
35 with MAFLD. The TyG-BMI index demonstrated superior predictive ability for MAFLD  
36 compared to other markers.  
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41 **Conclusions** The TyG-BMI index is an effective, simple, and promising tool for predicting  
42 MAFLD, especially in lean and female participants.  
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45 **Key Words:** Metabolic-associated fatty liver disease, triglyceride glucose-body mass index,  
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## 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 MAFLD 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  $<60\text{mL}/\text{min}/1.73\text{m}^2$ ; 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),  $\gamma$ -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]:

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

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

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

### 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 <sup>2</sup> )	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 <sub>male</sub>	92.38±7.73	82.84±7.46	<0.0001
WC <sub>female</sub>	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 <sub>male</sub>	692.52±86.67	577.04±77.69	<0.0001
TyG-WC <sub>female</sub>	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(%)
<b>Male (n=12343)</b>				
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
<b>Female (n=8579)</b>				
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<sup>2</sup>; 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(%)
<b>BMI&lt;23 (n=7377)</b>				
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
<b>23≤BMI&lt;25 (n=4799)</b>				
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
<b>BMI≥25 (n=8746)</b>				
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.



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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.

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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

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3 1 metabolic disorders, including dyslipidaemia and IR. The lack of oestrogen availability also  
4 2 decreases hepatic insulin clearance and allows the development of diet-induced IR. [30,31]  
5 3 Notably, in the current study, we observed that increased TyG-BMI values were closely  
6 4 related to the risk of MAFLD in female individuals. However, the specific mechanisms  
7 5 underlying this phenomenon remain to be elucidated.  
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11 7 Our study had several limitations. First, the diagnosis of MAFLD was based on  
12 8 ultrasonography, which may have showed decreased sensitivity when liver steatosis is below  
13 9 30%. [32] Therefore, using ultrasound to screen for MAFLD may have underestimated the  
14 10 true prevalence of MAFLD. Second, certain data were not available from the health  
15 11 examination, such as the liver biopsy data or the controlled attenuation parameter and liver  
16 12 stiffness measurement from the FibroScan Test. Hence, further studies on the relationships  
17 13 between TyG-related indices and the severity of MAFLD are needed. Third, we included  
18 14 asymptomatic individuals from a single centre; thus, selection bias to a certain extent was  
19 15 inevitable. In addition, we noticed that the 95% CIs of the quartile analysis were relatively  
20 16 wide, especially the 4<sup>th</sup> quartile of the TyG-BMI (263.25–551.05) index, which may be  
21 17 related to the insufficient sample size. Therefore, multicentre and prospective studies with  
22 18 larger and more diverse populations are required to validate our findings. Our study had  
23 19 several notable strengths. First and foremost, we provide novel evidence regarding the utility  
24 20 of the TyG-BMI index in predicting MAFLD in lean and female individuals. Moreover, we  
25 21 enrolled participants from diverse occupations and backgrounds and collected extensive  
26 22 clinical data to ensure statistical reliability and to validate our findings from multiple  
27 23 perspectives. In addition, our study has important clinical implications, as it is the first to  
28 24 demonstrate that the assessment of the TyG-BMI index could be helpful in identifying  
29 25 individuals with high-risk of MAFLD, especially among those who are lean and female.  
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33 27 In conclusion, the present study suggested that the TyG-BMI index was a promising  
34 28 predictor for MAFLD. Individuals with BMI values within the normal range but high  
35 29 TyG-BMI levels should undergo a more detailed assessment for MAFLD. Our findings  
36 30 extended previous investigations by demonstrating that the TyG-BMI index may be an ideal  
37 31 predictor for the presence of MAFLD in lean and female individuals.  
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## 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.

### Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

### 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.

### Acknowledgements

Not applicable.

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**REFERENCES**

- 1 Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018;15:11–20.
- 2 Huang SC, Su HJ, Kao JH, et al. Clinical and histologic features of patients with biopsy-proven metabolic dysfunction-associated fatty liver disease. *Gut Liver* 2021;15:451–58.
- 3 Guerreiro GTS, Longo L, Fonseca MA, et al. Does the risk of cardiovascular events differ between biopsy-proven NAFLD and MAFLD? *Hepatol Int* 2021;15:380–91.
- 4 Kim D, Konyn P, Sandhu KK, et al. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *J Hepatol* 2021;75:1284–91.
- 5 Tarantino G, Crocetto F, Di Vito C, et al. Association of NAFLD and insulin resistance with non metastatic bladder cancer patients: A cross-sectional retrospective study. *J Clin Med* 2021;10:346.
- 6 Xian YX, Weng JP, Xu F. MAFLD vs. NAFLD: Shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. *Chin Med J (Engl)* 2020;134:8–19.
- 7 Abe M, Fujii H, Funakoshi S, et al. Comparison of body mass index and waist circumference in the prediction of diabetes: A retrospective longitudinal study. *Diabetes Ther* 2021;12:2663–76.
- 8 Aizawa M, Inagaki S, Moriyama M, et al. Modeling the natural history of fatty liver using lifestyle-related risk factors: Effects of body mass index (BMI) on the life-course of fatty liver. *PLOS ONE* 2019;14:e0223683.
- 9 Eslam M, El-Serag HB, Francque S, et al. Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight. *Nat Rev Gastroenterol Hepatol* 2022;19:638–51.
- 10 Gastaldelli A, Folli F, DeFronzo RA. The Product of triglycerides and glucose as index of insulin resistance. Validation in the SAM study. *J Clin Endocrinol Metab* 2010;95.

- 11 Khamseh ME, Malek M, Abbasi R, et al. Triglyceride glucose index and related parameters (triglyceride glucose-body mass index and triglyceride glucose-waist circumference) identify nonalcoholic fatty liver and liver fibrosis in individuals with overweight/obesity. *Metab Syndr Relat Disord* 2021;19:167–73.
- 12 Cho YK, Lee J, Kim HS, et al. Triglyceride glucose-waist circumference better predicts coronary calcium progression compared with other indices of insulin resistance: A longitudinal observational study. *J Clin Med* 2020;10:92.
- 13 Raimi TH, Dele-Ojo BF, Dada SA, et al. Triglyceride-glucose index and related parameters predicted metabolic syndrome in Nigerians. *Metab Syndr Relat Disord* 2021;19:76–82.
- 14 Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* 2008;6:299–304.
- 15 Er LK, Wu S, Chou HH, et al. Triglyceride glucose-body mass index is a simple and clinically useful surrogate marker for insulin resistance in nondiabetic individuals. *PLOS ONE* 2016;11:e0149731.
- 16 Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. The TRIPOD Group. *Circulation* 2015;131:211–19.
- 17 Eslam M, Sanyal AJ, George J et al. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020;158:1999–2014.e1
- 18 Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020;73:202–9.
- 19 Fan JG, Farrell GC. Epidemiology of non-alcoholic fatty liver disease in China. *J Hepatol* 2009;50:204–10.
- 20 Taheri E, Pourhoseingholi MA, Moslem A, et al. The triglyceride-glucose index as a clinical useful marker for metabolic associated fatty liver disease (MAFLD): A population-based study among Iranian adults. *J Diabetes Metab Disord* 2022;21:97–107.
- 21 Liu Z, He H, Dai Y, et al. Comparison of the diagnostic value between triglyceride-glucose index and triglyceride to high-density lipoprotein cholesterol ratio in metabolic-associated fatty liver disease patients: A retrospective cross-sectional study. *Lipids Health Dis* 2022;21:55.

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5 2 22 Xue Y, Xu J, Li M, et al. Potential screening indicators for early diagnosis of  
6 3 NAFLD/MAFLD and liver fibrosis: Triglyceride glucose index-related parameters.  
7 4 *Front Endocrinol (Lausanne)* 2022;13:951689.  
8 5  
9 6 23 Chen YL, Li H, Li S, et al. Prevalence of and risk factors for metabolic associated fatty  
10 7 liver disease in an urban population in China: A cross-sectional comparative study. *BMC*  
11 8 *Gastroenterol* 2021;21:212.  
12 9  
13 10 24 Vilarinho S, Ajmera V, Zheng M, et al. Emerging role of genomic analysis in clinical  
14 11 evaluation of lean individuals with NAFLD. *Hepatology* 2021;74:2241–50.  
15 12  
16 13 25 Feng RN, Du SS, Wang C, et al. Lean-non-alcoholic fatty liver disease increases risk for  
17 14 metabolic disorders in a normal weight Chinese population. *World J Gastroenterol*  
18 15 2014;20:17932–40.  
19 16  
20 17 26 Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese  
21 18 or lean non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Lancet*  
22 19 *Gastroenterol Hepatol* 2020;5:739–52.  
23 20  
24 21 27 Gutiérrez-Cuevas J, Santos A, Armendariz-Borunda J. Pathophysiological molecular  
25 22 mechanisms of obesity: A link between MAFLD and NASH with cardiovascular  
26 23 diseases. *Int J Mol Sci* 2021;22:11629.  
27 24  
28 25 28 Chan JC, Malik V, Jia W, et al. Diabetes in Asia: Epidemiology, risk factors, and  
29 26 pathophysiology. *JAMA* 2009;301:2129–40.  
30 27  
31 28 29 Della Torre S. Non-alcoholic fatty liver disease as a canonical example of metabolic  
32 29 inflammatory-based liver disease showing a sex-specific prevalence: Relevance of  
33 30 estrogen signaling. *Front Endocrinol (Lausanne)* 2020;11:572490.  
34 31  
35 32 30 Alemany M. Estrogens and the regulation of glucose metabolism. *World J Diabetes*  
36 33 2021;12:1622–54.  
37 34  
38 35 31 Palmisano BT, Zhu L, Stafford JM. Role of estrogens in the regulation of liver lipid  
39 36 metabolism. *Adv Exp Med Biol* 2017;1043:227–56.  
40 37  
41 38 32 Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of  
42 39 ultrasonography for the detection of fatty liver: A meta-analysis. *Hepatology*  
43 40 2011;54:1082–90.  
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11 **FIGURE LEGENDS**

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13 6 **Figure 1** Flowchart of the study design

14 7 **Figure 2** Flowchart of diagnostic criteria for MAFLD

15 8 **Figure 3** MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and  
16 9 TyG-WC in the total population

17 10 **Figure 4** ROC curve of each parameter for predicting MAFLD according to sex

18 11 **Figure 5** ROC curve of each parameter for predicting MAFLD in different BMI subgroups  
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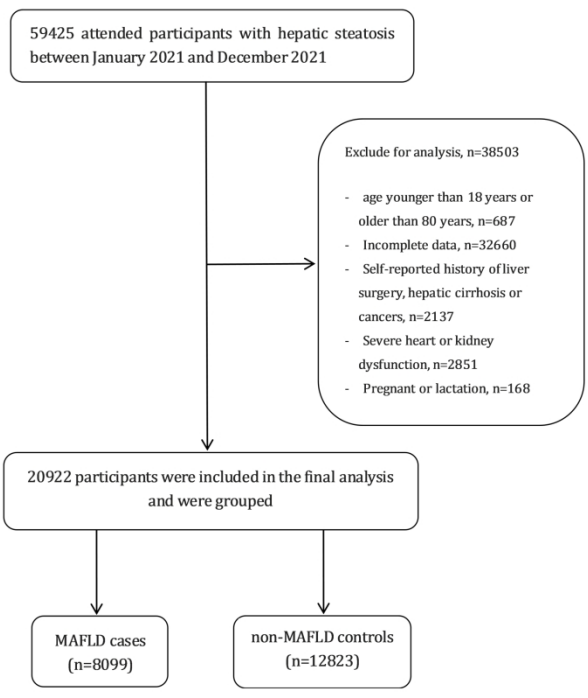


Figure 1 Flowchart of the study design

259x195mm (300 x 300 DPI)

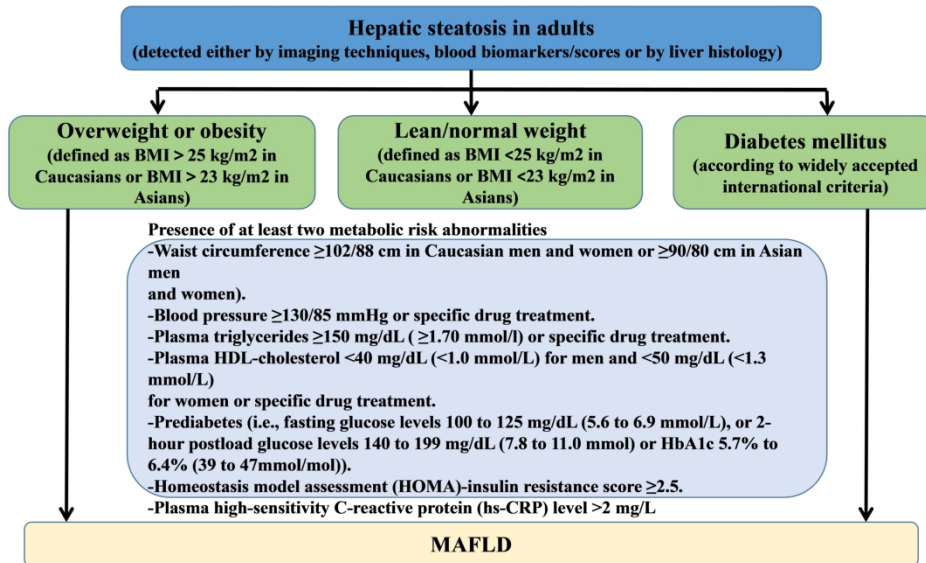


Figure 2 Flowchart of diagnostic criteria for MAFLD

267x195mm (300 x 300 DPI)

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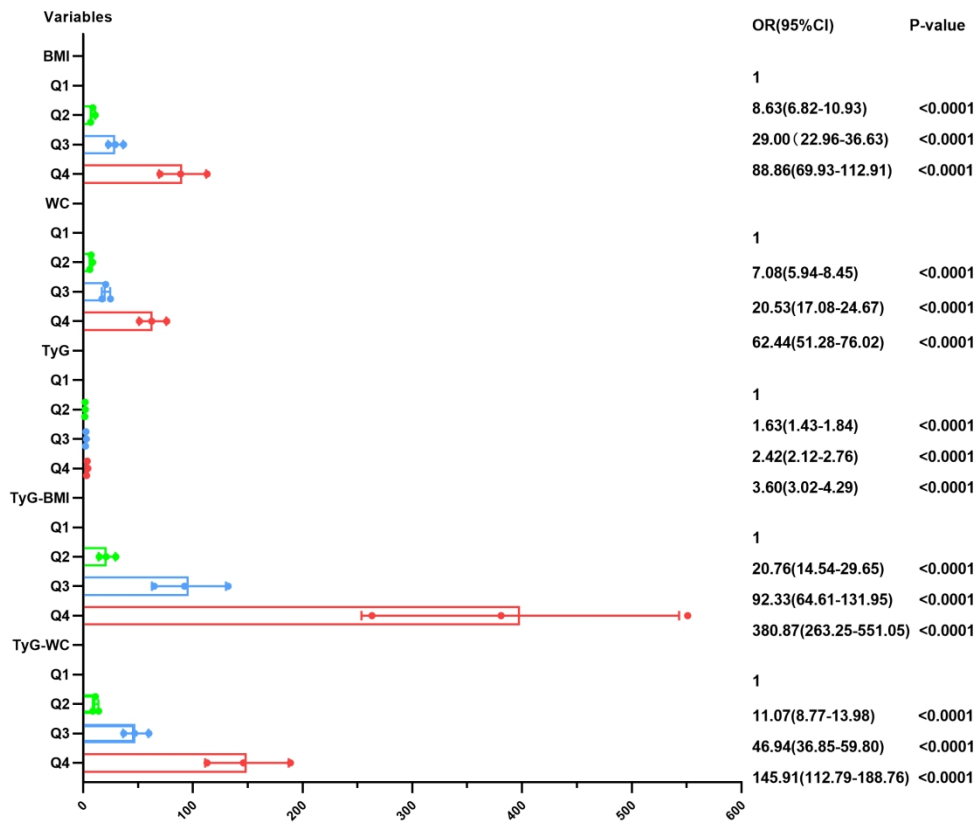


Figure 3 MAFLD ORs and CIs according to the quartiles of BMI, WC, TyG, TyG-BMI, and TyG-WC in the total population

197x166mm (300 x 300 DPI)



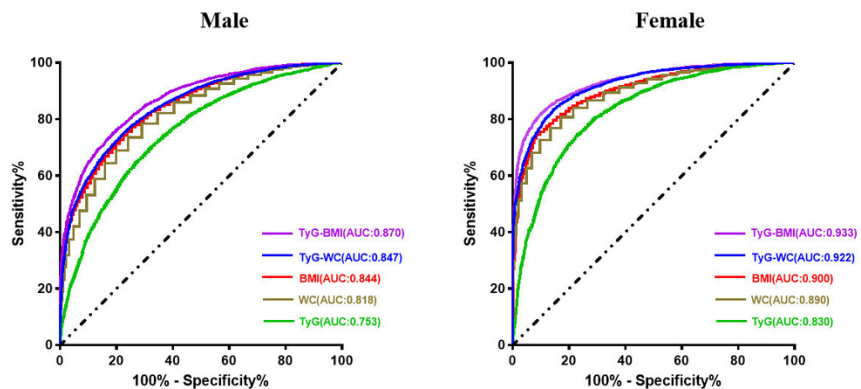


Figure 4 ROC curve of each parameter for predicting MAFLD according to sex

97x38mm (300 x 300 DPI)

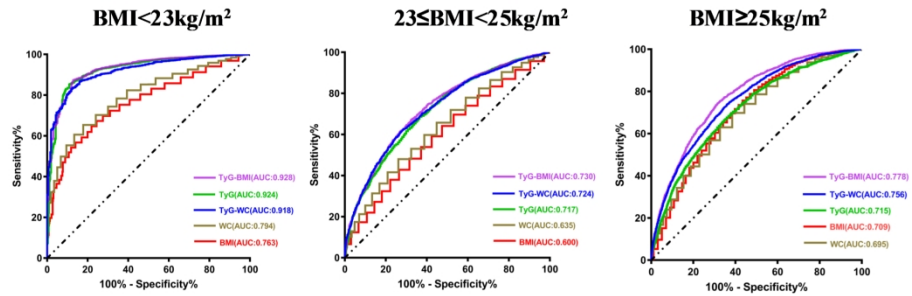


Figure 5 ROC curve of each parameter for predicting MAFLD in different BMI subgroups

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 TRIPOD reporting 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
<b>Title</b>		
	<a href="#">#1</a> Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
<b>Abstract</b>		
	<a href="#">#2</a> Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
<b>Introduction</b>		
	<a href="#">#3a</a> 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.

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7		<a href="#">#3b</a>	Specify the objectives, including whether the study describes the development or validation of the model or both. 4
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12	<b>Methods</b>		
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16	Source of data	<a href="#">#4a</a>	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
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22	Source of data	<a href="#">#4b</a>	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. 4
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26	Participants	<a href="#">#5a</a>	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. 4
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32	Participants	<a href="#">#5b</a>	Describe eligibility criteria for participants. 4-5
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36	Participants	<a href="#">#5c</a>	Give details of treatments received, if relevant NA. This study was not relevant to treatment.
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43	Outcome	<a href="#">#6a</a>	Clearly define the outcome that is predicted by the prediction model, including how and when assessed. 5
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48	Outcome	<a href="#">#6b</a>	Report any actions to blind assessment of the outcome to be predicted. NA. This study did not involve blind assessment.
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56	Predictors	<a href="#">#7a</a>	Clearly define all predictors used in developing or validating the multivariable prediction model, including how 5
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and when they were measured

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4	Predictors	<a href="#">#7b</a>	Report any actions to blind assessment of predictors for the outcome and other predictors.
5			NA. This study did not
6			involve blind
7			assessment.
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11	Sample size	<a href="#">#8</a>	Explain how the study size was arrived at.
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14	Missing data	<a href="#">#9</a>	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.
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20	Statistical	<a href="#">#10a</a>	If you are developing a prediction model describe how predictors were handled in the analyses.
21	analysis methods		6
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25	Statistical	<a href="#">#10b</a>	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.
26	analysis methods		6
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31	Statistical	<a href="#">#10c</a>	If you are validating a prediction model, describe how the predictions were calculated.
32	analysis methods		NA. This study did not
33			involve a
34			validating
35			model.
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40	Statistical	<a href="#">#10d</a>	Specify all measures used to assess model performance and, if relevant, to compare multiple models.
41	analysis methods		6
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45	Statistical	<a href="#">#10e</a>	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done
46	analysis methods		NA. This study did not
47			involve a
48			validating
49			model.
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54	Risk groups	<a href="#">#11</a>	Provide details on how risk groups were created, if done.
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57	Development vs.	<a href="#">#12</a>	For validation, identify any differences from the
58			NA. This
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1	validation	development data in setting, eligibility criteria, outcome,	study did not
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8	<b>Results</b>		
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11	Participants	<a href="#">#13a</a> Describe the flow of participants through the study,	6
12		including the number of participants with and without the	
13		outcome and, if applicable, a summary of the follow-up	
14		time. A diagram may be helpful.	
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18	Participants	<a href="#">#13b</a> Describe the characteristics of the participants (basic	6
19		demographics, clinical features, available predictors),	
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21		predictors and outcome.	
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26	Participants	<a href="#">#13c</a> For validation, show a comparison with the development	NA. This
27		data of the distribution of important variables	study did not
28		(demographics, predictors and outcome).	involve a
29			validating
30			model.
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35	Model	<a href="#">#14a</a> If developing a model, specify the number of participants	7-10
36	development	and outcome events in each analysis.	
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40	Model	<a href="#">#14b</a> If developing a model, report the unadjusted association, if	7-9
41	development	calculated between each candidate predictor and	
42		outcome.	
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46	Model	<a href="#">#15a</a> If developing a model, present the full prediction model to	7-10
47	specification	allow predictions for individuals (i.e., all regression	
48		coefficients, and model intercept or baseline survival at a	
49		given time point).	
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54	Model	<a href="#">#15b</a> If developing a prediction model, explain how to the use it.	8-9
55	specification		
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1	Model	<a href="#">#16</a>	Report performance measures (with CIs) for the prediction	8-9
2	performance		model.	
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5	Model-updating	<a href="#">#17</a>	If validating a model, report the results from any model	NA. This
6			updating, if done (i.e., model specification, model	study did not
7			performance).	involve a
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14	<b>Discussion</b>			
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17	Limitations	<a href="#">#18</a>	Discuss any limitations of the study (such as	12
18			nonrepresentative sample, few events per predictor,	
19			missing data).	
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23	Interpretation	<a href="#">#19a</a>	For validation, discuss the results with reference to	NA. This
24			performance in the development data, and any other	study did not
25			validation data	involve a
26				validating
27				model.
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33	Interpretation	<a href="#">#19b</a>	Give an overall interpretation of the results, considering	10
34			objectives, limitations, results from similar studies, and	
35			other relevant evidence.	
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39	Implications	<a href="#">#20</a>	Discuss the potential clinical use of the model and	12
40			implications for future research	
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44	<b>Other</b>			
45	<b>information</b>			
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48	Supplementary	<a href="#">#21</a>	Provide information about the availability of supplementary	13
49	information		resources, such as study protocol, Web calculator, and	
50			data sets.	
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55	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for	NA. This
56			the present study.	study did not
57				involve any
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fundings.

None The TRIPOD checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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