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

Zhi Liu

Sichuan University

He He

West China Hospital of Sichuan University

Yuzhao Dai

Sichuan University

Lidan Yang

West China Hospital of Sichuan University

Shenling Liao

Sichuan University

Zhenmei An (✉ azmhxnfm@163.com)

West China Hospital of Sichuan University

Shuangqing Li

West China Hospital of Sichuan University

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Abstract

Background: The triglyceride and glucose index (TyG) and triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) are substitute markers of insulin resistance (IR). In a retrospective cross-sectional study, the authors aimed to compare the efficacy of the two indicators in diagnosing metabolic-associated fatty liver disease (MAFLD) to construct a novel disease diagnosis model.

Methods: Overall, 229 patients (97 MAFLD and 132 Non-MAFLD at West China Hospital of Sichuan University) were included. MAFLD was diagnosed using ultrasonography. Biochemical indexes were collected and analyzed by logistic regression to screen out indicators that were expressed differently in MAFLD patients and healthy controls, which were incorporated into a diagnostic model.

Results: After adjusting for age, sex, and body mass index (BMI), serum alanine transaminase (ALT), aspartate transaminase (AST), AST/ALT (A/A), fasting plasma glucose (FPG), cystatin C, uric acid, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), non-HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, TG/HDL-C, TC/HDL-C, TyG, and TyG-BMI were risk factors for MAFLD. The odds ratio of TG/HDL-C and TyG were 5.387 (95%CI: 2.986-9.718) and 107.945 (95%CI: 25.824-451.222), respectively. In identifying MAFLD, TyG, TG/HDL-C, and TG were found to be the most vital indexes based on the random forest method, with the area under the curve (AUC) greater than 0.9. In addition, the combination of gender, BMI, ALT, TG, HDL-C, TyG, and TyG-BMI had a high diagnostic efficiency for MAFLD.

Conclusions: TyG and TG/HDL-C were potential risk factors for MAFLD, and the former performed better in diagnosing MAFLD. The combination of gender, BMI, ALT, TG, HDL-C, TyG, and TyG-BMI improved the diagnostic capability for MAFLD.

Background

Considering the current understanding of its pathogenesis and its rising prevalence, nonalcoholic fatty liver disease (NAFLD) is now regarded as metabolic-associated fatty liver disease (MAFLD) [1]. Affecting more than a quarter of adults worldwide, MAFLD is becoming one of the most common liver diseases [2]. The incidence of MAFLD continues to increase in developed countries such as the US and European countries like Germany, France, Italy, and the United Kingdom, causing a tremendous economic burden [3]. In China, a significant increase in the occurrence of MAFLD is expected, from 243.66 million in 2016 to 314.58 million in 2030 [4]. In China, several challenges associated with MAFLD are expected such as having a large number of cases, high genetic susceptibility, and occurrence in young patients, as well as, causing low body mass index (BMI) and absence of attention and recognition, along with the lack of adequate diagnostic methods and treatments [5].

Although the pathogenesis theory of MAFLD has changed from the two-stroke theory to the multi-stroke theory, insulin resistance (IR) still plays a significant role in the development of MAFLD [6]. Regarded as the gold standard method to measure IR, hyperinsulinemic-euglycemic clamp (HIEC) is complicated, time-

consuming, and expensive. Triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) and triglyceride and glucose index (TyG) have been shown to be useful biomarkers for identifying individuals with IR in a large group of Chinese individuals [7,8]. Early in 2005, TG/HDL-C was considered an important factor in predicting IR and was shown to increase the risk of cardiovascular diseases in patients [9]. As a result, TG/HDL-C is correlated with the occurrence of diabetes mellitus with related vascular diseases and fatty liver disease [10–12]. TyG, calculated using fasting plasma glucose (FPG) and triglycerides (TG), has a close connection with IR, which is related to glucolipid metabolism [13]. In detecting IR, TyG is cheaper and more convenient than the homeostasis model assessment of insulin resistance (HOMA-IR) index, which is commonly used as a substitute for the hyperinsulinemic-euglycemic glucose clamp technique [14]. TyG is also associated with cardiometabolic diseases and is a risk prognostic factor for stroke, diabetes mellitus, acute myocardial infarction, and acute coronary syndrome [15–17]. In addition, TyG may be a useful indicator of MAFLD not only in adults but also in children and the elderly [18–20]. Therefore, this study aimed to compare the ability of TG/HDL-C and TyG to distinguish MAFLD from healthy people and establish a better prediction model for MAFLD.

Methods

Overall, 229 participants were enrolled from West China Hospital between October 2018 and March 2021, including 97 patients with MAFLD (experimental group) and 132 individuals who underwent a physical examination (control group). MAFLD was diagnosed by experienced clinicians based on the abdominal ultrasound diagnosis of hepatic steatosis and evidence of any of the following three conditions: overweight/obesity, type 2 diabetes mellitus (T2DM), or metabolic disorders [21].

Fasting blood samples from the median cubital vein were used to quantify alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), FPG, TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (URIC), and cystatin C (Cys-C) using Roche's automatic biochemical analyzer and the corresponding kit (Roche, Mannheim, Germany). In this study, TyG was calculated using established formulas: $TyG = \ln [TG (mg/dl) \times FPG (mg/dl)/2]$ [14]. The formula used for converting mmol/L to mg/dL is as follows: for FPG, 1 mmol/L = 18 mg/dL; for TG, 1 mmol/L = 88.5 mg/dL.

Statistical analysis and graph drawing was done using SPSS 22.0 (IBM, Corp., N.Y., USA), R software 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism 9.0 (GraphPad Software, San Diego, California USA). Values are expressed as mean $\pm$ standard deviation (SD) or median (25-75 percentiles) for continuous variables and frequencies for categorical variables. Student's t-test and Mann-Whitney U test were used to compare two groups of normal or non-normal distributed continuous variables, respectively. Pearson's chi-square test was used for categorical variables. Logistic regression analysis was used to identify independent risk factors for MAFLD, and the OR value was expressed with a 95% confidence interval (CI). A receiver operating characteristic curve (ROC curve) was used for diagnostic value analysis, and the maximum value of the Youden index (sensitivity+specificity-1) was taken as the optimal cut-off value. Hosmer-Lemeshow test and calibration plot were used for calibration

capability analysis and decision curve analysis (DCA) for determining the net clinical benefits. Differences were considered statistically significant at $P < 0.05$.

Results

Baseline characteristics of the study participants

Overall, 229 patients were enrolled in this study. Table 1 lists the baseline characteristics of subjects with and without MAFLD. Individuals with MAFLD had higher levels of BMI, ALT, AST, FPG, UREA, CREA, Cys-C, URIC, TG, TC, ALP, GGT, LDH, HBDH, non-HDL-C, TyG, TyG-BMI, and lower A/A, TP, ALB, GLB, and HDL-C levels (all $P < 0.005$). As a result, the ratios of the above indicators, such as LDL-C/HDL-C, non-HDL-C/HDL-C, TG/HDL-C, and TC/HDL-C were greater in MAFLD patients than in the control group.

Table 1. The basic characteristics of the Non-MAFLD and MAFLD groups

Variable selection and model construction

Among these indexes, 29 variables showed significant differences between the MAFLD and non-MAFLD groups. The differences in 18 variables remained after adjusting for a variety of factors, including age, sex, and BMI (Table 2). A predictive model consisting of gender, BMI, ALT, TG, HDL-C, TyG, and TyG-BMI by binary logistic regression was then constructed. As shown in Figure 1, a dynamic nomogram was used to describe the probability of the MAFLD in the model. For example, a female patient with a BMI of 32.0 kg/m², ALT of 35 IU/L, TG of 2.0 mmol/L, HDL-C of 1.4 mmol/L, TyG of 9.00, and TyG-BMI of 288 had a likelihood of MAFLD of 0.944 based on the model.

Table 2. logistic regression analysis of risk factors for MAFLD patients after adjusting age, gender and BMI

Diagnostic performance of vital indexes and the predictive model in MAFLD

	Non-MAFLD (n=132)	MAFLD (n=97)	P value	Using the random forest method, patients were randomly divided into a training set and a test set at a ratio of 2:1. When all the variables in the model were adopted, a graph provided an overview of the importance score of each variable in predicting MAFLD. As shown in Figure 2, TyG, TG/HDL-C, and TG are the most important indicators for identifying MAFLD. ROC curve analyses were conducted to identify the diagnostic value of TG, TG/HDL-C, TyG, and the predictive model (Figure 3). As a result, the area under the receiver operating characteristic curve (AUROC) of the predictive model was 0.989 (95% CI 0.980-0.998) with 0.979
age	36.00 (32.00,46.00)	43.00 (33.00,51.00)	0.019	
Male/Female	80/52	75/22	0.008	
BMI	22.56 (20.90,24.91)	27.38 (25.25,29.24)	<0.001	
TBIL	11.85 (9.50,16.05)	12.10 (9.00,15.90)	0.918	
DBIL	3.40 (2.70,4.50)	3.40 (2.60,4.40)	0.597	
IBIL	8.10 (6.50,11.22)	8.80 (6.20,11.90)	0.606	
ALT	17.50 (14.00,25.00)	46.00 (28.00,76.00)	<0.001	
AST	19.00 (16.00,23.00)	31.00 (24.00,42.00)	<0.001	
A/A	1.06 (0.89,1.29)	0.67 (0.53,0.86)	<0.001	
TP	76.10(3.35)	74.74(4.48)	0.010	
ALB	48.91(2.40)	48.17(2.78)	0.033	
GLB	26.85 (25.48,29.20)	25.40 (23.60,29.00)	0.012	
A/G	1.81 (1.67,1.93)	1.90 (1.66,2.04)	0.111	
GLU	4.83 (4.63,5.18)	5.86 (4.92,7.33)	<0.001	
UREA	4.45 (3.80,5.20)	4.70 (4.20,5.50)	0.015	
CREA	70.00 (60.00,80.00)	77.00 (67.00,89.00)	0.001	
Cys-C	0.79 (0.73,0.86)	0.86 (0.81,0.93)	<0.001	
URIC	329.10(65.94)	393.14(102.24)	<0.001	
TG	1.06 (0.78,1.32)	2.47 (1.76,3.32)	<0.001	
TC	4.59(0.66)	4.87(1.02)	0.011	
HDL-C	1.50 (1.28,1.70)	1.00 (0.90,1.20)	<0.001	
LDL-C	2.77(0.61)	2.87(0.84)	0.284	
ALP	69.50 (58.75,83.00)	82.00 (68.00,99.00)	<0.001	
GGT	20.00 (13.00,28.00)	50.00 (34.00,74.00)	<0.001	
CK	96.50 (74.00,137.75)	109.00 (73.00,131.00)	0.586	
LDH	169.50 (155.75,188.00)	183.00 (171.00,208.00)	<0.001	
HBDH	131.00 (120.00,145.00)	138.00 (126.00,160.00)	0.003	
nonHDL-C	3.07(0.71)	3.84(1.00)	<0.001	

LDL-C/HDL-C	1.87 (1.52,2.37)	3.00 (2.46,3.27)	<0.001	sensitivity and 0.947 specificity when the cut-off value was 0.323, showing the best capacity for assessing MAFLD. TG, TG/HDL-C, and TyG could also detect MAFLD as shown in Table 3.
nonHDL-C/HDL-C	2.05 (1.63,2.63)	3.94 (3.03,4.45)	<0.001	
TG/HDL-C	0.70 (0.48,1.05)	2.43 (1.51,3.76)	<0.001	
TC/HDL-C	3.05 (2.63,3.63)	4.94 (4.03,5.45)	<0.001	
TyG	8.30 (7.99,8.54)	9.36 (9.01,9.66)	<0.001	
TyG-BMI	112.58 (87.85, 153.62)	201.52 (150.72, 261.22)	<0.001	
	OR	95% CI	PValue	

ALT	1.123	(1.078, 1.170)	.000
AST	1.210	(1.130, 1.296)	.000
A/A	.024	(0.006, 0.101)	.000
FPG	7.158	(3.342, 15.334)	.000
Cys-C	100.408	(3.698, 2726.533)	.006
URIC	1.009	(1.005, 1.014)	.000
TG	13.550	(5.747, 31.944)	.000
HDLC	.007	(0.001, 0.040)	.000
ALP	1.020	(1.004, 1.037)	.016
GGT	1.050	(1.029, 1.071)	.000
nonHDL-C	2.261	(1.464, 3.492)	.000
LDL-C/HDL-C	1.905	(1.251, 2.902)	.003
nonHDL-C/HDL-C	2.285	(1.628, 3.207)	.000
TG/HDL-C	5.387	(2.986, 9.718)	.000
TC/HDL-C	2.285	(1.628, 3.207)	.000
TyG	107.945	(25.824, 451.222)	.000
TyG-BMI	1.191	(1.130, 1.256)	.000

Table 3 Areas under the curve (AUC) of TG, TG/HDL-C, TyG and the predictive model for MAFLD

Variable	AUROC	95%CI	Cut-off value	Sensitivity (%)	Specificity (%)
TG	0.921	0.886 to 0.957	1.745	75.3	97.0
TG/HDL-C	0.925	0.892 to 0.959	1.260	83.5	90.9
TyG	0.943	0.913 to 0.973	8.804	87.6	93.9
Predictive model	0.989	0.980 to 0.998	0.323	97.9	94.7

As for calibration capability, the *P*-value of the Hosmer-Lemeshow test of the predictive model was 0.3869. The calibration plot and DCA curves of the model are shown in Figures 4 and 5, respectively.

Discussion

This retrospective cross-sectional study assessed the ability of TG, TG/HDL-C, and TyG to predict MAFLD and constructed a novel model for diagnosing MAFLD. TyG performed the best among the three indices. The sensitivity and specificity of the new diagnostic model based on sex, BMI, ALT, TG, HDL-C, TyG, and TyG-BMI improved to more than 90%. It was apparent from the Hosmer-Lemeshow test and the pictures of the calibration plot and DCA curve that the model fits well and could improve the net benefit.

MAFLD is not only the leading cause of chronic liver disease but also an increasing cause of hepatocellular carcinoma (HCC). With MAFLD-HCC, patients were older and had shorter survival times and more advanced tumors [22]. Therefore, the identification of MAFLD is of vital importance. Liver biopsy is still the gold standard for MAFLD diagnosis, although it has a variety of associated risks, such as bleeding, pain, and death [23,24]. In addition, sampling errors and sampling biases exist [25]. Noninvasive biomarkers that are cheap and effective for diagnosing MAFLD have been studied.

In MAFLD, TG accumulates in the liver and blood. Interestingly, TG/HDL-C and TyG, which are surrogate IR markers, are both derived from triglycerides. Independent of age, BMI, and waist circumference, it was observed that the expression of TG/HDL-C was higher in fatty liver patients with normal or even higher levels of ALT [26]. Subsequently, several studies found that TG/HDL-C can be considered as a risk factor and even a predictor of MAFLD with a lower cut-off value and a greater AUROC in women than in men [27,28]. In addition, in a randomized controlled study, a decrease in TG and TG/HDL-C was associated with the resolution of non-alcoholic steatohepatitis (NASH) [29]. In another study, TC/HDL-C, a lipid ratio parameter, was used to diagnose MAFLD with an AUROC of 0.645 [30]. Both higher levels of TC/HDL-C and TG/HDL-C indicated more severe liver steatosis, while the former showed higher specificity [31]. However, in this study, TG/HDL-C exhibited higher diagnostic efficiency (AUC =92.541, 95%CI:81.454-91.211) than TC/HDL-C (AUC =86.332, 95%CI:81.454-91.211). It was previously shown that TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C were positively related to the severity of hepatic steatosis [32]. From the results of this research, all of them were risk factors for MAFLD independent of age, sex, and BMI.

Previous studies have shown that the incidence of MAFLD also significantly increases with the increase in TyG [33,34]. In other studies, the AUCs of the TyG index to detect adult MAFLD were 0.714-0.782, with MAFLD diagnosed by ultrasound[19,35–39]. A study showed that the AUC of TyG was larger than that of ALT, with the AUC of TyG at 0.9 (95%CI 0.84-0.94) in biopsy-proven MAFLD with 80% sensitivity and 92% specificity when the cut-off value was 8.38 [40]. Similarly, the AUC of TyG in diagnosing MAFLD in this study was 0.943 (95%CI 0.913-0.973) with 87.6% sensitivity and 93.9% specificity when the cut-off value was 8.804. Furthermore, among 50 asymptomatic women who underwent a liver biopsy, TyG displayed high sensitivity in screening simple steatosis and NASH [41]. Based on a large number of MAFLD participants (n=11424) in a follow-up study, it was found that patients with a high TyG index were more likely to have MAFLD progression [42]. TyG-BMI, a modified TyG index, showed a better ability to identify MAFLD than TyG itself, not only in males but also in females. The AUROC of TyG-BMI in diagnosing MAFLD ranged from 0.774-0.9084 [43–45]. In this study it was discovered that the AUROC of TyG-BMI was 0.949 (95% CI 0.922-0.976), which was higher than that reported in other studies. As for non-obese subjects, TyG-BMI could identify MAFLD and predict its occurrence effectively [46,47]. In addition to liver steatosis, TyG and its related marker TyG-BMI were found to be related to liver fibrosis [39,48].

Strength and limitations

Previous studies demonstrated that TyG and TG/HDL-C were increased in MAFLD patients and could be used as diagnostic markers. The current study compared these two IR-related indicators and found that both had good diagnostic efficacy for MAFLD. Based on this, a better diagnostic model was established. This study has several limitations. First, a gold standard for the diagnosis of MAFLD by liver biopsy is lacking. Ultrasound detection of steatosis less than 20% has limited sensitivity. It also performs poorly when differentiating between steatosis and fibrosis and is inconsistent. Furthermore, the detection capability is highly dependent on the examiner [49]. Second, the relationships between TG/HDL-C, TyG and HOMA-IR aren't verified in this research. Finally, to measure the diagnostic significance of the indicators for MAFLD more accurately, the suspected population of MAFLD should be included; otherwise, the value of these indicators will be exaggerated.

Conclusion

This study compared the ability of two surrogate indices for IR, TG/HDL-C, and TyG, in predicting MAFLD for the first time. TyG and TG/HDL-C can be easily measured with high accuracy and is low cost because TG, FPG, and HDL-C can be conveniently measured. When the cut-off point value was 8.804, the sensitivity and specificity of TyG in the diagnosis of MAFLD were higher than TG/HDL-C. In addition, the combination of gender, BMI, ALT, TG, HDL-C, TyG, and TyG-BMI could improve the diagnosis of MAFLD. This study suggested that overweight women with abnormal glycolipid metabolism and liver function were more likely to develop MAFLD, which is conducive to promoting the screening and management of MAFLD.

Abbreviations

TyG: triglyceride and glucose index

TG/HDL-C: triglyceride-to-high density lipoprotein cholesterol ratio

IR: insulin resistance

MAFLD: Metabolic-Associated Fatty Liver Disease

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

A/A: AST/ALT

GGT: gamma-glutamyl transferase

ALP: alkaline phosphatase

FPG: Fasting plasma glucose

TC: Total cholesterol

TG: Triglyceride

HDL-C: high-density lipoprotein cholesterol

LDL-C: low-density lipoprotein cholesterol

URIC: uric acid

Cys-C: cystatin C

NAFLD: Nonalcoholic Fatty Liver Disease

NASH: Nonalcoholic steatohepatitis

T2DM: type 2 diabetes mellitus

AUROC: area under receivers operating characteristic curve

BMI: body mass index

HOMA-IR: Homeostatic model assessment of insulin resistance

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China Hospital (Approval No.977 in 2019).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

DYZ and YLD collected the data of MAFLD patients. LSL collected the data of healthy controls. LZ and HH analyzed and interpreted these data and were contributed equally in writing the manuscript. AZM and LSQ designed the study and corrected the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

dynamic nomogram of the diagnostic model

Figure 2

importance score of different variable

Figure 3

ROC curves of TG, TG/HDL-C, TyG and the predictive model for MAFLD.

Figure 4

Calibration plot of the model

Figure 5

DCA curves of the model