

Non-Traditional Blood Lipid Indices for Metabolism Dysfunction-Associated Fatty Liver Disease Prediction in Non-Obese Type 2 Diabetes Mellitus

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Objective: This study aims to investigate the predictive value of non-traditional blood lipid indices for metabolism dysfunction-associated fatty liver disease (MAFLD) in non-overweight/obese patients with type 2 diabetes mellitus (T2DM).

Methods: A retrospective observational study was conducted, including non-overweight/obese patients with T2DM who visited the Fourth Hospital of Hebei Medical University between August 2018 and August 2022. The low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio, the triacylglycerol-glucose index (TyG) multiplied by body mass index (BMI), and TyG/HDL-C ratio were calculated.

Results: The study involved 190 participants, of whom 34 were diagnosed with MAFLD (24 males and 10 females), while 156 did not have MAFLD (64 males and 92 females). Multivariable analysis revealed that aspartate transaminase (AST) (OR=1.216, 95% CI: 1.059–1.374, P=0.006), blood uric acid (BUA) (OR=1.017, 95% CI: 1.002–1.032, P=0.022), TyG*BMI (OR=1.231, 95% CI: 1.051–1.442, P=0.010), and TyG/HDL-C (OR=3.162, 95% CI: 1.228–8.141, P=0.017) were independently associated with MAFLD. The TyG*BMI index exhibited an area under the ROC curve (AUC) of 0.812, with 91.2% sensitivity and 69.2% specificity for MAFLD. The TyG/HDL-C index had an AUC of 0.929, with 85.3% sensitivity and 88.5% specificity for MAFLD.

Conclusion: The results indicate that TyG*BMI and TyG/HDL-C are independently associated with MAFLD in non-overweight/obese patients with T2DM.

Keywords: metabolism dysfunction-associated fatty liver disease, body mass index, type 2 diabetes mellitus, cholesterol, LDL-C, HDL-C, obesity, TyG

Introduction

Metabolism dysfunction-associated fatty liver disease (MAFLD), previously known as nonalcoholic fatty liver disease (NAFLD), is a progressive liver disorder that is closely linked to metabolic disorders, insulin resistance, lipotoxicity, inflammatory cell infiltration, activation of hepatic stellate cells (HSCs), fibrogenesis, and hepatic fat accumulation.^{1–3} MAFLD encompasses various pathological processes, including simple steatosis, nonalcoholic steatohepatitis (NASH), and fibrosis, with NASH posing a risk factor for the development of hepatocellular carcinoma (HCC). Recent studies have established a strong mechanistic connection between the NASH microenvironment and HCC development, indicating that immune response alterations are closely associated with the progression of NASH and subsequent HCC development.^{4,5}

MAFLD is strongly associated with obesity, type 2 diabetes mellitus (T2DM), and other metabolic disorders, leading to a wide range of complications.^{2,3} The adoption of the name “MAFLD” instead of “NAFLD” highlights the importance of recognizing the metabolic nature of the disease and emphasizes the potential for therapeutic interventions targeting metabolic pathways to enhance disease awareness and clinical management. However, this change in nomenclature has not affected the disease's prevalence.^{6,7} Globally, the prevalence of MAFLD is increasing, affecting approximately 24%

to 45% of the global population.³ Furthermore, MAFLD is projected to become the leading cause of liver failure, liver cancer, and liver transplantation.^{8,9} By categorizing NAFLD as MAFLD, healthcare professionals can better identify the warning signs that increase the risks of morbidity and mortality, particularly when attempting to diagnose metabolic issues at an early stage.^{10,11}

Currently, the clinical detection of fatty liver mainly relies on abdominal ultrasound, which has limitations due to factors such as instrument sensitivity and imaging technology. Liver biopsy is the most accurate diagnostic technique for MAFLD, but it is invasive and challenging to perform.¹² Therefore, there is a significant need for non-invasive diagnostic markers that are simple, cost-effective, and highly accurate.

Several studies have revealed strong associations between NAFLD and non-traditional blood lipid parameters, including low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C),¹³ the triacylglycerol-glucose index (TyG),¹⁴ blood uric acid (BUA),¹⁵ TyG multiplied by body mass index (BMI),^{16–18} and TyG/HDL-C.¹⁹ These markers have shown potential for predicting NAFLD. Notably, the TyG index has been used as an indicator to assess NAFLD in various research studies, such as the association of insulin resistance, type 2 diabetes mellitus, and NAFLD with bladder cancer.²⁰ However, the extent to which these parameters can accurately predict MAFLD, considering the diverse metabolic considerations involved, remains an open question.¹³

Patients with NAFLD often have comorbid obesity and type 2 diabetes mellitus,^{2,3} and previous studies have predominantly focused on obese populations.^{13–16,19} Limited research has targeted non-obese populations, despite the occurrence of NAFLD in this group.²¹ Although non-obese NAFLD may be less severe, the metabolic profile of these patients poses a significantly higher risk of developing type 2 diabetes mellitus and metabolic syndrome compared to non-obese individuals without NAFLD.²² Therefore, further attention to this area is warranted to enhance our understanding of the disease and develop more effective treatments and preventive measures.²³

The aim of this study was to investigate the predictive value of non-traditional lipid indices for MAFLD in non-overweight/obese patients with type 2 diabetes mellitus. The findings will contribute to the development of clinical diagnosis and treatment strategies for this patient population.

Methods

Study Design and Patients

This retrospective observational study included patients with type 2 diabetes mellitus (T2DM) who visited the Department of Endocrinology at the Fourth Hospital of Hebei Medical University between August 2018 and August 2022. The inclusion criteria were as follows: 1) Age ≥ 18 years, 2) BMI of 18.5–23.9 kg/m²,^{17,18} 3) Diagnosed with T2DM according to the 1999 WHO criteria,²⁴ and 4) Ultrasound examination indicating fatty liver.⁶ The exclusion criteria consisted of the following: 1) Patients with acute coronary syndrome, acute cerebral infarction, cerebral hemorrhage, cancer, serious infections, or severe liver or kidney dysfunction, 2) A history of liver operation, or 3) Mental health issues that limited their ability to comply with the study requirements.²⁵

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethical Committee of The Fourth Hospital of Hebei Medical University (2022KY384). Due to the retrospective nature of the study, the requirement for informed consent was waived.

Data Collection and Definitions

The researchers collected patient data, including sex, age, height, weight, BMI, duration of T2DM, history of alcohol consumption, history of hypertension, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), alanine aminotransferase (ALT), albumin (ALB), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), and blood uric acid (BUA). The LDL-C/HDL-C ratio,¹³ TyG*BMI (TyG multiplied by BMI),¹⁶ and TyG/HDL-C ratio¹⁹ were collected and calculated. The TyG index was calculated as $\ln(\text{fasting triglyceride [mg/dl]} \times \text{fasting glucose [mg/dl]}/2)$.¹⁴

The diagnostic criteria for MAFLD were based on liver biopsy, imaging, and blood biomarkers, combined with one of the following conditions: overweight/obesity, T2DM, and metabolic dysfunction. The criteria included: 1) waist

circumference: Asian men ≥ 90 cm and women > 80 cm, 2) blood pressure: $\geq 130/85$ mmHg or receiving blood pressure-lowering medications, 3) blood triglycerides: ≥ 1.70 mmol/L or receiving lipid-lowering drugs, 4) plasma HDL-C: men < 1.0 mmol/L, women < 1.3 mmol/L, or receiving lipid-regulating drugs, 5) prediabetes: FBG 5.6–6.9 mmol/L or 2-hour postprandial blood glucose 7.8–11.0 mmol/L or HbA1c 5.7%–6.4%, 6) evaluation of islet resistance index by the steady-state model: ≥ 2.5 , and 7) blood hypersensitive C-reactive protein (hsCRP): > 2 mg/L.^{6,26} In non-overweight/obese populations, patients with fatty liver disease (normal BMI) but with two or more risk factors for metabolic abnormalities should also be considered as diagnostic criteria for MAFLD.^{6,23}

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 23.0 (IBM, Armonk, NY, USA). The continuous variables in this study were found to have a non-normal distribution and were presented as medians and quartiles. The Mann–Whitney *U*-test was used for analysis. Categorical variables were presented as counts and percentages and analyzed using the chi-square test. Multivariable logistic regression analysis was performed to examine the association between MAFLD and LDL-C/HDL-C, TyG*BMI, and TyG/HDL-C. The associations were adjusted for sex, drinking history, duration of diabetes, TG, ALP, AST, and BUA. Variables with a P-value < 0.05 in the univariable analyses were entered into the multivariable logistic regression analysis. Receiver operating characteristics (ROC) curve analysis was used to assess and compare the parameters. Statistical significance was defined as a two-tailed P-value < 0.05 .

Results

This study included a total of 190 participants, with 34 diagnosed with MAFLD (24 males and 10 females, Figure 1). Compared to the non-MAFLD group, the MAFLD group had a higher proportion of males (70.6% vs 41.0%, $P=0.002$), a higher prevalence of patients with a history of drinking (23.5% vs 10.9%, $P=0.048$), a longer duration of diabetes (> 10 years: 52.9% vs 20.5%, $P=0.001$), a higher BMI (23.66 vs 21.63 kg/m², $P<0.001$), higher levels of LDL-C (3.81 vs 2.79 mmol/L, $P=0.034$), lower levels of HDL-C (0.72 vs 1.01 mmol/L, $P=0.001$), higher AST levels (28.1 vs 21.4 U/L), higher levels of alkaline phosphatase (ALP) (141.0 vs 73.7 U/L, $P<0.001$), higher levels of BUA (378.0 vs 288.8 $\mu\text{mol/L}$,

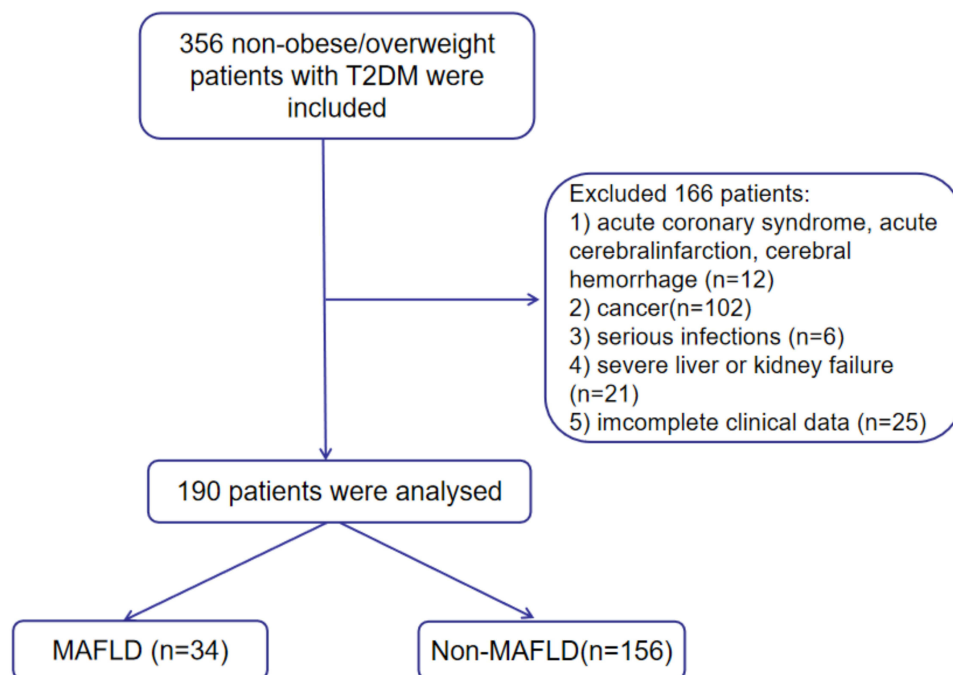


Figure 1 Flowchart of Patients.

$P < 0.001$), higher TyG values (9.36 vs 8.99, $P < 0.001$), higher TyG*BMI values (212.55 vs 203.00, $P = 0.002$), higher TyG/HDL-C values (12.61 vs 9.31, $P < 0.001$), and higher LDL-C/HDL-C values (3.96 vs 2.94, $P < 0.001$) (Table 1).

After adjusting for sex, drinking history, duration of diabetes, TG, ALP, AST, and BUA, the multivariable logistic analysis revealed that TyG*BMI (OR=1.231, 95% CI: 1.051–1.442, $P = 0.010$) and TyG/HDL-C (OR=3.162, 95% CI: 1.228–8.141, $P = 0.017$) were independently associated with MAFLD (Table 2).

TyG*BMI demonstrated an area under the ROC curve (AUC) of 0.812, with a sensitivity of 91.2% and specificity of 69.2% for MAFLD. The Youden index for TyG*BMI was 0.604, indicating a cutoff value of 210.9743. For TyG/HDL-C, the AUC was 0.929, with a sensitivity of 85.3% and specificity of 88.5% for MAFLD. The Youden index for TyG/HDL-C was 0.738, corresponding to a cutoff of 10.6706. The Youden index is calculated as sensitivity plus specificity minus one (Table 3 and Figure 2).

The subgroup analysis by sex using multivariate logistic regression demonstrated that TyG/HDL-C (OR=6.129, 95% CI: 1.011–7.135, $P = 0.049$) was independently associated with MAFLD in female patients (Table 4). The AUC of TyG/

Table 1 Clinical Characteristics of the Patients

Variables	MAFLD (n=34)	Non-MAFLD (n=156)	P
Sex			0.002*
Male	24 (70.6%)	64 (41%)	
Female	10 (29.4%)	92 (59%)	
Age (years)	50 (46,60)	57 (46,64)	0.150
Drinking history	8 (23.5%)	17 (10.9%)	0.048*
Hypertension	1 (2.9%)	4 (2.6%)	0.451
Duration of diabetes			0.001*
<5 years	12 (35.3%)	90 (57.7%)	
5–10 years	4 (11.8%)	34 (21.8%)	
≥10 years	18 (52.9%)	32 (20.5%)	
BMI (kg/m ²)	23.66 (22.28,23.78)	21.63 (21.22,23.44)	<0.001*
SBP (mmHg)	144 (128,149)	145 (127,150)	0.729
DBP (mmHg)	87 (81,90)	86 (80,90)	0.169
TC (mmol/L)	4.19 (3.75,5.59)	4.19 (3.37,5.78)	0.365
LDL-C (mmol/L)	3.81 (2.36,3.95)	2.79 (2.11,3.81)	0.034*
HDL-C (mmol/L)	0.72 (0.56,0.91)	1.01 (0.90,1.26)	<0.001*
TG (mmol/L)	1.63 (1.34,1.899)	1.34 (1.01,1.71)	0.001*
ALT (U/L)	40.7 (23.4,43.4)	35.6 (22.6,43.4)	0.180
AST (U/L)	28.1 (18.3,36.4)	21.4 (15.5,34.1)	0.031*
HCY (μmol/L)	15.7 (10.9,16.7)	14.7 (12.1,16.7)	0.547
ALB (g/L)	43.0 (38.0,46.3)	38.0 (37.3,43.9)	0.583
FBG (mmol/L)	8.04 (7.71,9.62)	8.31 (5.71,9.97)	0.615
HbA1c (%)	8.5 (6.2,10.8)	7.7 (6.4,10.6)	0.679
Cr (μmol/L)	62.0 (48.0,63.0)	56.1 (38.0,65.2)	0.247
ALP (U/L)	141.0 (82.4,158.0)	73.7 (56.0,98.6)	<0.001*
Lip-α (mg/L)	113.1 (78.8,377.5)	125.5 (75.5,366.4)	0.912
BUA (μmol/L)	378.0 (349.9,404.6)	288.8 (238.2,369.0)	<0.001*
TyG	9.36 (9.08,9.52)	8.99 (8.52,9.38)	<0.001*
TyG*BMI	212.551 (202.356,225.156)	203.00 (180.248,211.570)	0.002*
TyG/HDL-C	12.614 (10.193,16.7141)	9.311 (7.135,10.6495)	<0.001*
LDL-C/HDL-C	3.959 (3.405,5.676)	2.936 (2.344,3.619)	<0.001*

Notes: Data are shown as n (%) or median (range). * $P < 0.05$ was considered statistically significant.

Abbreviations: MAFLD, metabolism dysfunction-associated fatty liver disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBG, fasting plasma glucose; HbA1c, glycated hemoglobin; TG, total triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; HCY, homocysteine; Cr, creatinine; ALP, alkaline phosphatase; Lip-α, lipoprotein-α; BUA, blood uric acid; ALB, albumin; TyG, triacylglycerol-glucose index.

Table 2 The Multivariable Logistic Regression of MAFLD

Variables	OR	95% CI	P
Sex	0.374	0.020–6.893	0.508
Drinking history	0.744	0.054–10.253	0.825
Duration of diabetes	0.552	0.113–2.283	0.412
TG	0.280	0.057–1.374	0.117
ALP	0.994	0.996–1.004	0.932
AST	1.216	1.059–1.374	0.006*
BUA	1.017	1.002–1.032	0.022*
TyG*BMI	1.231	1.051–1.442	0.010*
TyG/HDL-C	3.162	1.228–8.141	0.017*
LDL-C/HDL-C	1.445	0.421–4.954	0.558

Note: *P<0.05 was considered statistically significant.

Abbreviations: MAFLD, metabolism dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval; TG, total triglyceride; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUA, blood uric acid; TyG, triacylglycerol-glucose index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3 Predictive Values of the TyG*BMI and TyG/HDL-C

Parameters	Area Under the ROC Curve	95% CI		P	Cutoff value	Sensitivity (%)	Specificity (%)
TyG*BMI	0.812	0.744	0.880	<0.001*	210.943	91.2	69.2
TyG/HDL-C	0.929	0.884	0.973	<0.001*	10.607	85.3	88.5

Note: *P<0.05 was considered statistically significant.

Abbreviations: ROC, received operating characteristics; CI, confidence interval; TyG, triacylglycerol-glucose index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

HDL-C for MAFLD in females was 0.892, with a sensitivity of 87.5% and specificity of 78.5%. The Youden index for TyG/HDL-C in females was 0.66, indicating a cutoff value of 10.1509 (Table 5 and Figure 3).

Discussion

The findings of this study suggest that TyG*BMI and TyG/HDL-C are independently associated with MAFLD in non-overweight/obese patients with T2DM. These parameters exhibit high area under the curve (AUC) values for the diagnosis of MAFLD, indicating their potential as markers for early identification of the disease in this population.

MAFLD is characterized by elevated blood lipid levels, insulin resistance, and increased fasting and postprandial glucose levels.²⁷ Although the prevalence of MAFLD is high, there are currently no specific drugs available for its treatment. Early diagnosis of this common disease is beneficial, considering the promising pipeline of drugs being investigated for the treatment of NAFLD, as demonstrated in recent studies. For instance, studies have shown the potential of SGLT-2 inhibitors in improving NAFLD through autophagy.^{28–31}

The TyG index is widely recognized as a reliable measure of insulin resistance and has been established as an important tool for predicting insulin resistance in various patient groups.^{32,33} Moreover, it serves as an effective and cost-efficient diagnostic method for NAFLD.^{14,16} Body mass index (BMI) is commonly used to assess obesity levels and is associated with the likelihood of developing metabolic conditions, including insulin resistance, NAFLD, and other related diseases.³⁴ Previous studies have demonstrated that TyG*BMI, which combines these two indices, is a more accurate indicator of insulin resistance in NAFLD and possesses a high diagnostic value.^{14,16,35}

Furthermore, research has revealed that the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) is independently associated with insulin resistance, obesity, and metabolic syndrome. It can also be utilized as a predictive marker for NAFLD.^{16,19} LDL-C is commonly considered an unfavorable type of cholesterol, while

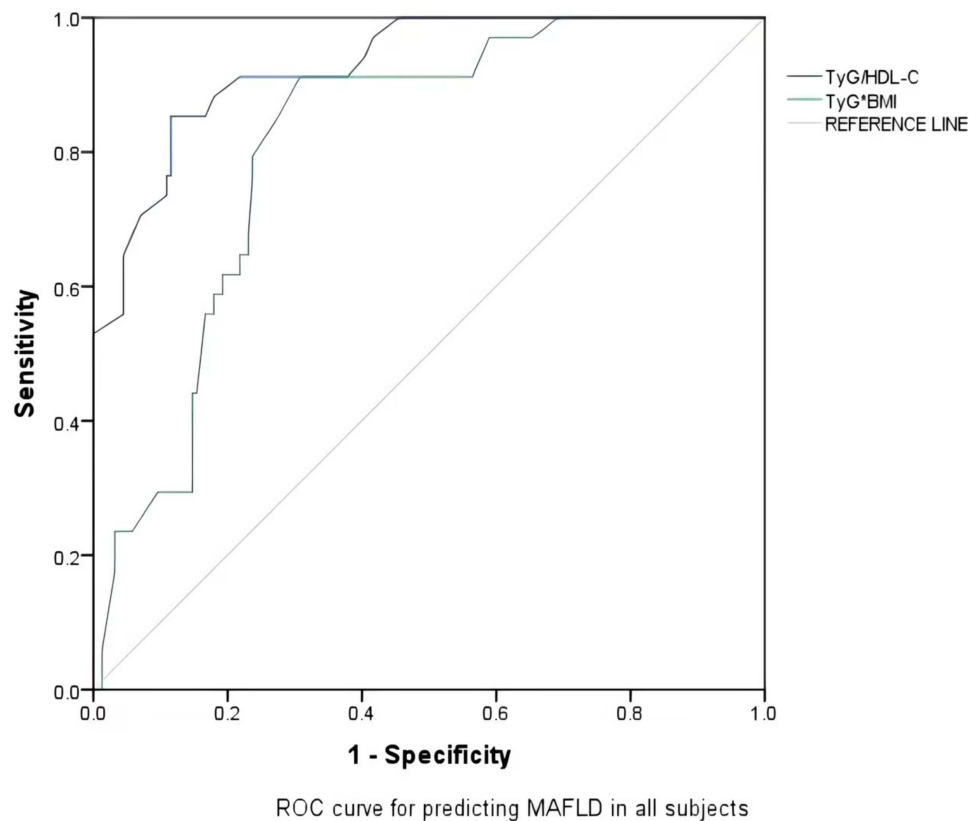


Figure 2 Receiver-Operating Characteristics (ROC) Curve of Each Parameter for Predicting Metabolic Dysfunction-Associated Fatty Liver Disease.

HDL-C is regarded as a beneficial form of cholesterol. A study conducted on Chinese individuals who were neither overweight nor had abnormal cholesterol levels found that LDL-C/HDL-C was a robust indicator of NAFLD, surpassing other blood lipid measurements in terms of accuracy.¹³ Building upon these findings, the present study further evaluated the aforementioned parameters and compared their diagnostic value and accuracy for MAFLD. The results demonstrated that both TyG*BMI and TyG/HDL-C were capable of identifying MAFLD in this study.

Table 4 The Multivariable Logistic Regression of MAFLD in Female Patients

Variables	OR	95% CI	P
Drinking history	0.000	0.000–1.000	0.999
Duration of diabetes	0.331	0.040–2.772	0.308
TG	0.170	0.003–9.076	0.382
ALP	0.998	0.985–1.011	0.728
AST	1.401	0.965–2.035	0.077
BUA	1.029	1.006–1.052	0.015*
TyG*BMI	1.499	0.979–2.146	0.064
TyG/HDL-C	6.129	1.011–7.135	0.049*
LDL-C/HDL-C	0.74	0.155–3.525	0.706

Note: *P<0.05 was considered statistically significant.

Abbreviations: MAFLD, metabolism dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval; TG, total triglyceride; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUA, blood uric acid; TyG, triacylglycerol-glucose index; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 5 Predictive Values of the TyG/HDL-C

Parameters	Area Under the ROC Curve	95% CI		P	Cutoff value	Sensitivity (%)	Specificity (%)
TyG/HDL-C	0.892	0.784	1.000	<0.000*	10.151	87.5	78.5

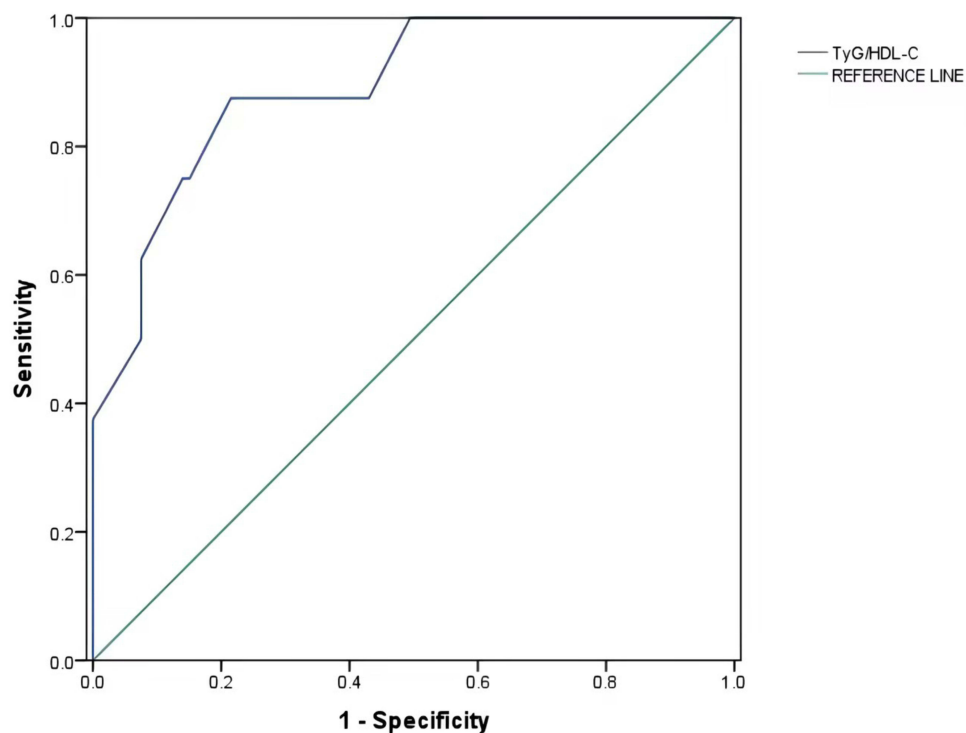
Note: *P<0.05 was considered statistically significant.

Abbreviations: TyG, triacylglycerol-glucose index; HDL-C, high-density lipoprotein cholesterol.

Among them, TyG/HDL-C exhibited the highest area under the receiver operating characteristic curve (AUC) with a value of 0.929 (95% CI 0.887–0.973) and a cutoff point of 10.607. This parameter demonstrated 85.3% sensitivity and 88.5% specificity. Subgroup analysis data revealed that TyG/HDL-C was able to identify MAFLD in female participants, yielding an AUC of 0.892 (95% CI 0.784–1.000). However, in male patients, the correlation analysis did not indicate an independent predictive value for these indicators.

The indices evaluated in this study rely on routine biochemistry parameters that do not require rare, difficult-to-obtain, or expensive tests. Their calculation is straightforward and simple, allowing for easy utilization in clinical settings to predict the presence of MAFLD. There is a certain risk of underdiagnosing MAFLD, as the previous nomenclature and diagnosis of NAFLD were based on exclusion criteria, leading to delays in diagnosis and underdiagnosis.^{36,37} Consequently, the concept of MAFLD was proposed, facilitating a more streamlined diagnosis by incorporating factors known to contribute to fatty liver.^{38,39} A better understanding of MAFLD and earlier diagnosis should contribute to a more favorable prognosis.⁴⁰

This study has several limitations. It was conducted at a single center over a limited period, resulting in a relatively small sample size. Furthermore, due to its retrospective nature, establishing causality between MAFLD and the various indicators tested was not possible. Additionally, this study focused on Chinese adults with T2DM, and the diagnostic



ROC curve for predicting MAFLD in females

Figure 3 Gender Subgroup Analysis: ROC Curves for Parameters Predictive of Metabolic Dysfunction-Associated Fatty Liver Disease in Female Patients.

criteria for MAFLD based on BMI and waist circumference may vary among different nations, thus limiting the generalizability of the findings.

Conclusion

The results suggest that TyG*BMI and TyG/HDL-C were independently associated with MAFLD in non-overweight/obese patients with T2DM. TyG*BMI and TyG/HDL-C showed high AUCs for the diagnosis of MAFLD. These indices might be practical markers for the early identification of MAFLD.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Statement

The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and received approval from the Ethical Committee of The Fourth Hospital of Hebei Medical University (2022KY384). The subjects' personal information is strictly confidential. Testing blood and recording all other variables included in our analysis are routine, essential for diagnosis and treatment, and are not additional for research purposes, and the data is anonymous. Based on the standardization of program design and execution, we have reason to believe that there will be no adverse impact on the study object. For these reasons, informed written consent was not obtained from each subject.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research is supported by the Department of Science and Technology of Hebei Province of China (No.20221266).

Disclosure

The authors declare that they have no competing interests in this work.

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