Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Analysis of the Association Between TG/HDL, TyG, TyG-BMI, and ZJU Indices with Metabolic Dysfunction-Associated Fatty Liver Disease in Patients with Type 2 Diabetes

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Background: TG/HDL, TyG, TyG-BMI, and ZJU indices are associated with metabolic syndrome and cardiovascular diseases. This study aims to evaluate the relationships between these indices and metabolic dysfunction-associated fatty liver disease (MAFLD) in patients with type 2 diabetes (T2DM).

Methods: We analyzed 598 T2DM patients, with MAFLD diagnosed based on abdominal ultrasound and clinical manifestations. Clinical characteristics and laboratory results were collected. Correlation analysis assessed the relationship between insulin resistance (IR) indicators and MAFLD. Logistic regression and restrictive cubic spline (RCS) analyses were performed to evaluate associations, and ROC curve analysis identified the most effective IR indicator for MAFLD.

Results: Among the IR indices, the strongest association with MAFLD was observed for TyG-BMI ($p < 0.001$). Logistic regression analysis indicated a significant relationship between TyG-BMI and the diagnosis of MAFLD ($P = 0.006$). RCS curve analysis showed distinct trends: TG/HDL-C (J-shaped), TyG (inverted U-shaped), and TyG-BMI (linear), with TyG-BMI showing the most robust relationship. ROC curve analysis identified TyG-BMI as the most effective diagnostic indicator. Subgroup analysis revealed that TG/HDL, TyG, and the ZJU index had stronger effects in females, with TG/HDL being the most effective.

Conclusion: TyG-BMI is a significant determinant for the diagnosis of MAFLD in T2DM patients, while TG/HDL is more effective for screening in female patients.

Keywords: TG/HDL, TyG, TyG-BMI, ZJU, T2DM, MAFLD

Introduction

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) is a chronic liver disorder characterized by the buildup of fat within the liver (hepatic steatosis). It is diagnosed when hepatic steatosis is observed, associated with at least one of the following conditions: overweight or obesity, and Type 2 diabetes mellitus (T2DM), or indicators of metabolic dysfunction.[1,2] In 2020, the term "MAFLD" was introduced to replace the previous designation of "Non-Alcoholic Fatty Liver Disease (NAFLD)", offering a more precise reflection of its strong connection to metabolic disorders.[3] In contrast to NAFLD, the updated definition of MAFLD highlights the pivotal role of various metabolic abnormalities—such as overweight, insulin resistance, dyslipidemia, T2DM, and metabolic inflammation—in the progression of fatty liver. It also emphasizes the significance of addressing these metabolic cardiovascular risk factors to prevent liver disease and its associated complications. Recently, Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has become the most widely accepted term for fatty liver diseases linked to metabolic dysfunction.[4] MASLD expands disease recognition to include individuals with both

Received: 2 July 2025
Accepted: 12 September 2025
Published: 9 October 2025

metabolic dysfunction and hepatic steatosis, refining the clinical approach to liver disease in the context of metabolic disorders. This definition closely aligns with MAFLD but emphasizes metabolic underpinnings, offering a broader framework for understanding liver disease associated with metabolic syndrome. MAFLD has emerged as the most prevalent chronic liver condition worldwide, impacting over 30% of the global population.[5] As the disease progresses to later stages, it can go beyond simple steatosis, leading to hepatic inflammation (non-alcoholic steatohepatitis, NASH), fibrosis, cirrhosis, and potentially leading to hepatocellular carcinoma.[6] As one of the liver diseases with the most rapidly increasing incidence and mortality rates, MAFLD poses a substantial long-term medical burden, lowers quality of life, and exerts considerable clinical pressure. As a result, its effective management has become a critical public health challenge worldwide.[7]

T2DM is a metabolic disorder marked by insulin resistance (IR) and a gradual deterioration in pancreatic β-cell function, leading to chronic hyperglycemia.[8] The global prevalence of diabetes continues to increase, and it is estimated that by 2030, the number of individuals affected will approach 366 million, with over 90% of these cases being T2DM.[9] Epidemiological studies show that China has become the country with the largest number of T2DM patients, with a prevalence rate of 11.2%.[10] T2DM and MAFLD are closely related, sharing key pathogenic mechanisms, including IR, increased oxidative stress, liver glucose dysregulation, and lipid metabolism abnormalities.[11] However, it is important to note that there is considerable heterogeneity in the pathogenesis of MAFLD/MASLD, which is particularly relevant for the risk of cardiovascular diseases (CVD).[12,13] Individuals with T2DM have a 50–75% greater risk of developing MAFLD compared to the general population.[2] In T2DM patients, about one-third progress to NASH, with approximately 20% of these cases showing accelerated progression to fibrosis.[14] In contrast, epidemiological studies indicate that individuals with MAFLD have a risk of developing T2DM that is nearly double the rate seen in the general population, independent of obesity or other common metabolic risk factors.[15]

T2DM, a condition defined by hyperglycemia, insulin resistance, and impaired insulin secretion, facilitates increased lipolysis, resulting in an accumulation of free fatty acids in the liver.[16,17] At the same time, excessive lipid deposition in the liver disrupts insulin signaling, inhibits glycogen synthesis, and promotes gluconeogenesis, thus exacerbating fluctuations in blood glucose and insulin levels.[18] As a result, a vicious cycle forms between T2DM and MAFLD. Once T2DM patients exhibit hepatic steatosis, they are diagnosed with MAFLD. Alarmingly, although cardiovascular event mortality has decreased in both diabetic and non-diabetic populations, liver disease-related mortality has shown an increasing trend only in T2DM patients.[19] Given the widespread occurrence and substantial risks linked to MAFLD in individuals with T2DM, early detection and the implementation of effective intervention strategies are essential for achieving disease remission or slowing its progression to more severe stages.

Although liver biopsy is widely considered as the "gold standard" for diagnosing liver fibrosis, its invasiveness, potential sampling errors, low patient acceptability, and the extremely high prevalence of MAFLD greatly limit its widespread use in clinical practice.[20] IR is not only a core driver of MAFLD pathogenesis but also significantly accelerates its progression to NASH and fibrosis.[21] Therefore, insulin resistance indicators based on combinations of lipid profiles and glucose parameters have shown diagnostic and prognostic potential in various disease models. Among them, the triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-c)[22] and the triglyceride-glucose index (TyG) and its derived indicator, the triglyceride-glucose-body mass index (TyG-BMI),[23–25] have been extensively acknowledged as indicators of metabolic syndrome and cardiovascular diseases. The ZJU index is an innovative metabolic parameter that integrates changes in aspartate transaminase (AST), triglycerides (TG), alanine transaminase (ALT), body mass index (BMI), and blood glucose concentrations. Recent studies suggest that the ZJU index could serve as a useful tool for assessing the risk of NAFLD in individuals who are not obese.[26] However, the effectiveness of this index in identifying MAFLD in T2DM populations remains unclear. Building on this, the current study seeks to comprehensively assess the diagnostic efficacy of TG/HDL-c, TyG, TyG-BMI, and the ZJU index in detecting MAFLD in individuals with T2DM.

Methods

Study Design and Topic

The study adopts a cross-sectional design and consecutively includes 598 patients with T2DM from January 2024 to March 2025 at the Putuo Hospital, Shanghai University of Traditional Chinese Medicine. The criteria for inclusion are

outlined as follows: meeting the World Health Organization (WHO) diagnostic criteria for T2DM; age ≥18 years; complete biochemical parameters and clinical data, as well as available abdominal ultrasound results. The exclusion criteria include: liver diseases caused by other factors (such as drug-induced or viral hepatitis); heavy alcohol intake (greater than 30 g/day for males, and more than 20 g/day for females); severe metabolic disorders (including diabetic ketoacidosis, hyperglycemic hyperosmolar state, hyperlipidemic pancreatitis, etc).; major clinical events occurring within the last 3 months (such as myocardial infarction, cerebral hemorrhage, acute infections, major surgeries, or stress conditions); severe liver and kidney dysfunction (Child-Pugh class C or an eGFR lower than 30 mL/min/1.73m²), acute infections, and patients with a history of stress conditions; pregnant or breastfeeding women.

The main reasons for hospital admission among the patients were routine diabetes management and control of associated complications, including diabetic retinopathy, diabetic nephropathy, and diabetic foot. Some patients were admitted for management of acute exacerbations, such as hyperglycemic crisis or infections. Others were referred for specialized consultations related to diabetes-related comorbidities, including cardiovascular diseases and metabolic disorders.

This study adheres to the guidelines set forth in the Helsinki Declaration and has received approval from the hospital's ethics committee (PTEC-A-2024-73(S)-1). Written informed consent was obtained from all participants. Figure 1 illustrates the participant selection process, with a total of 598 patients included in the analysis.

Data Acquisition and Assessment

Demographic details such as age and sex, along with clinical information, were documented for each patient. The data collected included information on the duration of diabetes, a history of hypertension, and any previous cardiovascular conditions. Height and weight were assessed using standardized procedures, and the body mass index (BMI) was calculated using the formula: BMI = weight (kg) / height (m)². Venous blood samples were obtained after an overnight fast on the morning following the patient's admission (after fasting for ≥12 hours). The tested items included: glycated hemoglobin (HbA1c, measured using the Tosoh G8 fully automated analyzer), fasting blood glucose (FPG), fasting C-peptide (FCP), fasting insulin (F-ins), blood urea nitrogen (BUN), serum creatinine (Scr), uric acid (UA), estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol

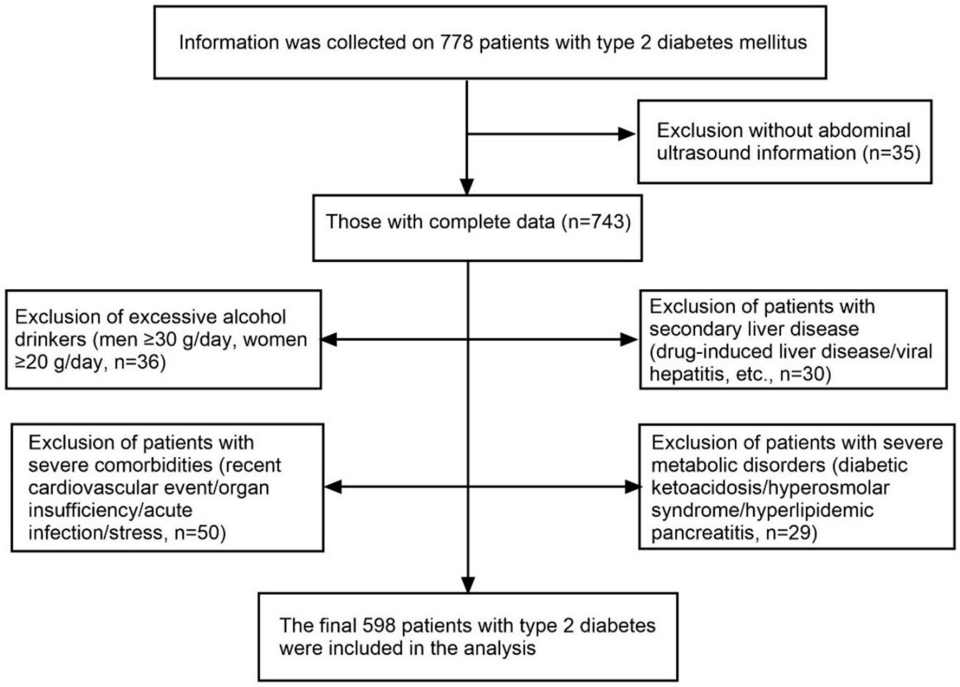

Figure 1 Participant Recruitment Flowchart.

https://doi.org/10.2147/DMSO.S549457

(TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). A Roche fully automated biochemical analyzer was employed to assess all biochemical markers.

Abdominal Ultrasound and Criteria for Diagnosing MAFLD

Abdominal ultrasound evaluations were performed by skilled sonographers following standardized procedures. Given the subjective nature of ultrasound assessment, a professional radiologist (ultrasonographer) was involved in this study, which helped ensure consistency and accuracy in diagnosing hepatic steatosis. Hepatic steatosis was identified through established sonographic characteristics, including enhanced liver-kidney echo contrast and significant echo attenuation.[27] Considering that all study participants were individuals with T2DM, the diagnosis of MAFLD was determined based on the criteria set by an international expert panel comprising representatives from 22 countries.[2] Specifically, MAFLD was diagnosed in the presence of hepatic steatosis, along with at least one of the following criteria: overweight (BMI ranging from 25 to 29.9 kg/m²), obesity (BMI exceeding 30 kg/m²), Type 2 diabetes, or signs of metabolic dysfunction.

Calculation of Insulin Resistance Indicators

Insulin resistance indices, including TG/HDL, TyG, TyG-BMI, and ZJU index, were calculated using the following formulas.

$$\text{TG/HDL-c ratio} = \text{TG (mmol/L)} / \text{HDL-c (mmol/L)}.[22]$$

$$\text{TyG index} = \text{Ln}\left[\text{TG (mg/dL)} \times \text{FPG (mg/dL)} / 2\right].[28]$$

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

$$\text{ZJU index} = \text{FPG (mmol/L)} + \text{BMI (kg/m}^2\text{)} + 3*\text{ALT (U/L)} / \text{AST (U/L) ratio (+2 if female)} + \text{TG (mmol/L)}.[29]$$

Statistical Analysis

Data analysis was performed using IBM SPSS version 27.0 software. Continuous variables with a normal distribution were presented as mean ± standard deviation (x ± s), and comparisons between groups were performed using the independent samples *t*-test. For continuous variables that were not normally distributed, the median (interquartile range) [M (P25, P75)] was calculated, and comparisons between groups were conducted using the Mann–Whitney *U*-test. Qualitative data were presented as frequency percentages, and comparisons between groups were performed using the chi-square test. Point-Biserial correlation analysis was used to assess the relationship between each IR index and MAFLD. For the correlation between continuous IR indices, Pearson correlation was employed. A multivariable logistic regression analysis was conducted to evaluate the association between IR indices and the risk of MAFLD, while controlling for potential confounding factors such as age, sex, disease duration, and hypertension history, cardiovascular history, ALT, AST, and other relevant factors. Restrictive cubic spline (RCS) analysis was conducted to examine the continuous relationship between IR indices and the risk of MAFLD. Receiver operating characteristic (ROC) curve analysis was utilized to compute the area under the curve (AUC) and evaluate the diagnostic performance of each index for identifying MAFLD. Subgroup and interaction analyses were performed based on critical clinical characteristics. A *p*-value below 0.05 was regarded as statistically significant.

Results

Demographic and Clinical Characteristics at Baseline

This study included a total of 598 patients diagnosed with T2DM. Based on the presence or absence of MAFLD, the patients were divided into two groups: the T2DM group (n=403) and the T2DM with MAFLD group (n=195). Table 1 presents the baseline characteristics of the study cohort and the comparative results between the groups. Notable differences were found between the two groups across various metabolic and liver-related indicators. Patients in the

Table 1 Baseline Demographic and Clinical Characteristics

Variables	Total (n = 598)	T2DM (n = 403)	T2DM-MAFLD (n = 195)	*P*
Age	55.00 (47.00, 58.00)	55.00 (48.00, 59.00)	54.00 (43.50, 58.00)	0.037
Course of disease	5.00 (0.50, 10.00)	5.00 (1.00, 10.00)	3.00 (0.20, 10.00)	0.004
Gender, n(%)				0.049
Female	174 (29.10)	107 (26.55)	67 (34.36)	
Male	424 (70.90)	296 (73.45)	128 (65.64)	
HBP, n(%)				0.116
No	328 (54.85)	230 (57.07)	98 (50.26)	
Yes	270 (45.15)	173 (42.93)	97 (49.74)	
CVD, n(%)				0.265
No	504 (84.28)	335 (83.13)	169 (86.67)	
Yes	94 (15.72)	68 (16.87)	26 (13.33)	
BMI (kg/m²)	24.76 (22.20, 27.07)	24.24 (21.56, 26.64)	25.69 (23.66, 28.65)	<0.001
Hba1c (%)	9.30 (7.70, 11.10)	9.30 (7.77, 11.33)	9.40 (7.70, 10.90)	0.640
FPG (mmol/L)	8.70 (6.50, 11.57)	8.70 (6.40, 11.50)	8.65 (6.60, 11.83)	0.727
FCP (ng/mL)	1.25 (0.73, 1.85)	1.10 (0.65, 1.73)	1.38 (1.00, 1.95)	<0.001
F-ins (mU/L)	9.47 (4.93, 14.69)	8.57 (4.80, 14.37)	10.66 (6.99, 15.00)	0.017
BUN (mmol/L)	5.70 (4.70, 6.90)	5.80 (4.88, 6.90)	5.50 (4.45, 6.80)	0.051
SCr (umol/L)	63.00 (51.00, 76.00)	64.00 (51.00, 77.00)	61.00 (51.50, 74.00)	0.324
UA (umol/L)	322.50 (260.00, 398.75)	310.00 (253.50, 389.50)	342.00 (277.75, 420.25)	0.003
eGFR (mL/min/1.73 m²)	107.83 (90.86, 131.91)	106.07 (88.60, 129.60)	114.23 (95.24, 134.42)	0.028
ALT (U/L)	21.00 (15.00, 34.00)	21.00 (14.00, 32.00)	23.00 (16.00, 36.00)	0.045
AST (U/L)	20.00 (16.00, 26.00)	20.00 (15.77, 25.00)	20.00 (16.00, 28.50)	0.167
TC (mmol/L)	4.74 (3.96, 5.61)	4.83 (4.00, 5.67)	4.64 (3.91, 5.46)	0.347
TG (mmol/L)	1.78 (1.17, 2.62)	1.64 (1.07, 2.48)	2.04 (1.51, 2.81)	<0.001
HDL-C (mmol/L)	1.01 (0.86, 1.22)	1.02 (0.88, 1.25)	0.96 (0.83, 1.16)	0.003
LDL-C (mmol/L)	3.12 (2.49, 3.74)	3.17 (2.46, 3.74)	3.06 (2.58, 3.71)	0.848
TG/HDL	1.78 (1.07, 2.79)	1.54 (0.97, 2.57)	2.06 (1.43, 3.27)	<0.001
Tyg	8.63 (8.05, 9.20)	8.54 (7.93, 9.16)	8.73 (8.26, 9.24)	0.004
Tyg-BMI	210.78 (184.23, 244.84)	203.64 (178.85, 239.02)	224.12 (201.33, 257.97)	<0.001
ZJU	39.66 (35.90, 44.72)	39.05 (35.07, 43.93)	41.41 (37.40, 45.63)	0.001

Notes: Unit conversion: FPG (mg/dL) /18 = mmol/L; TG (mg/dL) /88.57 = mmol/L; TC, LDL-C, and HDL-C (mg/dL) /38.67 = mmol/L.

T2DM-MAFLD group exhibited significantly higher BMI, FCP, fasting insulin, UA, eGFR, ALT, TG, TG/HDL, TyG index, TyG-BMI index, and ZJU index. Additionally, HDL-L levels in the T2DM-MAFLD group were considerably reduced. In terms of demographic characteristics, the T2DM-MAFLD group was slightly younger than the T2DM-only group and had a shorter diabetes duration. Gender distribution also differed, with a notably higher percentage of females in the T2DM-MAFLD group versus the T2DM group. We analyzed antidiabetic and lipid-lowering drugs, finding no significant differences between the two groups for metformin, sulfonylureas, glinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors, insulin, GLP-1RA, statins, and fibrates (see Table S1).

Correlation Analysis of IR Indices and T2DM-MAFLD

Since MAFLD is a dichotomous variable, Point-Biserial correlation analysis was used to assess the relationship between each IR index and MAFLD (see Table 2 and Figure 2). Among the IR indices, the strongest correlation with MAFLD was observed for TyG-BMI. For the correlation between continuous IR indices, Pearson correlation was employed. A significant positive correlation was found between the different IR indices ($p < 0.05$), indicating a strong relationship between these insulin resistance indicators.

Table 2 Correlation Analysis of IR Indices and T2DM-MAFLD

r	MAFLD	TG/HDL	TyG	TyG-BMI	ZJU
MAFLD	1.00	0.02	0.12*	0.21**	0.12*
TG/HDL	0.02	1.00	0.74**	0.47**	0.49**
TyG	0.120*	0.74**	1.00	0.59**	0.75**
TyG-BMI	0.21**	0.47**	0.59**	1.00	0.88**
ZJU	0.12*	0.49**	0.75**	0.88**	1.00

Notes: *p<0.05, **p<0.001.

Regression Analysis of the Association Between IR Indices and T2DM-MAFLD

In this study, a stratified adjustment model was used to investigate the association between insulin resistance indices and the diagnosis of T2DM-MAFLD (see Table 3 and Figure 3). In the model with full adjustments (Model 3), after adjusting for age, sex, disease duration, renal function, liver enzymes, and cardiovascular diseases, the TyG-BMI index showed the strongest diagnostic stability. Each 1-unit increase as a continuous variable was significantly associated with a 1% increase in the diagnosis of MAFLD (OR = 1.01, 95% CI: 1.00–1.01, P = 0.006). When grouped by quartiles, the Q3 group (210.78–244.75) had a 117% increase in risk (OR = 2.17, 95% CI: 1.14–4.14, P = 0.018), and the Q4 group (>244.75) had a 147% increase in risk (OR = 2.47, 95% CI: 1.27–4.83, P = 0.008). Trend tests confirmed that the diagnosis of MAFLD increased with higher indices (P for trend = 0.005). The TG/HDL ratio exhibited a significant threshold effect, with no significant association observed in the continuous variable analysis (P = 0.114). However, subgroup analysis showed that the risk gradually increased across Q2–Q4 (Q2: OR = 2.95; Q3: OR = 2.57; Q4: OR = 3.38), demonstrating a significant dose–response relationship (P for trend = 0.009). The TyG index demonstrated a relatively strong ability to determine the diagnosis, whereas the ZJU index showed limited capacity. After full

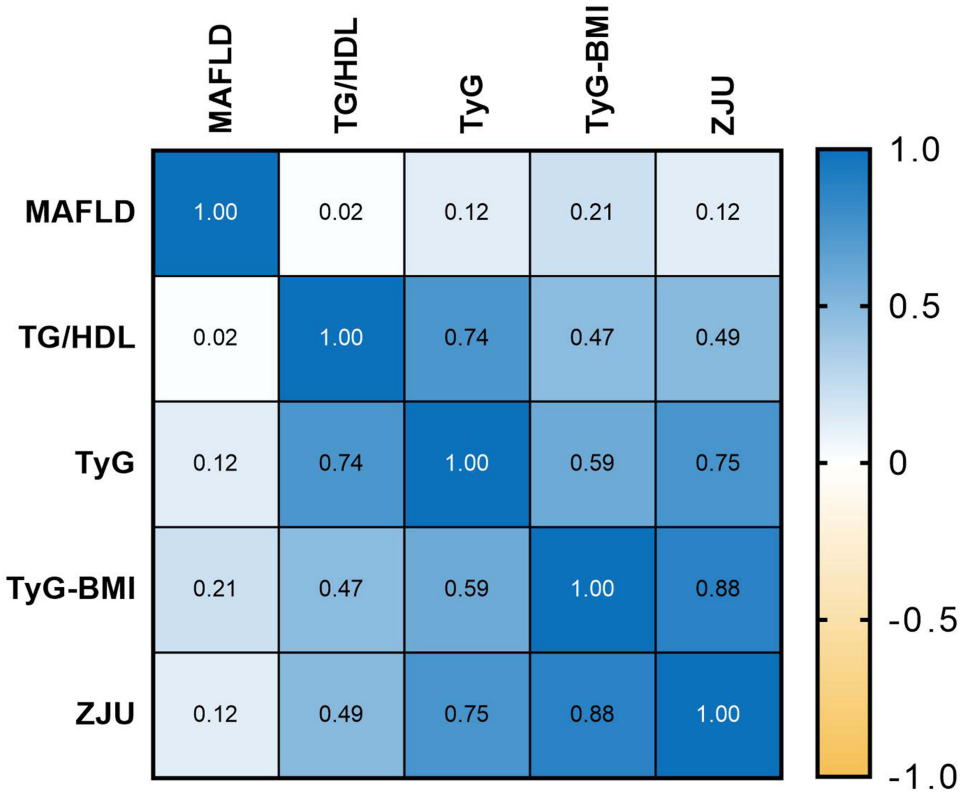

Figure 2 Heat map of correlation analysis.
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; TG/HDL, triglyceride/high-density lipoprotein cholesterol ratio; TyG, triglyceride-glucose index; TyG-BMI, triglyceride-glucose-body mass index; ZJU, biomarker for NAFLD in Chinese population.

Table 3 Regression Analysis of the Association Between IR Metrics and Risk of T2DM-MAFLD

Variables	Model 1	Model 2	Model 3
	OR (95% CI) *p* value	**OR (95% CI) *p* value**	**OR (95% CI) *p* value**
TG/HDL	1.01 (0.97, 1.04) 0.680	1.00 (0.97, 1.04) 0.947	1.09 (0.98, 1.21) 0.114
TG/HDL group			
Q1	1.0	1.0	1.0
Q2	2.94 (1.64, 5.28) <0.001	3.02 (1.67, 5.46) <0.001	2.95 (1.55, 5.60) 0.001
Q3	3.45 (1.93, 6.18) <0.001	3.59 (1.97, 6.51) <0.001	2.57 (1.32, 5.00) 0.005
Q4	3.86 (2.17, 6.89) <0.001	3.78 (2.06, 6.92) <0.001	3.38 (1.71, 6.68) <0.001
P for trend	<0.001	0.001	0.009
Per SD increase	1.29 (1.13, 1.47)	1.27 (1.10, 1.46)	1.25 (1.06, 1.48)
TyG	1.35 (1.08, 1.69) 0.009	1.28 (1.01, 1.62) 0.042	1.24 (0.93, 1.65) 0.149
TyG group			
Q1	1.0	1.0	1.0
Q2	1.60 (0.90, 2.83) 0.106	1.45 (0.81, 2.58) 0.210	1.67 (0.88, 3.17) 0.118
Q3	2.63 (1.51, 4.58) 0.001	2.37 (1.34, 4.17) 0.003	2.18 (1.14, 4.16) 0.018
Q4	1.97 (1.12, 3.45) 0.018	1.71 (0.95, 3.08) 0.071	1.67 (0.85, 3.28) 0.139
P for trend	0.006	0.028	0.102
Per SD increase	1.49 (1.12, 1.98)	1.39 (1.04, 1.88)	1.33 (0.94, 1.89)
TyG-BMI	1.01 (1.01, 1.01) <0.001	1.01 (1.00, 1.01) <0.001	1.01 (1.00, 1.01) 0.006
TyG-BMI group			
Q1	1.0	1.0	1.0
Q2	1.67 (0.92, 3.03) 0.093	1.77 (0.97, 3.24) 0.064	1.41 (0.73, 2.71) 0.309
Q3	2.76 (1.55, 4.91) <0.001	2.89 (1.61, 5.20) <0.001	2.17 (1.14, 4.14) 0.018
Q4	3.38 (1.91, 6.01) <0.001	3.18 (1.77, 5.73) 0.001	2.47 (1.27, 4.83) 0.008
P for trend	<0.001	<0.001	0.005
Per SD increase	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)	1.01 (1.00, 1.01)
ZJU	1.03 (1.01, 1.06) 0.009	1.02 (1.00, 1.05) 0.070	1.02 (0.99, 1.05) 0.291
ZJU group			
Q1	1.0	1.0	1.0
Q2	1.80 (1.02, 3.19) 0.042	1.73 (0.97, 3.07) 0.062	1.58 (0.83, 2.99) 0.162
Q3	2.28 (1.30, 4.00) 0.004	2.04 (1.15, 3.61) 0.014	1.60 (0.84, 3.04) 0.151
Q4	2.36 (1.35, 4.14) 0.003	2.03 (1.14, 3.63) 0.016	1.70 (0.88, 3.28) 0.112
P for trend	0.003	0.021	0.155
Per SD increase	1.05 (1.02, 1.08)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)

Notes: The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding *p*-values. A p-value less than 0.05 was considered statistically significant. Regression analysis of IR variables was conducted to assess associations, and categorical analysis was performed by dividing the variables into quartiles to examine potential trends. Model 1:Non-adjusted. Model 2:Adjust I model adjust for: Gender; Age Model 3:Adjust II model adjust for: BUN; Scr; UA; eGFR; ALT; AST; Gender; Age; Course of disease; HBP; CVD.

adjustment, the TyG index lost significance (continuous variable: OR = 1.24, $P = 0.149$; only Q3 group was borderline significant OR = 2.18, $P = 0.018$), and the ZJU index showed no statistical significance in all fully adjusted models (continuous variable: $P = 0.291$; highest group OR = 1.70, $P = 0.112$).

RCS Curve Analysis of IR Indices and T2DM-MAFLD

The RCS model was used to assess the association between four metabolic indices and the diagnosis of T2DM-MAFLD (Figure 4a–d). Nonlinear analysis showed that the TG/HDL-C ratio exhibited a J-shaped curve with MAFLD diagnosis (P for overall < 0.001, P for nonlinear < 0.001), while the TyG index showed an inverted U-shaped curve with MAFLD diagnosis (P for overall = 0.006, P for nonlinear = 0.027). The TyG-BMI index demonstrated a robust linear association

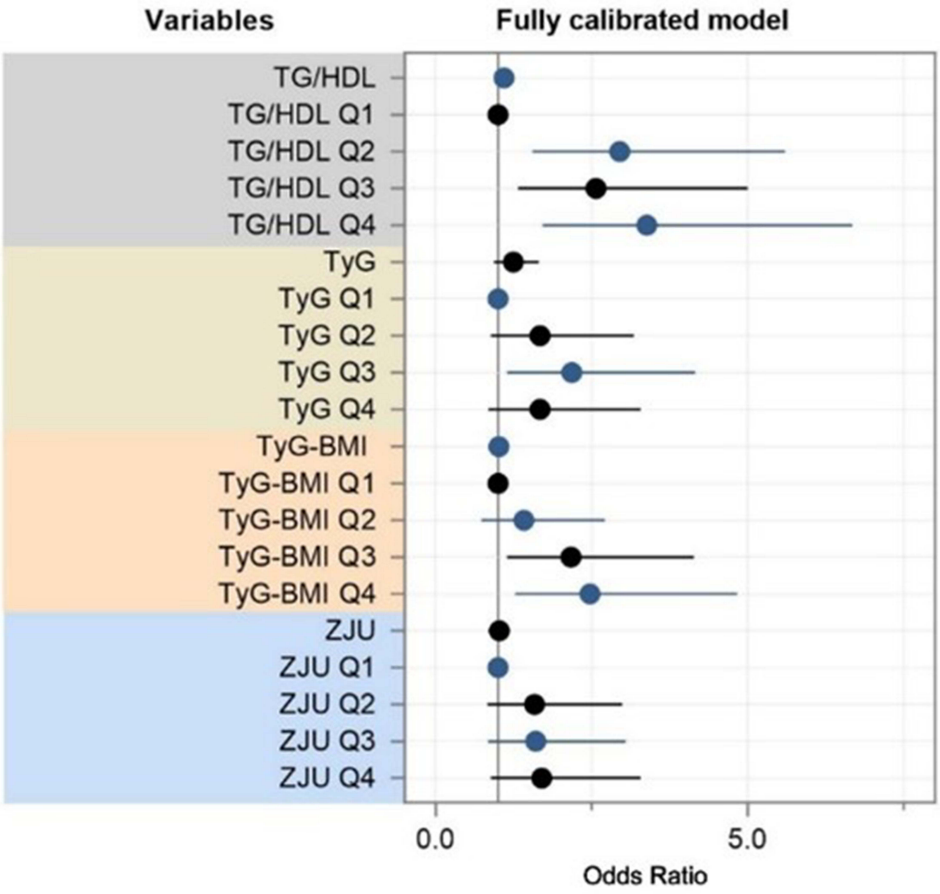

Figure 3 Forest plot of regression analysis.

(*P* for overall < 0.001, *P* for nonlinear = 0.349), supporting its continuous diagnostic value. Although the ZJU index was overall significant, it lacked clear nonlinear characteristics (*P* for overall = 0.022, *P* for nonlinear = 0.093).

Comparison of IR Indices

This study evaluated the diagnostic accuracy of each index for T2DM-MAFLD using ROC curves (Table 4). Among the four IR indices, TyG-BMI demonstrated the best performance (AUC = 0.632, 95% CI: 0.580–0.684), outperforming TyG (AUC = 0.581, *P* = 0.021) and ZJU (AUC = 0.588, *P* = 0.038). TG/HDL ranked second (AUC = 0.623, 95% CI: 0.574–0.671), with an optimal cutoff value of 1.36, providing 80.1% sensitivity but only 44.4% specificity. In the female population, TG/HDL showed the most prominent diagnostic performance (AUC = 0.679, 95% CI: 0.596–0.762), achieving the optimal balance at a threshold of 1.20 (sensitivity 80.0%, specificity 53.5%). In the male population, TG/HDL had the highest sensitivity (83.6%) but the lowest specificity (39.0%), while TyG-BMI showed the best overall performance (AUC = 0.622, sensitivity 77.1%).

Subgroup Analysis

This study revealed significant population heterogeneity in the effect of key metabolic indices on the diagnosis of T2DM-MAFLD through interaction tests (Figure 5). For the TG/HDL ratio (Figure 5a), a significant gender interaction was found (*P* interaction = 0.006), with a 40% higher likelihood of diagnosis in females (OR = 1.40; 95% CI: 1.09–1.81; *P* = 0.009), while no significant association was found in males (OR = 1.00; *P* = 0.882). There was a significant interaction with hypertension status (*P* interaction = 0.025). For the TyG index (Figure 5b), the likelihood of diagnosis was higher in females (OR = 1.77 vs males OR = 1.28), despite the lack of statistical significance in the interaction (*P* = 0.252). For the

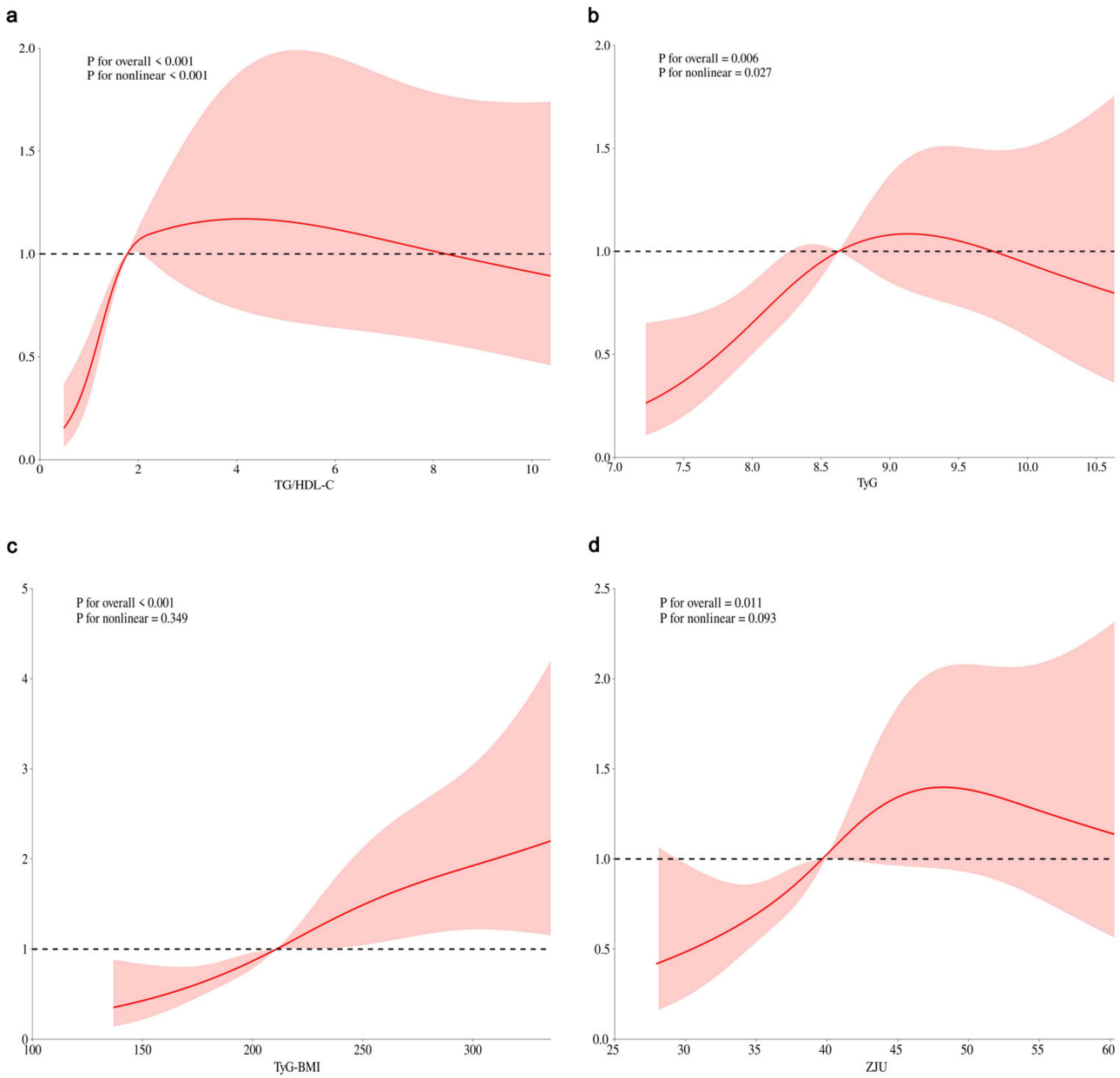

Figure 4 RCS curve analysis of IR metrics vs T2DM-MAFLD. (**a**) RCS curve of TG/HDL; (**b**) RCS curve of TyG; (**c**) RCS curve of TyG-BMI; (**d**) RCS curve of ZJU index.

TyG-BMI index (Figure 5c), a consistent significant effect was observed across the entire population (females OR = 1.01, $P = 0.002$; males OR = 1.01, $P < 0.001$). A significant interaction with hypertension status was found (P interaction = 0.032). In the ZJU index (Figure 5d), the effect was more pronounced in females (OR = 1.06 vs males OR = 1.03), but the interaction did not reach the threshold for significance ($P = 0.286$), while a significant interaction with hypertension status was observed (P interaction = 0.039).

Discussion

This is the first study to comprehensively evaluate the relationship and diagnostic capabilities of four IR indices (TG/HDL-c, TyG, TyG-BMI, and the ZJU index) in relation to MAFLD within a cohort of 598 T2DM patients. First, we discovered that among the IR indices, the strongest association with MAFLD was observed for TyG-BMI. Multivariate logistic regression provided additional evidence that TyG-BMI is an independent determinant of MAFLD, maintaining a significant association

https://doi.org/10.2147/DMSO.S549457

Table 4 ROC Analysis

Variables	ROC Area (AUC)	95% CI Lower	95% CI Upper	Best Threshold	Specificity	Sensitivity
TG/HDL	0.623	0.574	0.671	1.363	0.444	0.801
TyG	0.581	0.529	0.633	8.393	0.445	0.715
TyG-BMI	0.632	0.580	0.684	202.733	0.491	0.736
ZJU	0.588	0.536	0.641	37.521	0.416	0.739
Male						
TG/HDL	0.611	0.552	0.670	1.363	0.390	0.836
TyG	0.573	0.509	0.636	8.392	0.425	0.748
TyG-BMI	0.622	0.557	0.686	200.928	0.441	0.771
ZJU	0.578	0.514	0.643	42.006	0.677	0.486
Female						
TG/HDL	0.679	0.596	0.762	1.201	0.535	0.800
TyG	0.609	0.515	0.703	8.593	0.685	0.621
TyG-BMI	0.668	0.579	0.756	203.845	0.607	0.690
ZJU	0.603	0.511	0.696	37.518	0.400	0.800

even after adjusting for confounding variables such as age and sex, and disease duration. RCS analysis revealed heterogeneity in the associations between the indices and the diagnosis of MAFLD, considering dose-response relationships: TG/HDL-c followed a J-shaped curve, TyG exhibited an inverted U-shaped curve, while TyG-BMI demonstrated a strong, linear positive correlation, and the ZJU index also demonstrated a significant overall association. In terms of diagnostic performance, ROC curve analysis revealed that TyG-BMI demonstrated the greatest overall ability to distinguish between groups, highlighting its potential as a non-invasive screening tool. Notably, subgroup analysis revealed gender-specific differences, with the effects of TG/HDL-c, TyG, and ZJU indices being significantly stronger in female patients. Among these, TG/HDL-c exhibited superior screening value for MAFLD in females.

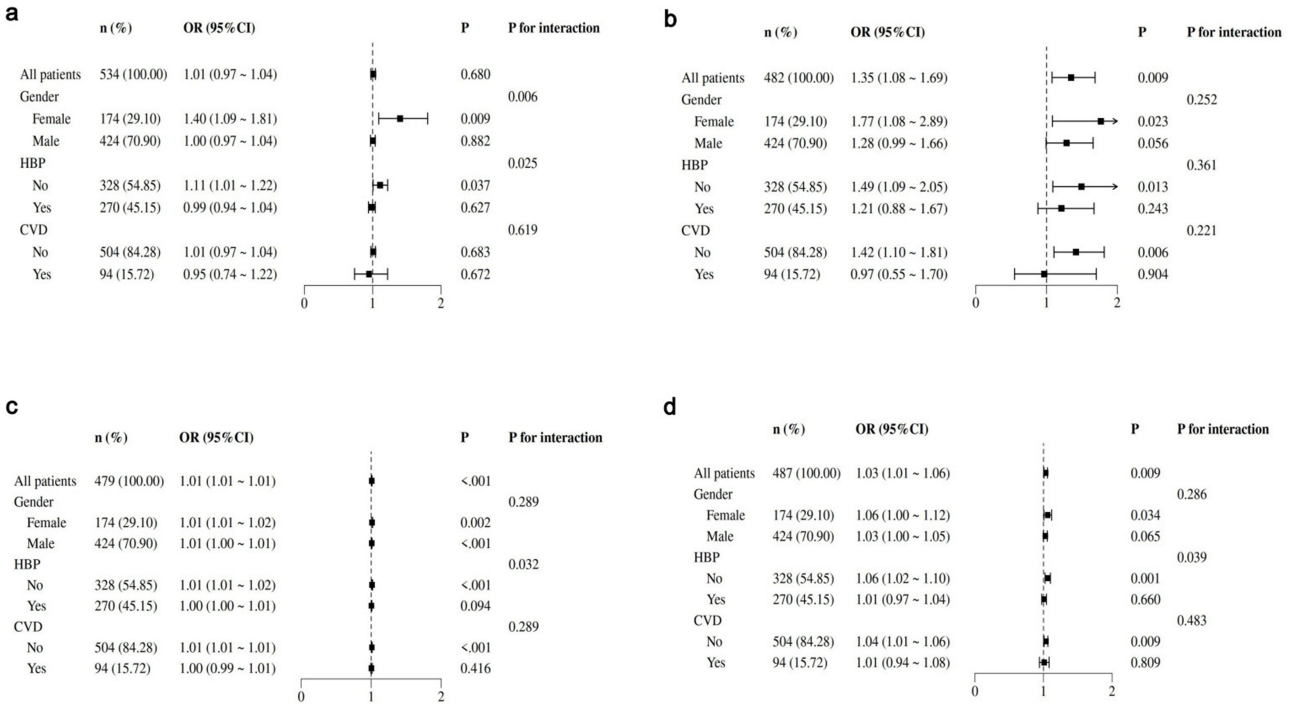

Figure 5 Forest plot for subgroup analysis. (**a**) TG/HDL ratio and its association with T2DM-MAFLD; (**b**) TyG index and its association with T2DM-MAFLD; (**c**) TyG-BMI index and its association with T2DM-MAFLD; (**d**) ZJU index and its association with T2DM-MAFLD.

Earlier research has demonstrated a significant association between a higher TG/HDL-C ratio and unfavorable metabolic traits, such as dyslipidemia, obesity, and diabetes.[30,31] Recently, there has been increasing attention on the association between this ratio and fatty liver disorders. A study conducted in Korean children revealed that a high TG/HDL-C ratio was linked to more severe hepatic steatosis and a higher risk of diabetes.[32] In a Japanese population cohort, the TG/HDL-C ratio has been shown to predict the risk of NAFLD, with a higher ratio is closely linked to an increased risk of both fatty liver and NAFLD.[33] Notably, a cross-sectional study by Wang et al[34] further demonstrated that the TG/HDL-C ratio had a non-linear positive correlation with the prevalence of NAFLD (trend test $P < 0.001$). Following multivariable adjustment, individuals in the highest quartile group (compared to those in the lowest group) exhibited a significantly higher risk of NAFLD (OR = 3.61, 95% CI: 2.94–4.38). In line with this, data from our study on the T2DM population showed that the diagnosis of MAFLD in the highest quartile of TG/HDL-C was significantly increased (adjusted OR = 3.38, 95% CI: 1.71–6.68; $P < 0.001$). Furthermore, Catanzaro established its independent relationship with both NAFLD and metabolic syndrome (MetS).[35] Ma et al's research found that the TG/HDL-C ratio was independently linked to the risk of MAFLD, with females exhibiting a notably higher risk of MAFLD compared to males within the same TG/HDL-C strata.[36] The study by Fan et al[37] within the healthy Chinese population further supported the diagnostic value of this ratio, with better predictive ability in females, which is highly consistent with the female-specific advantage revealed in our study. Considering that the protective effect of estrogen on hepatic lipid metabolism diminishes after menopause,[38] the above findings may partly be attributed to the decline in metabolic defense mechanisms in postmenopausal women.

The TyG index, which integrates FPG and TG levels, has become an effective and cost-efficient marker for assessing IR.[39] Earlier research has validated that this index is predictive of the occurrence of NAFLD.[40,41] Recent evidence further indicates that higher TyG index is strongly positively associated with a higher risk of MAFLD, highlighting its potential to serve as an accessible diagnostic tool.[42] Notably, the TyG-BMI index, which is modified by BMI, has shown superior performance in evaluating the severity of IR and identifying high-risk individuals for NASH.[43] Song et al[44] found that TyG-BMI demonstrated the most significant connection to the development and progression of MASLD to liver fibrosis, outperforming other cardiometabolic markers like TyG. This suggests that TyG-BMI could serve as the most effective non-invasive clinical biomarker for the early identification of MASLD and hepatic fibrosis. This study also confirms that the strength of the relationship between TyG-BMI and MAFLD, along with its overall discriminatory ability, ranks first among the four IR indices, which is highly consistent with previous conclusions. This advantage is further emphasized in histological validation studies. Zhang et al analyzed 393 NAFLD patients diagnosed by liver biopsy and found that individuals in the highest quartile of TyG-BMI exhibited a notably increased risk of developing NASH (OR = 4.2, 95% CI: 2.1–8.3), pronounced fibrosis (OR = 3.8, 95% CI: 1.9–7.6), and advanced liver fibrosis (OR = 5.1, 95% CI: 2.3–11.4).[45] Zou[46] further confirmed in a MAFLD cohort that TyG-BMI was independently linked to liver fibrosis scores, and its predictive power for significant liver fibrosis (SLF) continued to outperform TyG and other non-invasive models, suggesting that TyG-BMI has the potential to identify the early risk of MASLD and SLF. Importantly, the linear association characteristic of TyG-BMI provides an advantage for its clinical applicability. Ma et al[47] through RCS analysis based on NHANES data, indicated that the TyG index had a non-linear association with high-risk NASH, while TyG-BMI exhibited a robust linear trend. This finding is highly consistent with the RCS results of this study, showing that TyG-BMI demonstrates a clear linear dose-response relationship in determining the diagnosis of MAFLD, avoiding the interference of complex curve patterns in clinical interpretation.

The ZJU index, as a multidimensional metabolic indicator that integrates blood glucose, blood lipids, liver enzymes, and body composition, is receiving increasing attention for its value in liver risk assessment. A study utilizing the NHANES database was the first to identify a substantial positive relationship between the ZJU index and both the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) in adult NAFLD patients within the United States. This finding suggests that the ZJU index could serve as a non-invasive marker for assessing the extent of hepatic steatosis and fibrosis severity.[48] Zou et al[49] further validated through a dual-cohort study that the ZJU index is applicable to the newly defined MASLD diagnostic framework, showing potential for use in high-risk population screening. In terms of diagnostic performance, a cross-sectional study[50] systematically compared five non-invasive indices (ZJU index, hepatic steatosis index (HSI), fatty liver index (FLI), visceral adiposity index (VAI), and lipid accumulation product (LAP)). The findings indicated that the ZJU index significantly outperformed other indices in

identifying NAFLD, with stable performance across different age and sex subgroups, emphasizing its consistency as a comprehensive screening tool.[46] Notably, Chen et al[51] in their histological study set boundaries for the application of the ZJU index: while it was significantly correlated with mild steatosis ($P < 0.01$), its diagnostic sensitivity for moderate to severe steatosis (liver fat content > 20%) was only 58.3%, indicating its limited ability to detect advanced hepatic steatosis. In contrast, this study showed that although the ZJU index demonstrated a significant overall association with MAFLD, its area under the ROC curve was lower compared to TG/HDL-c and TyG-BMI. We consider that this difference in diagnostic performance may be due to the ZJU index not incorporating key insulin resistance indicators (such as FPG, which accounts for only 1/5 of the weight), whereas TyG-BMI directly integrates the triple risk factors of blood glucose, blood lipids, and obesity, making it more aligned with the pathological features of T2DM-MAFLD.

While the exact mechanisms linking TG/HDL-c, TyG, TyG-BMI, and the ZJU index to MAFLD remain incompletely understood, existing research indicates that IR is crucial in the pathogenesis of the disease, driving its progression through various mechanisms.[52] At the level of lipoprotein metabolism, IR promotes the liver's synthesis of TG-rich VLDL by activating SREBP-1c, while simultaneously inhibiting the expression of ATP-binding cassette transporter A1 (ABCA1), thereby enhancing the clearance of HDL-C.[53,54] These effects together elevate the TG/HDL-c ratio, thereby making it a highly sensitive serum biomarker for IR. In terms of hepatic lipid deposition, IR exerts its effects through two pathways: on one hand, it activates hormone-sensitive lipase (HSL) within adipose tissue, which enhances the transport of free fatty acids (FFAs) to the liver. Conversely, IR activates ChREBP, driving de novo lipogenesis (DNL) in the liver.[55,56] These processes further trigger a vicious cycle in glucose and lipid metabolism—intracellular FFA accumulation inhibits insulin signaling (through suppression of the IRS-1/PI3K pathway), leading to increased hepatic glucose output and peripheral glucose utilization impairment, while sustained hyperglycemia exacerbates DNL by activating ChREBP, thus forming a self-reinforcing pathological loop.[57,58] This cycle is the core pathological basis of the TyG index (which integrates FPG and TG). The outstanding diagnostic performance of TyG-BMI is attributed to its incorporation of the multidimensional network associated with IR: the TyG component captures glucose-lipid metabolic disorders (reflecting the above-mentioned glucose-lipid cycle), while the BMI component quantifies adipose tissue expansion (the source of lipolysis hyperactivity and inflammatory secretion). Visceral fat accumulation not only promotes the overflow of FFAs but also exacerbates IR and hepatic inflammation directly by secreting inflammatory mediators such as TNF-α and IL-6.[59] The amplification effect of this metabolic-inflammation cascade explains the robust linear association exhibited by TyG-BMI in MAFLD risk prediction. In contrast, although the ZJU index integrates liver enzymes (ALT/AST) and basic metabolic parameters, it is insufficient in capturing obesity-related metabolic inflammatory responses; TG/HDL-c mainly reflects lipoprotein remodeling and does not fully encompass the dimensions of glucose metabolism disorder. In a recent comprehensive investigation of diabetes-induced hepatic pathophysiological changes, Dai et al[60] highlighted several important findings. Initially, the study demonstrated that the pathological molecule Tgfb1i1 (HIC5) is essential in driving the overactivation of hepatic stellate cells (HSCs). Secondly, liver overexpression of TXNIP impairs antioxidant defenses, leading to elevated oxidative stress (ROS), which subsequently induces pathological alterations in hepatocytes. Thirdly, the capillarization of liver sinusoidal endothelial cells (LSEC) correlates with elevated levels of fatty acid-binding protein 4 (FABP4). These pathophysiological changes are triggered under under conditions of high fat and high glucose, or high fat combined with advanced glycation end products (AGEs), suggesting that these factors interact to worsen liver pathology. Managing both lipid and glucose levels, or targeting these specific molecules, could provide an innovative and effective approach to preventing diabetic liver disease. This finding provides a deeper explanation for the clinical value of TyG-BMI, confirming that by simultaneously quantifying the "obesity load-glucose-lipid imbalance-inflammatory stress" triad, it becomes the non-invasive predictive tool closest to the physiological essence of MAFLD, which is consistent with its optimal discriminatory performance and linear dose-response effect shown in this study.

Strengths and Limitations

This study is the first to thoroughly examine the relationship and diagnostic effectiveness of four IR indices—TG/HDL-c, TyG, TyG-BMI, and the ZJU index—in relation to MAFLD. It fills a gap in existing literature and provides novel perspectives for the non-invasive diagnosis of MAFLD. The study not only explored the association between the four IR

indices and MAFLD but also conducted multivariable logistic regression analysis to further confirm the role of TyG-BMI as an independent determinant of MAFLD. Additionally, the study used RCS analysis to reveal the dose-response association between the IR indices and MAFLD, enhancing the scientific rigor and reliability of the results. The subgroup analysis suggested that the impacts of TG/HDL-c, TyG, and ZJU index were significantly enhanced in females, and this gender-specific result could guide future MAFLD screening strategies, offering important clinical significance. ROC curve analysis demonstrated that TyG-BMI displayed the best diagnostic performance among the four IR indices, demonstrating its potential as a non-invasive screening tool and providing a scientific basis for early clinical screening of MAFLD. In addition to its diagnostic value, the TyG-BMI index shows promise in improving cardiometabolic risk prediction models, which are of growing interest to the scientific community. Its ability to integrate multiple metabolic disturbances, such as glucose-lipid metabolism disorders and adipose tissue expansion, makes it a valuable tool in refining predictions of both cardiometabolic risks and long-term mortality.[61] Incorporating TyG-BMI into existing risk models could offer more precise stratification for patients at risk of both MAFLD and associated cardiovascular complications. The clinical application of TyG-BMI in this context could enhance the effectiveness of personalized treatment strategies and improve patient outcomes.

Nevertheless, it is essential to acknowledge a number of limitations inherent in this study. First, the assessment of hepatic steatosis was conducted using abdominal ultrasound, rather than liver biopsy, which is considered the gold standard for diagnosis. This methodological variation may lead to discrepancies in diagnostic precision. While abdominal ultrasound is widely used in clinical practice, the addition of Fibroscan with controlled attenuation parameter (CAP) could have provided more accurate assessments of both hepatic steatosis and fibrosis. Fibroscan is often used after liver biopsy and MRI-based PDFF (proton density fat fraction) and spectroscopy. Future studies may consider incorporating such advanced techniques for more comprehensive assessments of liver conditions. Furthermore, this study employed a cross-sectional design, which, while useful for identifying associations between insulin resistance indices and MAFLD, is unable to establish causality. The inability to establish causal relationships is a major limitation of cross-sectional studies, and future prospective cohort studies would be more valuable in establishing the potential causal influence of insulin resistance indices on the progression of MAFLD. Additionally, the study lacked long-term follow-up data, which restricted the assessment of the predictive capacity of these indices for MAFLD progression and prognosis. Long-term follow-up studies could further assess their potential role in disease progression. Although this study included a large sample of T2DM patients, the homogeneity of the sample (mainly focused on the diabetic population) may limit its generalizability to other high-risk populations, such as non-diabetic individuals or different ethnic groups. Moreover, the exclusion criteria were extensive, and while MAFLD's definition does not necessitate the absence of viral hepatitis, we excluded patients with viral hepatitis. This decision limits the generalizability of our findings to all MAFLD patients, particularly those with co-existing viral infections. Future research should consider including patients with viral hepatitis to provide a broader understanding of MAFLD across different patient groups. Additionally, although the study included 598 diabetic patients, only 195 patients were diagnosed with both MAFLD and T2DM, which is lower than expected. This may be due to the specific inclusion criteria, and further studies could explore larger cohorts to better understand the co-occurrence of T2DM and MAFLD. Lastly, the data for this study were exclusively gathered from a single center within the Chinese population. Therefore, caution should be exercised when extrapolating the results to other populations, as differences related to race and ethnicity may influence the findings. Furthermore, the study did not focus on the "Lean MAFLD" group, a distinct subgroup of patients with MAFLD who have a normal BMI. This group may have different metabolic characteristics and responses to insulin resistance, and future studies should aim to explore this subgroup to gain a more comprehensive understanding of MAFLD in diverse patient populations.

Conclusion

In conclusion, this study identified a correlation between the TG/HDL ratio, TyG index, TyG-BMI index, ZJU index, and MAFLD. Significantly, the TyG-BMI index outperformed the other three indices in terms of diagnostic accuracy for MAFLD. These results suggest that the TyG-BMI index may be a useful marker for detecting MAFLD. Overall, the findings highlight the potential of the TyG-BMI index as an efficient screening tool for MAFLD.

Data Sharing Statement

The original contributions of this study are contained within the article and the data supporting the findings are available upon reasonable request. For further inquiries, please contact the corresponding author.

Ethical Approval

This study was carried out following the principles set forth in the Declaration of Helsinki and was approved by the Ethics Committee of Putuo Hospital, Shanghai University of Traditional Chinese Medicine (PTEC-A-2024-73(S)-1).

Author Contributions

Yunyi Yang and Hongping Wang should be considered as co-first authors.

Yunyi Yang: Investigation, Formal analysis, Data curation, Conceptualization, Writing – original draft. Hongping Wang: Investigation, Formal analysis, Data curation, Conceptualization, Writing – original draft. Yanming He: Investigation, Formal analysis, Data curation, Writing – review and editing. Xiaoli He: Data curation, Formal analysis, Investigation, Writing – review and editing. Zheng Yao: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – review and editing, Writing – original draft, Investigation. Hongjie Yang: Funding acquisition, Formal analysis, Data curation, Conceptualization, Writing – review and editing. All authors 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 study was funded by the National Natural Science Foundation of China (No. 82205009, No. 82274267), the Clinical Research Project of the Shanghai Health and Family Planning Commission (No. 20214Y0178), the Three-Year Action Plan for Accelerating the Inheritance and Innovation of Traditional Chinese Medicine in Shanghai (No. 1-2-3), and the Innovation and Transformation Capacity Training Program of the Three-Year Action Plan for Advancing Clinical Skills and Innovation in Municipal Hospitals in Shanghai (No. SHDC2022CRD009).

Disclosure

The authors declare no competing interests.

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