ORIGINAL RESEARCH

The Metabolic Score for Insulin Resistance Index is Superior to the Triglyceride and Glucose Index in Identifying Nonalcoholic Fatty Liver Disease in Hyperuricemia Subjects

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Purpose: Hyperuricemia (HUA) is a recognized risk factor for non-alcoholic fatty liver disease (NAFLD). Early diagnosis and the identification of predictive factors are important for the HUA population. This study aimed to investigate the potential relationship between the metabolic score for insulin resistance (METS-IR) index and the triglyceride and glucose (TyG) index with NAFLD in individuals with HUA.

Patients and Methods: A total of 5537 HUA participants were included in the study. Hepatic ultrasonography was conducted following the latest diagnostic criteria to diagnose NAFLD. The relationship between the TyG and METS-IR index and NAFLD was evaluated by multivariable logistic regression analysis and restricted cubic spline model (RCS). In addition, the area under the curve (AUC), positive likelihood ratio, and negative likelihood ratio were explored to compare the predictive value of IR surrogates for NAFLD with HUA. The AUCs of the two indicators were compared using the DeLong test.

Results: Multivariable logistic regression analysis revealed that elevated TyG (OR = 2.285, 95% CI: 1.525, 3.428) and METS-IR (OR = 1.242, 95% CI: 1.219, 1.266) indices significantly increase the risk of NAFLD. Meanwhile, the RCS analysis revealed a -log-shaped nonlinear relationship between NAFLD risk and the METS-IR index ($P_{non-linear} < 0.001$), contrasting with the linear association observed with the TyG index ($P_{non-linear} = 0.763$). Notably, the risk of NAFLD demonstrated a significant escalation when the METS-IR index exceeded the threshold of 39.208 (OR=1). Compared to the TyG index (AUC = 0.734, 95% CI: 0.721~0.748), the METS-IR index (AUC = 0.821, 95% CI: 0.810~0.832) demonstrated superior predictive value for NAFLD in individuals with HUA according to the DeLong test.

Conclusion: In the HUA population, the METS-IR index has a higher predictive value for NAFLD than the TyG index, contributing to early diagnosis and disease prevention.

Keywords: non-alcoholic fatty liver disease, hyperuricemia, the triglyceride and glucose index, the metabolic score for insulin resistance index, inflammation

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered one of the primary public health problems in the world. It has been reported that the prevalence of NAFLD worldwide is approximately 25%.[1] In Western countries, the prevalence ranges from 24% to 42%,[2] and there is an increasing impact of NAFLD on populations in Asian countries. A meta-analysis conducted in China revealed a staggering prevalence of NAFLD at 29.5%,[3] highlighting the urgency of addressing this issue. Notably, NAFLD not only has the potential to progress into chronic liver disease[4] but also represents a metabolic disorder that increases the risk of developing other conditions such as diabetes, hyperuricemia (HUA),[5] and cardiovascular disease.[6] These comorbidities significantly impact individuals' overall quality of life.

Purine nucleotides are catalyzed by xanthine oxidoreductase to produce uric acid (UA) in the intestine, liver, and muscle. The majority of UA is eliminated through renal excretion (70%), while a smaller portion is cleared through the gastrointestinal tract (30%).[7] Disturbances in purine metabolism or abnormal excretion of UA[8] or certain drugs[9] could lead to elevated serum uric acid (SUA) levels. Elevated uric acid levels not only serve as the pathological basis for gout but are also closely related to insulin resistance (IR),[8] hypertension,[10] and carotid atherosclerosis.[11]

In recent years, many scholars have explored the relationship between UA and NAFLD, consistently demonstrating a significant positive correlation between higher SUA levels and the incidence of NAFLD.[5,12] Wan et al[13] demonstrated that elevated SUA levels can lead to hepatocyte steatosis via NLRP3 inflammatory vesicles. Furthermore, increased SUA levels can induce endoplasmic reticulum stress in hepatocytes, leading to a significant rise in GRP78/94 levels and activation of SREBP-1c, subsequently disrupting hepatocyte lipid metabolism.[14] Additionally, it has been observed that high SUA can activate the NF-κB inflammatory signaling pathway by upregulating reactive oxygen species expression in liver cells, thereby exacerbating inflammatory damage in the liver.[15] Notably, elevated UA levels may promote IRS1 phosphorylation, which inhibits downstream Akt phosphorylation,[16] leading to IR and further contributing to an increase in lipid peroxidation products in hepatocytes. Detecting individuals within the HUA population who are more susceptible to NAFLD at an early stage can greatly contribute to the prevention and reduction of adverse liver-related prognostic events.

Since NAFLD often presents asymptomatically in its early stages, patients are often detected during health check-ups.[17] While liver biopsy is considered the gold standard for diagnosing liver-related diseases, its invasive nature limits its widespread acceptance. In addition, large-scale liver ultrasound screening for NAFLD can lead to the inefficient utilization of public health care resources. Therefore, there is an urgency to discover biological markers (non-invasive and accurate) conducive to early detection of NAFLD. The metabolic score for insulin resistance (METS-IR) index and the triglyceride and glucose (TyG) index are newly proposed, non-invasive IR surrogates for the assessment of IR levels.[18,19] The METS-IR index and TyG index are associated with metabolic and inflammatory diseases.[20,21] In addition, NAFLD is characterized with increased chronic inflammation.[22] Moreover, high UA levels are also correlated with inflammatory conditions such as hypertension,[23] thyroiditis,[24] metabolic syndrome,[25] type 2 diabetes mellitus (T2DM),[26] including new-onset diabetes,[27] and diabetic kidney disease.[28] UA levels are also associated with hepatic steatosis.[29] Thus, studying these markers in NAFLD patients with hyperuricemia makes sense. Our study aimed to investigate the predictive capacity of the TyG index and METS-IR index for NAFLD in individuals with HUA.

Materials and Methods
Participants
This study initially included 21,689 adults who had been checked up (including hepatic ultrasonic) at Zhenhai Lianhua Hospital, Ningbo, China, in 2020. The hospital's electronic medical record system was employed to compile participant data. Based on predefined inclusion and exclusion criteria, 1751 participants with excessive alcohol consumption and 14,401 participants without HUA were excluded from the analysis. Indicators with missing data exceeding 20% of the total were excluded, while those with missing data less than 20% underwent multiple imputations to fill in the gaps[30] (Figure 1). Ultimately, this study contained 5537 participants. Figure 2 shows the flowchart of the participants.

Inclusion criteria: UA concentrations above 420 μmol/L for males and 360 μmol/L for females; age ≥ 18 years.

Exclusion criteria: Diagnosed with viral liver disease or autoimmune liver disease; alcohol consumption: male ≥140 g/w or female ≥70 g/w.

Clinical Baseline Data
Information on participants' demographic information, vital signs, and laboratory tests was collected from the electronic medical record system. Clinical examinations were performed in the morning after an overnight fast, and participants avoided exercise the day before the examination. Standing height and weight were measured by the physician according to standard procedures. The seated blood pressure of the participants in a calm state was measured using an automatic sphygmomanometer. Fasting venous blood samples were collected for blood routine and biochemical analysis, including fasting blood glucose and lipid parameters.
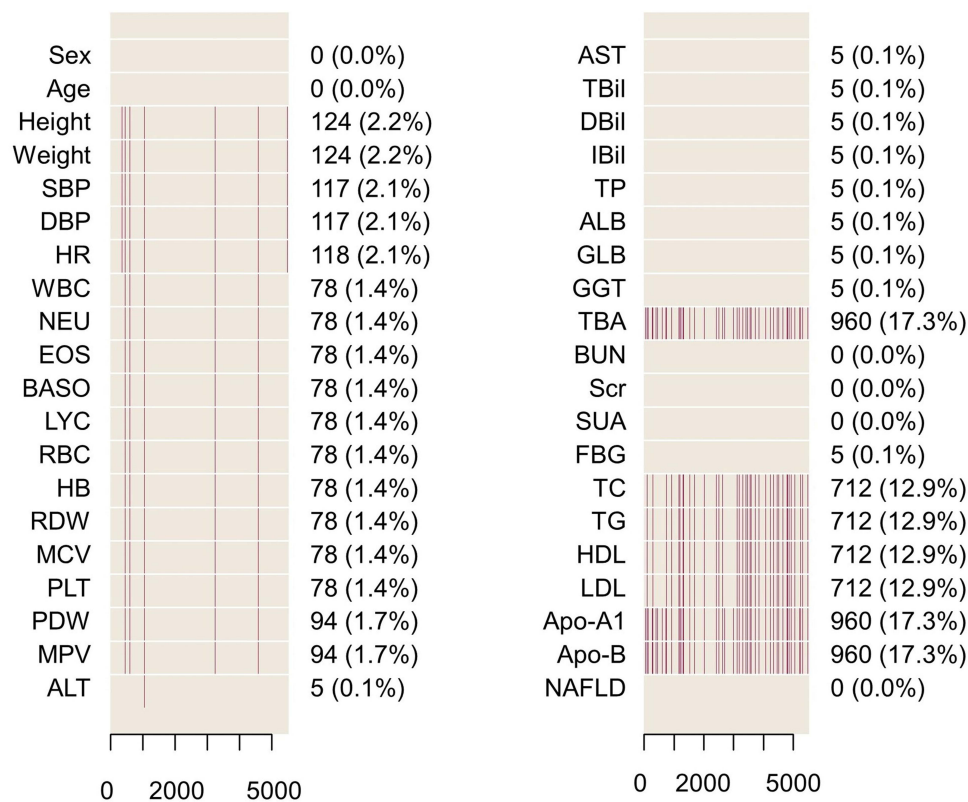
Variable	Missing	Variable	Missing
Sex	0 (0.0%)	AST	5 (0.1%)
Age	0 (0.0%)	TBil	5 (0.1%)
Height	124 (2.2%)	DBil	5 (0.1%)
Weight	124 (2.2%)	IBil	5 (0.1%)
SBP	117 (2.1%)	TP	5 (0.1%)
DBP	117 (2.1%)	ALB	5 (0.1%)
HR	118 (2.1%)	GLB	5 (0.1%)
WBC	78 (1.4%)	GGT	5 (0.1%)
NEU	78 (1.4%)	TBA	960 (17.3%)
EOS	78 (1.4%)	BUN	0 (0.0%)
BASO	78 (1.4%)	Scr	0 (0.0%)
LYC	78 (1.4%)	SUA	0 (0.0%)
RBC	78 (1.4%)	FBG	5 (0.1%)
HB	78 (1.4%)	TC	712 (12.9%)
RDW	78 (1.4%)	TG	712 (12.9%)
MCV	78 (1.4%)	HDL	712 (12.9%)
PLT	78 (1.4%)	LDL	712 (12.9%)
PDW	94 (1.7%)	Apo-A1	960 (17.3%)
MPV	94 (1.7%)	Apo-B	960 (17.3%)
ALT	5 (0.1%)	NAFLD	0 (0.0%)

Figure 1 Missing values of variables.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell count; NEU, neutrophil count; EOS, eosinophil count; BASO, basophil count; LYC, lymphocyte count; RBC, red blood cell count; HB, hemoglobin; RDW, red blood cell distribution width; MCV, mean red blood cell volume; PLT, platelet count; PDW, platelet distribution width; MPV, mean platelet volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; TP, total protein; ALB, albumin; GLB, globulin; GGT, gamma-glutamyl transpeptidase; TBA, total bile acids; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo-A1, apolipoprotein -A1; Apo-B, apolipoprotein-B; NAFLD, nonalcoholic fatty liver disease.

Definitions

Using liver biopsy as a reference, ultrasound had high sensitivity and specificity in distinguishing moderate to severe fatty liver from no steatosis.[31] Therefore, NAFLD was diagnosed by abdominal ultrasound after ruling out significant alcohol consumption (male ≥140 g/w or female ≥70 g/w), viral or autoimmune liver disease. Ultrasonography was performed by a sonographer who was blinded to the study design and laboratory data. Hepatic steatosis was diagnosed by characteristic echo patterns according to conventional diagnostic criteria. Typical ultrasonographic features are hyper echogenicity as compared to the right renal parenchyma, indistinct visualization of intrahepatic ductal structures, and attenuation of echoes in the distal region.[2] Weight divided by height squared was used to determine the body mass index (BMI). IR surrogates are the TyG index and the METS-IR index. These were computed utilizing the formulas below:

$$TyG = ln\left[\frac{TG(mg/dL)\times FBG(mg/dL)}{2}\right]^{19}$$

$$METS - IR = \frac{ln\left[2\times FPG\left(\frac{mg}{dL}\right)+TG(mg/dL)\right]\times BMI\left(kg/m^2\right)}{ln[HDL(mg/dL)]}^{18}$$

Statistical Analysis

The analysis of statistics was executed utilizing R version 4.1.2 software. Firstly, the normality of the relevant data was tested using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation for normally distributed variables. For variables that were not normally distributed, medians (interquartile range) are
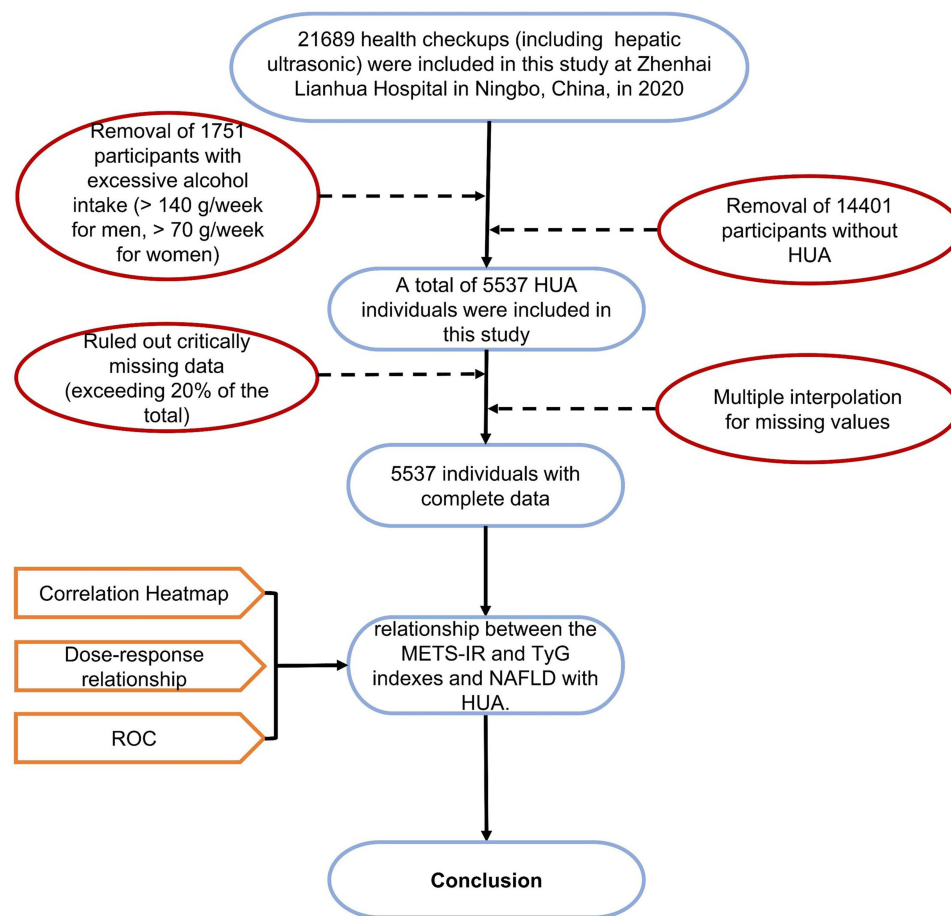
Figure 2 Flowchart of the participants.
Abbreviations: HUA, hyperuricemia; ROC, the receiver operating characteristic; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; NAFLD, nonalcoholic fatty liver disease.

reported. The Mann–Whitney U-test or independent sample t-test was utilized for the analysis of continuous variables. The chi-square test was utilized to evaluate the categorical variables, which were quantified as counts (%).

Multivariable logistic regression analysis was performed after adjusting for baseline age, DBP, HR, EOS, BASO, HB, MCV, PLT, AST, ALT, TP, GLB, GGT, Scr, SUA, TG, HDL, Apo-B, TyG, and METS-IR to ascertain the independent connection between IR surrogates and NAFLD with HUA. Furthermore, a restricted cubic spline (RCS) analysis was performed to explore any potential non-linear relationship between IR surrogates and NAFLD in individuals with HUA. The potential for prediction of the TyG and the METS-IR indexes for NAFLD with HUA was evaluated using the area under the receiver operating characteristic (ROC) curves (AUC). RCS analysis and ROC curves were implemented using the "rms" and "pROC" packages in the R software, respectively. The DeLong test was used to compare the statistical difference between AUCs. The researchers computed the Youden index, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) to conduct a comprehensive comparison of the predictive accuracy of the two IR surrogates. All statistical tests were two-tailed, and a significance level of $P < 0.05$ was considered statistically significant.

Results
Baseline Characteristics of the Study Population
A total of 5537 individuals underwent evaluation for this study, the median age of the participants was 47.00 (33.00, 61.00) years. Among them, there were 4483 (81.00%) males and 1054 (19.00%) females. Furthermore, 3167 (57.2%) of the participants were diagnosed with NAFLD. According to univariate analysis, patients with NAFLD exhibited a higher

likelihood of advanced age, elevated BMI, and increased susceptibility to dysregulated lipid metabolism, characterized by elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and apolipoprotein-B (Apo-B) as well as lower levels of high-density lipoprotein (HDL) (all $P < 0.001$). Additionally, the NAFLD group displayed higher values of white blood cell count (WBC), neutrophil count, eosinophil count, and lymphocyte count (LYC) than the non-NAFLD group. Notably, patients with NAFLD demonstrated markedly elevated values for both the METS-IR and TyG indices compared to those without the condition (all $P < 0.001$). Table 1 provides more basic information for participants.

Independent Risk Factors

We selected 35 variables with $P < 0.05$ in Table 1 to screen for independent risk factors. Before building the multivariable logistic regression model, the researchers examined the collinearity among the candidate variables by

Table 1 Univariate Analysis of NAFLD in the HUA Population

	Non-NAFLD	**NAFLD**	***P***
N	2370	3167	
Sex (Female), %	483 (20.40)	571 (18.00)	**0.03**
Age, years	43.00 (29.00, 60.00)	50.00 (35.00, 62.00)	**<0.001**
BMI, kg/m^2	23.05 (21.30, 24.91)	26.22 (24.43, 28.35)	**<0.001**
SBP, mmHg	128.00 (119.00, 138.00)	134.00 (125.00, 144.00)	**<0.001**
DBP, mmHg	77.65 (10.69)	82.02 (10.63)	**<0.001**
HR, times/min	79.00 (71.00, 88.00)	80.00 (72.00, 88.00)	**0.032**
WBC, ×10^9/L	5.90 (5.10, 6.90)	6.50 (5.60, 7.50)	**<0.001**
NEU, ×10^9/L	3.30 (2.70, 4.00)	3.70 (3.00, 4.40)	**<0.001**
EOS, ×10^9/L	0.11 (0.07, 0.19)	0.13 (0.08, 0.21)	**<0.001**
BASO, ×10^9/L	0.02 (0.01, 0.03)	0.02 (0.02, 0.03)	**<0.001**
LYC,×10^9/L	2.00 (1.60, 2.40)	2.20 (1.80, 2.60)	**<0.001**
RBC, ×10^{12}/L	5.03 (0.52)	5.14 (0.49)	**<0.001**
HB, g/L	152.00 (143.00, 161.00)	155.00 (146.00, 163.00)	**<0.001**
RDW, %	12.50 (12.20, 13.00)	12.60 (12.20, 13.00)	**<0.001**
MCV, fl	91.60 (89.00, 94.00)	91.00 (88.00, 94.00)	**<0.001**
PLT, ×10^9/L	229.00 (194.00, 267.00)	238.00 (201.00, 279.00)	**<0.001**
PDW, %	13.30 (12.10, 15.00)	13.30 (12.10, 14.90)	0.439
MPV, fl	11.05 (1.01)	11.01 (0.98)	0.126
ALT, U/L	19.00 (15.00, 26.00)	31.00 (22.00, 48.00)	**<0.001**
AST, U/L	22.00 (19.00, 27.00)	26.00 (22.00, 33.00)	**<0.001**
TBil, μmol/L	13.90 (10.90, 18.10)	13.70 (10.70, 17.60)	**0.021**
DBil, μmol/L	3.20 (2.60, 4.30)	3.00 (2.40, 3.90)	**<0.001**
IBil, μmol/L	10.70 (8.10, 13.90)	10.60 (8.00, 13.80)	0.433
TP, g/L	75.00 (3.91)	76.10 (4.03)	**<0.001**
ALB, g/L	46.04 (2.52)	46.09 (2.23)	0.422
GLB, g/L	28.80 (26.60, 31.10)	29.70 (27.50, 32.20)	**<0.001**
GGT, U/L	23.00 (17.00, 33.00)	36.00 (25.00, 56.00)	**<0.001**
TBA, μmol/L	2.66 (1.82, 3.99)	2.90 (2.03, 4.39)	**<0.001**
BUN, mmol/L	5.00 (4.29, 5.90)	5.04 (4.33, 5.86)	0.636
Scr, μmol/L	77.00 (69.00, 85.00)	76.00 (68.00, 84.00)	**<0.001**
SUA, μmol/L	450.00 (427.00, 484.00)	463.00 (432.00, 505.00)	**<0.001**
FBG, mmol/L	5.22 (4.92, 5.58)	5.45 (5.08, 5.89)	**<0.001**
TC, mmol/L	5.12 (0.99)	5.41 (1.03)	**<0.001**
TG, mmol/L	1.27 (0.93, 1.74)	1.91 (1.37, 2.70)	**<0.001**
HDL, mmol/L	1.16 (0.99, 1.41)	1.00 (0.87, 1.18)	**<0.001**

(Continued)

Table 1 (Continued).

	Non-NAFLD	**NAFLD**	**P**
LDL, mmol/L	3.00 (0.78)	3.20 (0.81)	**<0.001**
Apo-A1, g/L	1.36 (1.22, 1.53)	1.32 (1.19, 1.46)	**<0.001**
Apo-B, g/L	0.96 (0.25)	1.08 (0.26)	**<0.001**
TyG	8.61 (0.51)	9.06 (0.52)	**<0.001**
METS-IR	35.11 (5.72)	43.19 (6.87)	**<0.001**

Note: *P*-values less than 0.05 were bolded.
Abbreviations: NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell count; NEU, neutrophil count; EOS, eosinophil count; BASO, basophil count; LYC, lymphocyte count; RBC, red blood cell count; HB, hemoglobin; RDW, red blood cell distribution width; MCV, mean red blood cell volume; PLT, platelet count; PDW, platelet distribution width; MPV, mean platelet volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; TP, total protein; ALB, albumin; GLB, globulin; GGT, gamma-glutamyl transpeptidase; TBA, total bile acids; BUN, blood urea nitrogen; Scr, serum creatinine; SUA, serum uric acid; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo-A1, apolipoprotein -A1; Apo-B, apolipoprotein-B; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance.

analysis of covariance, in which variance inflation factors (VIF) >10 for WBC, NEU, METS-IR index, BMI, LDL, LYC, TC, TG, TyG index, red blood cell count, HDL. Ultimately, 20 variables (VIF < 10) were obtained by stepwise backward logistic regression analysis while retaining the IR surrogates. Furthermore, multivariable logistic regression analysis indicated that the TyG index (OR = 2.285, 95% CI: 1.525, 3.428) and METS-IR index (OR = 1.242, 95% CI: 1.219, 1.266) were all independent factors strongly associated with NAFLD (all $P < 0.001$), and the remaining independent risk factors were illustrated in Table 2.

Association Analysis of Independent Risk Factors

The correspondence of IR surrogates to other independent risk factors was visualized by heatmap (Figure 3). The METS-IR index indicated a strong positive correlation with both TG (r = 0.58, $P < 0.05$) and ALT (r = 0.44, $P < 0.05$). Meanwhile, TG and the TyG index (r = 0.97, $P < 0.05$) also exhibited a substantial positive connection. On the contrary, HDL displayed a relatively substantial negative association with the METS-IR index (r = −0.67, $P < 0.05$) and the TyG index (r = −0.44, $P < 0.05$) compared to other independent factors.

Table 2 Multivariable Logistic Regression Analysis

	P	**OR**	**95% CI**
Age (Per 10 years)	**<0.001**	1.48	1.39, 1.58
DBP (Per 10 mmHg)	**0.008**	1.10	1.03, 1.19
HR, times/min	**0.038**	0.94	0.88, 1.00
EOS, ×10⁹/L	0.109	0.56	0.27, 1.14
BASO, ×10⁹/L	**0.045**	1.06	1.00, 1.13
HB, g/L	0.181	1.00	1.00, 1.01
MCV, fl	**0.041**	0.98	0.97, 1.00
PLT, ×10⁹/L	**0.022**	1.00	1.00, 1.00
ALT, U/L	**<0.001**	1.06	1.05, 1.07
AST, U/L	**<0.001**	0.96	0.94, 0.97
TP, g/L	**<0.001**	1.11	1.06, 1.15
GLB, g/L	**<0.001**	0.92	0.88, 0.96
GGT, U/L	**<0.001**	1.01	1.00, 1.01
Scr, μmol/L	**<0.001**	0.98	0.98, 0.99

(*Continued*)

Table 2 (Continued).

	P	OR	95% CI
SUA, μmol/L	0.188	1.00	1.00, 1.00
HDL, mmol/L	**<0.001**	2.38	1.72, 3.29
TG, mmol/L	**<0.001**	0.65	0.53, 0.79
Apo-B, g/L	**0.009**	1.50	1.10, 2.04
TyG	**<0.001**	2.28	1.53, 3.43
METS-IR	**<0.001**	1.24	1.22, 1.27

Note: *P*-values less than 0.05 were bolded.
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; EOS, eosinophil count; BASO, basophil count; HB, hemoglobin; MCV, mean red blood cell volume; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; GLB, globulin; GGT, gamma-glutamyl transpeptidase; Scr, serum creatinine; SUA, serum uric acid; HDL, high-density lipoprotein; TG, triglycerides; Apo-B, apolipoprotein-B; TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance.

Dose-Response Relationship Between IR Surrogates and NAFLD

The RCS model was employed to simulate the nonlinear association between IR surrogates and the risk of NAFLD, and the results were visually presented (Figure 4). The analysis revealed a -log-shaped dose-response relationship between the METS-IR index and the risk of NAFLD ($P_{overall} < 0.001$, $P_{non-liner} = 0.002$). In contrast, a linear relationship was observed for the TyG index ($P_{overall} < 0.001$, $P_{non-liner} = 0.203$) based on the RCS model. Moreover, there was a positive correlation between the risk of NAFLD and IR surrogates, with the strength of this association intensifying as the levels of IR surrogates increased. Notably, the risk of NAFLD exhibited a substantial increase when the METS-IR index surpassed the threshold of 39.208 (OR = 1).

Predictive Value of Both IR Surrogates for NAFLD

Figure 5 illustrates the AUC values of the TyG index and METS-IR index for forecasting the risk of NAFLD with HUA. Both IR surrogates demonstrated promising predictive values for NAFLD with HUA. Compared with the TyG index (AUC = 0.734, 95% CI: 0.721~0.748), the METS-IR index had an improved AUC of 0.821 (95% CI: 0.810~0.832). Notably, the DeLong test showed that the METS-IR index demonstrated superior predictive value for NAFLD in HUA individuals ($P < 0.001$). Furthermore, the Youden index, NLR, PLR, and accuracy of the METS-IR index were 36.904, 0.258, 2.326, and 0.752, respectively. For the TyG index, these values were 8.870, 0.512, 2.272, and 0.670, respectively. Table 3 presents other indicators.

Discussion

In this study, the researchers analyzed the health check data of 5537 people with HUA from Ningbo, China. The findings revealed that the proportion of NAFLD within the HUA population was remarkably high at 57.20%, which surpassed the rate observed in the general population.[1,3] In addition, the results showed that both IR surrogates were significantly associated with NAFLD and the RCS analysis showed a nonlinear relationship between METS-IR and the risk of NAFLD in the HUA population. Additionally, while both IR surrogates demonstrated good predictive values for NAFLD, with AUC values exceeding 0.7, the METS-IR index exhibited superior predictive performance. These findings provide strong support for the utilization of the METS-IR index as a viable alternative screening instrument for the early detection of NAFLD within the HUA population.

The TyG index, initially introduced as an IR surrogate by Luis E Simental-Mendia in 2008,[19] has been extensively investigated for its associations with diabetes, hypertension, and cardiovascular diseases in recent years. Moreover, triglyceride-based markers are also associated with NAFLD and other inflammatory and metabolic disorders such as hypertension,[32] cardiovascular conditions,[33] and T2DM.[34] However, there is limited research on the relationship between
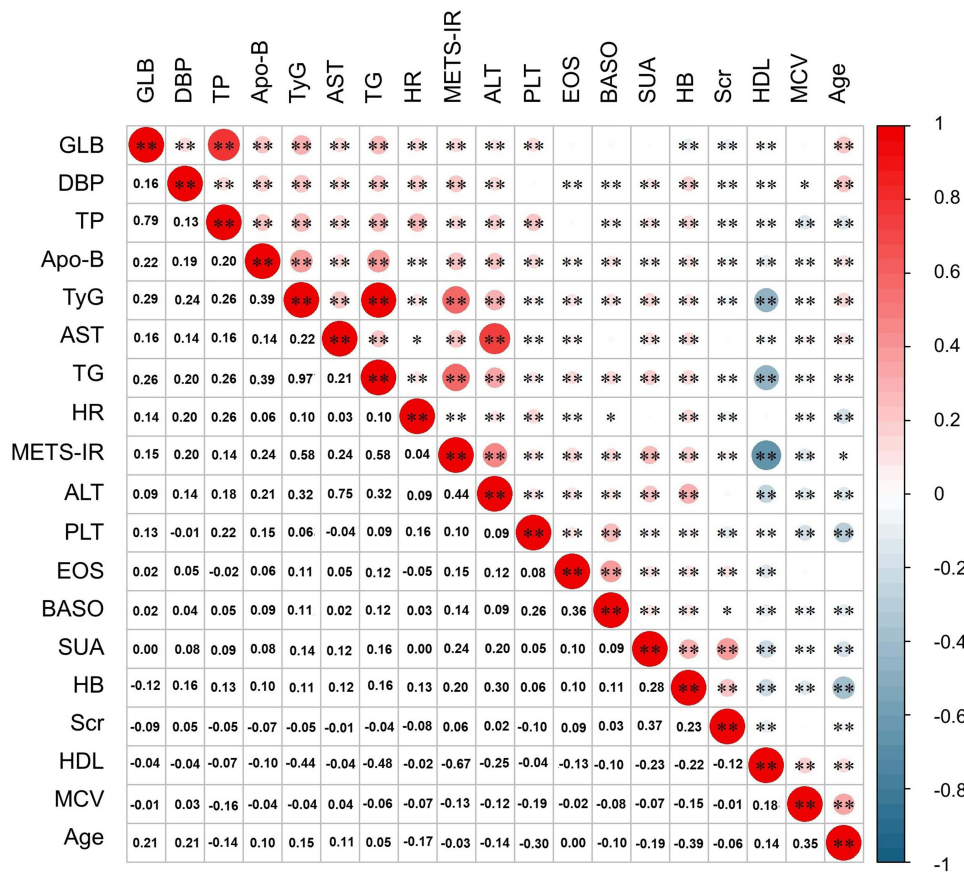
Figure 3 Association of independent risk factors.
Notes: The color determines the sign of the coefficient, where the red color represents a positive effect and the blue color indicates a negative one. The intensity of the color increases proportionally to the magnitude of the correlation coefficient among the genes. The values of the correlation coefficients are shown in the lower left corner. *$P < 0.05$, **$P < 0.001$.
Abbreviations: GLB, globulin; DBP, diastolic blood pressure; TP, total protein; Apo-B, apolipoprotein-B; TyG, triglyceride-glucose; AST, aspartate aminotransferase; TG, triglycerides; HR, heart rate; METS-IR, metabolic score for insulin resistance; ALT, alanine aminotransferase; PLT, platelet count; EOS, eosinophil count; BASO, basophil count; SUA, serum uric acid; HB, hemoglobin; Scr, serum creatinine; HDL, high-density lipoprotein; MCV, mean red blood cell volume.
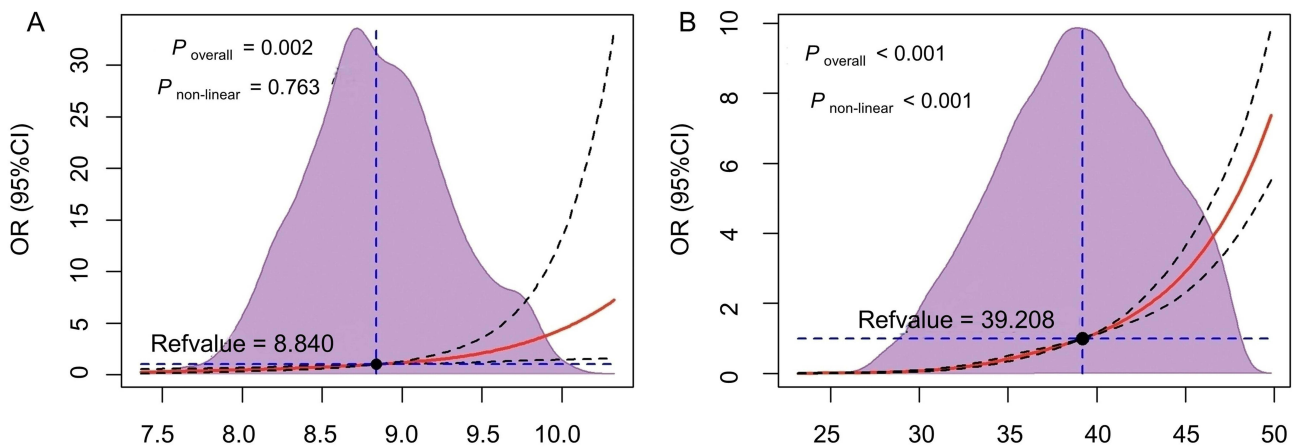
Figure 4 Dose–response association between the TyG index (**A**), the METS-IR index (**B**) and the risk of NAFLD with HUA modeled by using RCS.
Abbreviations: TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; NAFLD, nonalcoholic fatty liver disease; HUA, hyperuricemia.
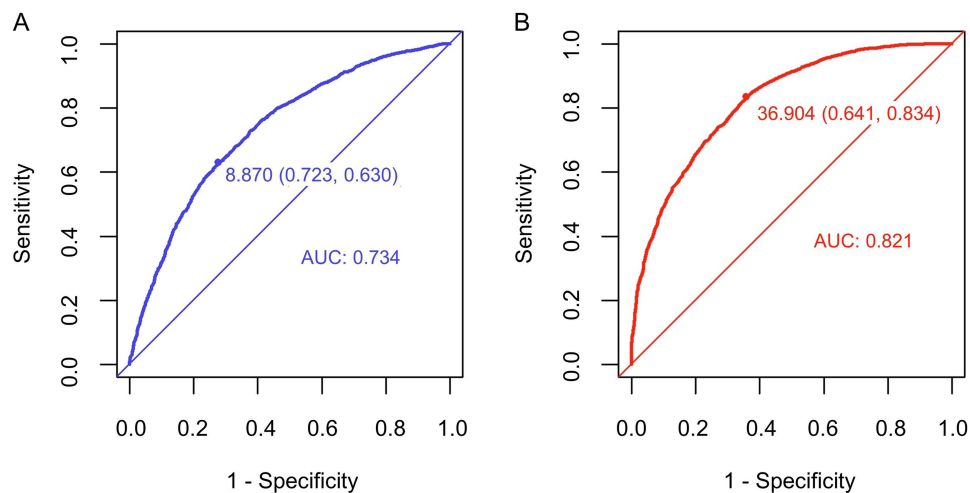
Figure 5 The ROC curves of the TyG index (**A**) and the METS-IR index (**B**) for prediction of NAFLD with HUA.
Abbreviations: TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; NAFLD, nonalcoholic fatty liver disease; HUA, hyperuricemia.

the TyG index and NAFLD. A study involving 10,761 healthy Chinese adults found that the TyG index could serve as a promising diagnostic tool for NAFLD in this population, with an optimal cut-off value of 8.5 (AUC = 0.782).[35] However, this study did not further analyze the dose-response relationship between the TyG index and NAFLD and only discussed the TyG index as a four-category variable. Moreover, Song et al[36] and Smiderle et al[37] demonstrated a significant association between the TyG index and NAFLD in youth and obese populations. However, our study provides a comprehensive assessment of the ability of the TyG index to screen and identify NAFLD in the HUA population to complement the existing literature on this topic.

The METS-IR index, originally proposed by Bello-Chavolla,[18] has been shown to outperform the TyG index in diagnosing incident T2DM in Mexican subjects. The METS-IR was also reported to be a better indicator of metabolic syndrome in obese subjects than HOMA-AD.[38] This superiority is attributed to the inclusion of anthropometric indicators in the calculation formula. Additionally, a study conducted in Korea with 15,798 participants demonstrated that the METS-IR index had better predictive capabilities for incident NAFLD compared to the HOMA-IR.[39] Similarly, our study observed that the METS-IR index (AUC = 0.821, 95% CI: 0.810~0.832) exhibited superior predictive value compared to the TyG index for the prevalence of NAFLD in the HUA population. There is a possible explanation for this. Prior research has demonstrated a temporal relationship wherein heightened UA levels antecede the onset of IR.[40] Furthermore, adiposity-related factors, including BMI, have been identified as potential mediators, capable of partially or entirely explaining the correlation between SUA and IR.[41] Moreover, peripheral IR enhances the uptake of FFA and TG in the liver.[42] Therefore, the METS-IR index incorporating BMI, FBG, HDL, and TG is more representative of

Table 3 Youden Index and Other Evaluation Measures of AUC

	TyG	**METS-IR**
Se (95% CI)	0.630 (0.613~0.647)	0.834 (0.821~0.847)
Sp (95% CI)	0 0.723 (0.705~0.741)	0.641 (0.622~0.661)
PLR (95% CI)	2.272 (2.118~2.438)	2.326 (2.199~2.460)
NLR (95% CI)	0.512 (0.486~0.539)	0.258 (0.238~0.281)
ACC	0.67	0.752
Youden	8.87	36.904

Abbreviations: TyG, triglyceride-glucose; METS-IR, metabolic score for insulin resistance; Se, sensitivity; Sp, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; ACC, accuracy; Youden, Youden index.

metabolic disturbances associated with NAFLD in the context of HUA. Furthermore, researchers also discovered a non-linear relationship between the METS-IR index and NAFLD within the HUA population, with a significant increase in the risk of NAFLD when the METS-IR index exceeded 39.208 (OR = 1).

The latest research has found that the prevalence of HUA in the adult population of China was 11.1% in 2015–2016, increasing to 14.0% in 2018–2019, showing an alarming rise over the course of three years.[43] The prevalence of NAFLD has increased with the alteration in food and lifestyle behaviors. Studies have shown that compared to the general population, individuals with HUA have a considerably higher incidence of NAFLD. A 4-year retrospective cohort study found that individuals with HUA had a cumulative incidence of NAFLD that was significantly higher than those with normal UA levels (29.0% vs 12.9%, $P<0.001$).[2] It is important to note that a severe type of NAFLD known as nonalcoholic steatohepatitis (NASH) can rapidly progress to end-stage liver disease. According to research, the progression rate from NAFLD to NASH ranges from 9% to 25%.[44] Within 8 years, approximately 21% to 26% of NASH patients develop cirrhosis.[45] Prior investigation has unequivocally established that HUA substantially elevates the risk of liver fibrosis among individuals with NAFLD.[46] Therefore, accurate, timely, and large-scale screening of NAFLD in HUA patients can achieve early intervention, prevent disease progression, and improve prognosis.

Our study includes the following strengths. Firstly, the study had a large sample size, which improved the credibility of the study. Secondly, this study reveals a -log-shaped non-linear relationship between the METS-IR index and NAFLD, which is a novel finding not previously shown. Thirdly, since commonly conducted biochemical tests in clinical include the necessary components (TG, FBG, HDL) for calculating the METS-IR index, individuals can make their initial assessment of NAFLD in a more efficient and cost-effective manner. It provides new perspectives and tools for risk assessment of NAFLD, which can promote more individualized and effective health management strategies in clinical practice.

This study has several limitations. First, compared to liver biopsy, the researchers solely relied on ultrasonography to identify NAFLD, potentially leading to missed cases. Second, given that this is a single-center cross-sectional study, caution should be exercised when extrapolating the research findings to the general population. Third, possible potential confounders such as socio-demographic variables and lifestyle, which are not available in the dataset, may lead to bias. Surrogates. Fourth, we did not compare the efficacy of the two IR surrogates in identifying NAFLD in a population without HUA, limiting the generalizability of the results.

Conclusion

This study demonstrates a significant association between the TyG and METS-IR indices and the presence of NAFLD in the HUA population. The findings establish the diagnostic value of the TyG and METS-IR indices for identifying individuals with NAFLD and also reveal dose-response relationships between these indices and the risk of NAFLD in the HUA population. Importantly, this research provides a cost-effective and practical approach to the management and prevention of NAFLD.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Medical School, Ningbo University, (In March 2023, renamed as The First Affiliated Hospital of Ningbo University), Ningbo, China (KY20191101). Written informed consent was obtained from all participants. The protocol of the study is compliant with the Declaration of Helsinki.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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