Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Diagnostic Utility of Triglyceride-Glucose Index in Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study on Lean Population

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Background: Approximately 10–20% of individuals with non-alcoholic fatty liver disease (NAFLD) are lean, and the underlying pathophysiology is not yet understood. This study aims to explore the characteristics and the diagnostic value of triglyceride-glucose index (TyG) in early diagnosis of lean NAFLD.

Methods: 99 patients with lean NAFLD and 1891 healthy controls were included in the health examination. The characteristics were compared between groups. Restricted cubic spline was utilized to analyze the relationship between TyG index and the risk of lean NAFLD. Logistic regression and receiver operating curve (ROC) were applied to explore the diagnostic value of TyG index for lean NAFLD.

Results: Overall, 99 (4.97%) patients had lean NAFLD. Patients with lean NAFLD have significant abnormal glycolipid metabolism and higher TyG index. Restriction cube spline analysis showed a significant dose-response relationship between the TyG index and risk of lean NAFLD. After adjusting for confounders, the relationship remained and the risk of developing lean NAFLD increased 2.99 times for per unit increase of TyG index (95% CI: 1.94, 4.67, $P<0.001$). The areas under the ROC of the TyG index for lean NAFLD detection were 0.851 (0.815 to 0.886).

Conclusion: The TyG index is positively associated with the risk of developing lean NAFLD and could be a useful marker for early diagnosis of lean NAFLD.

Keywords: lean non-alcoholic fatty liver disease, triglyceride-glucose index, insulin resistance

Introduction

Non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease (MASLD), is currently the most common of chronic liver disease worldwide, affecting at least one in four adults worldwide.[1] Although NAFLD is closely related to abdominal obesity and visceral fat accumulation, up to 40% of patients are not obese and almost 20% of patients have a BMI in the normal range, the so-called "lean NAFLD".[2] It is estimated that the prevalence of lean NAFLD is about 4.1% worldwide, particularly in Asians and middle-aged people, the prevalence of lean NAFLD is higher.[3,4] Patients with NAFLD have a significantly increased risk of cardiovascular disease (CVD) and cardiovascular mortality. Based on data from the National Health and Nutrition Examination Survey (NHANES), NAFLD is associated with a 23% increased risk of CVD, even after accounting for demographic, disease history, and metabolic factors.[5] CVD is also the leading cause of death in NAFLD patients. Results from two large prospective cohort studies showed that the risk of cardiovascular death was two to three times higher in NAFLD patients than in healthy controls.[6,7] This is mainly attributed to the common abnormalities of glycolipid metabolism, insulin

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resistance, immune and systemic inflammation, neuroendocrine homeostasis imbalance, thrombosis activation, and overactivation of the renin-angiotensin system in NAFLD patients.[8] Previous studies have shown that lean NAFLD patients have fewer metabolic disorders than overweight or obese NAFLD patients and are less likely to develop diabetes, hypertension, abdominal obesity, and metabolic syndrome.[4,9] However, other studies have found that patients with advanced lean NAFLD have more severe liver fibrosis and higher cardiovascular and all-cause mortality.[10,11] The pathophysiology, prognosis and management of lean NAFLD have become the focus of attention and research.

Insulin resistance (IR) refers to the reduced sensitivity of peripheral target organs or tissues to insulin, which is a central pathological mechanism in the development of NAFLD. Studies have shown that liver fat content of NAFLD patients is significantly positively correlated with fasting blood glucose and IR index HOMA-IR.[12,13] The hyperinsulinaemic-euglycaemic clamp has always been regarded as the "gold standard" for the assessment of insulin sensitivity. However, due to the complexity and invasiveness, its application in clinical practice has been limited. Many surrogated markers have been derived, such as the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and the glucose-triglyceride (TyG) index. As a simple surrogated indicator of IR, the TyG index can well reflect the degree of systemic insulin sensitivity and is widely used in clinical research and practice. Previous studies have shown that TyG and its associated metabolic index can well predict and diagnose NAFLD.[14] However, the diagnostic value of TyG index in lean NAFLD has not been reported. By continuously enrolled residents who underwent health checkups in our hospital, this study aims to compare clinical characteristics and metabolic profiles of patients with lean NAFLD and healthy controls matched by propensity scores, and explore the diagnostic value of TyG index for early detection lean NAFLD.

Methods

Study Population

The data for our analysis came from examinees aged over 18 years who underwent routine health examinations at the Second Affiliated Hospital of Xi'an Jiaotong University, a large tertiary hospital in Xi'an, between May 1 and June 30, 2020. Patients of NAFLD were diagnosed based on ultrasound features and those with BMI less than 23 kg/m^2 were defined as lean population. Enrolled participants were divided into lean NAFLD or lean healthy control according to their ultrasound examination. Individuals were excluded if (1) there are no abdominal ultrasound results, (2) basic anthropological data such as BMI and WC are missing, (3) BMI is greater than or equal to 23 kg/m^2, (4) data is missing on blood routine tests, incomplete lipids or liver function results, (5) subjects with a heavy alcohol drinking history (≥40 g/d for ≥5 years). Finally, 99 patients with lean NAFLD and 1891 healthy controls were included (Figure 1). The present study was a retrospective observational study that did not include data on patient privacy and was therefore exempt from informed consent by the patients. The study complied with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval number: 2022202). The diagnostic criteria for lean NAFLD are as follows: (1) Abdominal ultrasound indicates fatty liver, that is (a) the near-field echo of the liver is diffusely enhanced and exceeds the echo intensity of the kidneys; (b) the intrahepatic duct structure is not obvious; (c) gradual weakening of the far-field echoes of the liver. (2) BMI less than 23 kg/m^2 (Asian race).[15]

Serological and Biochemical Markers

The demographics, anthropological markers, smoking history were collected from electrical medical record. Fasting venous blood was collected from all patients in the morning on the day of health examination. The blood routine tests were measured using a Sysmex XN-9000 Automatic Hematology Analyzers (Sysmex, Kobe, Japan). The biochemical markers included total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), serum uric acid (SUA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), blood urine nitrogen (BUN) and serum creatinine. All of these serum biochemical markers were measured using a Beckman AU5800 Automatic Biochemical Analyzer (Beckman Coulter, Brea, CA, USA).

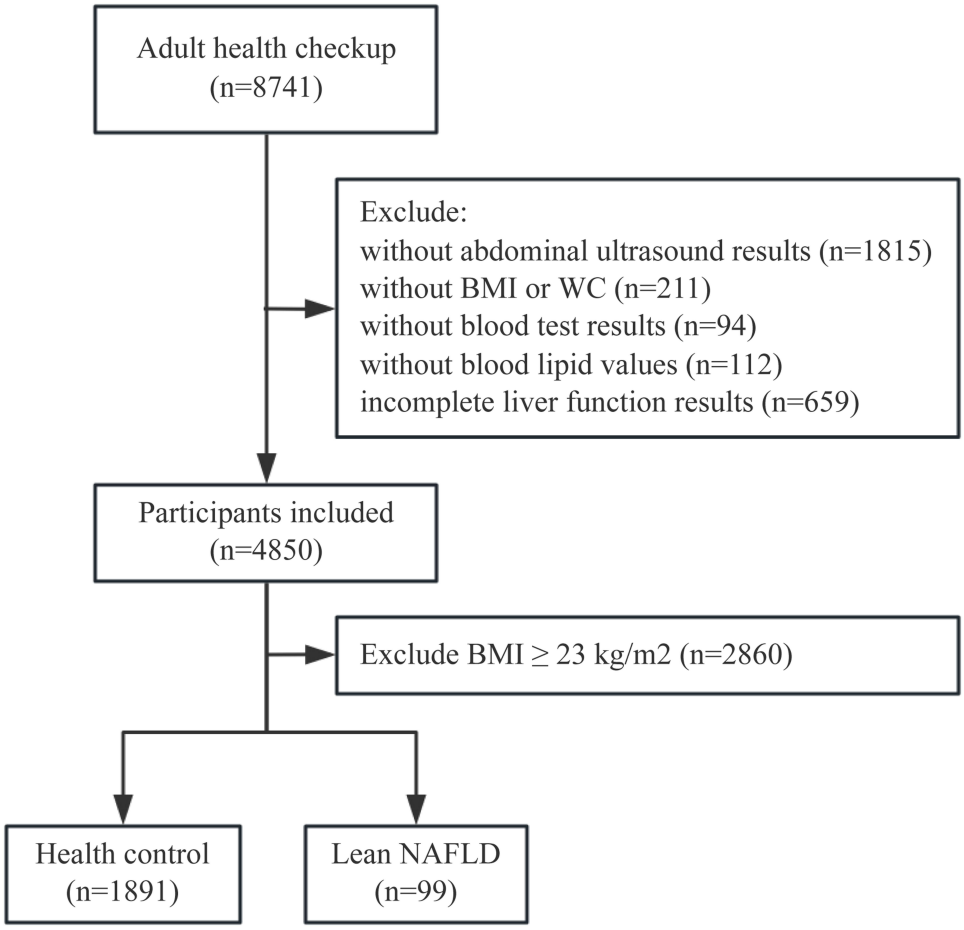

Figure 1 Inclusion and exclusion process of the study participants.

Abdominal Ultrasound

The abdominal ultrasonographic examinations for all patients was performed by a fixed senior and experienced clinician. The individuals should be examined after fasting for about 12 hours. The examinees took a supine position or left and right lateral position, fully expose their upper abdomen, and perform the examination with a convex matrix B-type ultrasonic diagnostic instrument (Philips) at a frequency of 3.5 MHz. The criteria for the diagnosis and degree of severity of ultrasonographic fatty liver were established according to the practice guideline of the American Gastroenterology Association.[16]

Surrogated Indicators Calculation

FLI was calculated based on TG, BMI, GGT and waist circumference (WC),[17] $FLI=e^{0.953\times lnTG+0.139\times BMI+0.718\times lnGGT+0.053\times WC-15.745}/(1+e^{0.953\times lnTG+0.139\times BMI+0.718\times lnGGT+0.053\times WC-15.745-15.745}) \times 100$. The TyG index was calculated using the following formula: TyG = ln [TG (mg/dL) × FBG (mg/dL) /2.[18] Systemic Inflammation Index (SII) was defined as platelet count × neutrophil count/lymphocyte count.

Propensity Score Matching

The propensity score (PS) of each participant was calculated based on age, gender, BMI, and waist circumference, and the "MatchIt" package in R software was used to match the lean NAFLD and healthy controls in a 1:2 ratio, where the caliper score was set to 0.02. Finally, 99 patients with lean NAFLD and 198 healthy controls were matched. The distribution and mean standard deviation of propensity scores between the two groups before and after matching are shown in Figure S1.

Statistical Analysis

Variables with missing values exceeding 25% were excluded to mitigate potential bias. Other variables with missing values were imputed using the random forest imputation method implemented in the missForest package of R software. Normality of continuous variables was determined by the Shapiro–Wilks test and expressed as medians with interquartile ranges due to non-normal distribution and compared with the nonparametric Mann–Whitney *U*-test. Categorical variables are presented as frequencies and percentages, and differences between groups were performed with a Pearson chi-square test or Fisher's exact test. The relationship between the TyG index and the risk of lean NAFLD were assessed with Spearman's rank correlation test or restricted cubic spline modelling. Multivariate *logistic* regression and LASSO (least absolute shrinkage and selection operator, Figure S2) were used to construct the models estimating the odds ratio (OR) and 95% confidence interval (CI) between the TyG index and lean NAFLD: model 1, unadjusted; model 2, adjusted for age, gender, BMI; model 3, adjusted for age, sex, BMI, DBP, waist circumference, lymphocyte, HDL-C, LDL-C, ALT and SUA. SPSS 26.0 (IBM SPSS Statistics, Armonk, NY, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis and graphics. A two-sided P-value < 0.05 was considered statistically significant for all analyses.

Results

Baseline Characteristics Before and After PS Matching

Finally, a total of 1990 subjects were included, including 99 patients (4.97%) with lean NAFLD. Before matching, there were significant differences in age, gender, BMI and waist circumference between the lean NAFLD and healthy controls. Patients with lean NAFLD tend to be older [46.0 (36.0, 56.0) vs 39.0 (31.0, 50.0) years] and male (56. 6% vs 32.9%), with a higher BMI [22.1 (21.4, 22.6) vs 20.9 (19.7, 21.9) kg/m2] and larger waist circumference [78 (72, 81) vs 70 (66, 76) cm] compared to the healthy control group. As for the physiologic parameters, there were significant differences in arterial blood pressure, blood cell count, hepatic transaminase, creatinine, blood lipids and FBG levels between the two groups. After 1:2 propensity score matching, significant differences in age, gender, BMI, and waist circumference between the two groups disappeared (Table 1). However, the mean arterial blood pressure was still significantly higher in the lean NAFLD group vs the healthy control group [systolic blood pressure 123 (116, 132) vs 117 (110, 127) mmHg, P<0.001; diastolic blood pressure 81 (74, 85) vs 76 (71, 83) mmHg, P=0.002].

Table 1 Comparison of General Characteristics Before and After PS Matching

Variables	Before Matching			After Matching		
	Healthy Control (N=1891)	Lean NAFLD (N=99)	*P* value	Healthy Control (N=198)	Lean NAFLD (N=99)	*P* value
Age, years	39.0 (31.0, 50.0)	46.0 (36.0, 56.0)	<0.001	46.0 (34.0, 55.2)	46.0 (36.0, 56.0)	0.596
Male, n (%)	623 (32.9)	56 (56.6)	<0.001	102 (51.5)	56 (56.6)	0.411
BMI, kg/m^2	20.9 (19.7, 21.9)	22.1 (21.4, 22.6)	<0.001	22.1 (21.5, 22.6)	22.1 (21.4, 22.6)	0.628
WC, cm	70.0 (66.0, 76.0)	78.0 (72.0, 81.0)	<0.001	77.0 (72.0, 82.0)	78.0 (72.0, 81.0)	0.862
SBP, mmHg	114.0 (106.0, 123.0)	123.0 (116.0, 132.0)	<0.001	117.0 (109.8, 127.0)	123.0 (116.0, 132.0)	<0.001
DBP, mmHg	74.0 (68.0, 81.0)	81.0 (74.0, 85.0)	<0.001	76.0 (71.0, 83.0)	81.0 (74.0, 85.0)	0.002
Smoker, n (%)	70 (3.70)	9 (9.09)	0.016	10 (5.05)	9 (9.09)	0.391
RBC count, ×10^9/L	4.52 (4.25, 4.85)	4.82 (4.45, 5.29)	<0.001	4.69 (4.36, 5.05)	4.82 (4.45, 5.29)	0.010
Hemoglobin, g/L	137 (128, 148)	149 (136, 161)	<0.001	143 (132, 155)	149 (136, 161)	0.015
Platelet count, ×10^9/L	214 (180, 251)	209 (187, 245)	0.934	210 (166, 250)	209 (187, 245)	0.351
Neutrophil, ×10^9/L	2.90 (2.35, 3.61)	3.16 (2.74, 4.01)	<0.001	2.94 (2.37, 3.54)	3.16 (2.74, 4.01)	0.003
Monocyte, ×10^9/L	0.32 (0.26, 0.40)	0.36 (0.29, 0.45)	0.001	0.33 (0.25, 0.40)	0.36 (0.29, 0.45)	0.005
Lymphocyte, ×10^9/L	1.67 (1.37, 1.98)	1.82 (1.51, 2.16)	0.002	1.73 (1.41, 2.02)	1.82 (1.51, 2.16)	0.046
Total bilirubin, μmol/L	10.6 (8.1, 14.1)	11.3 (7.7, 14.1)	0.894	10.8 (8.0, 15.0)	11.3 (7.7, 14.1)	0.659
Direct bilirubin, μmol/L	4.3 (3.4, 5.5)	4.1 (3.3, 5.1)	0.235	4.5 (3.4, 5.7)	4.1 (3.3, 5.1)	0.168
Indirect bilirubin, μmol/L	6.3 (4.4, 8.7)	6.9 (4.6, 8.9)	0.443	6.4 (4.5, 9.3)	6.9 (4.6, 8.9)	0.972

(*Continued*)

Table 1 (Continued).

Variables	Before Matching			After Matching		
	Healthy Control (N=1891)	Lean NAFLD (N=99)	*P* value	Healthy Control (N=198)	Lean NAFLD (N=99)	*P* value
ALT, IU/L	12 (9, 17)	21 (15, 29)	<0.001	14 (11, 21)	21 (15, 29)	<0.001
AST, IU/L	17 (15, 21)	21 (18, 24)	<0.001	19 (16, 22)	21 (18, 24)	<0.001
GGT, IU/L	12.0 (9.0, 16.0)	23.0 (16.0, 39.0)	<0.001	13.0 (12.0, 20.0)	23.0 (16.0, 39.0)	<0.001
ALP, IU/L	55.0 (46.0, 68.0)	68.0 (57.0, 77.0)	<0.001	60.0 (48.0, 71.0)	68.0 (57.0, 77.0)	<0.001
Albumin, g/L	46.0 (44.4, 47.5)	46.5 (45.1, 47.8)	0.029	46.1 (44.5, 47.6)	46.5 (45.1, 47.8)	0.077
BUN, mmol/L	4.00 (3.35, 4.80)	4.20 (3.40, 5.10)	0.085	4.10 (3.50, 5.00)	4.20 (3.40, 5.10)	0.662
Serum creatinine, mmol/L	59.0 (52.0, 68.0)	62.0 (55.0, 74.0)	0.008	64.0 (56.0, 73.0)	62.0 (55.0, 74.0)	0.558
TC, mmol/L	4.17 (3.71, 4.70)	4.53 (4.04, 5.15)	<0.001	4.33 (3.73,4.89)	4.53 (4.04, 5.15)	0.008
TG, mmol/L	0.88 (0.66, 1.22)	1.74 (1.26, 2.50)	<0.001	1.07 (0.68, 1.49)	1.74 (1.26, 2.50)	<0.001
HDL-C, mmol/L	1.38 (1.17, 1.57)	1.07 (0.95, 1.27)	<0.001	1.23 (1.06, 1.50)	1.08 (0.95, 1.27)	<0.001
LDL-C, mmol/L	2.37 (1.97, 2.87)	2.57 (2.19, 3.19)	<0.001	2.50 (2.08, 3.01)	2.57 (2.19, 3.19)	0.114
SUA, μmol/L	242 (205, 288)	301 (260, 361)	<0.001	267 (227, 318)	301 (260, 361)	<0.001
FBG, mmol/L	4.89 (4.66, 5.14)	5.17 (4.82, 5.64)	<0.001	4.98 (4.74, 5.31)	5.17 (4.82, 5.65)	0.004
TyG	8.15 (7.84, 8.50)	8.90 (8.60, 9.32)	<0.001	8.35 (8.01, 8.76)	8.90 (8.60, 9.32)	<0.001
FLI	4.06 (2.15, 8.31)	17.91 (12.07, 28.83)	<0.001	8.62 (4.86, 15.06)	17.92 (12.07, 28.83)	<0.001
SII	375.0 (274.1, 497.0)	395.9 (306.1, 485.4)	0.379	356.1 (243.1, 484.3)	395.9 (306.1, 485.4)	0.091

Abbreviations: BMI body mass index, WC waist circumference, SBP systolic blood pressure, DBP diastolic blood pressure, RBC red blood cell, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT γ-glutamyl transferase, ALP alkaline phosphatase, BUN blood urea nitrogen, TC total cholesterol, TG triglyceride, LDL low-density lipoprotein, HDL high-density lipoprotein, FBG fasting blood glucose, SUA serum uric acid, TyG index triglyceride glucose index, FLI fatty liver index, SII systemic inflammation index.

In terms of hematological indicators, the peripheral blood hemoglobin concentration and neutrophil, monocyte and lymphocyte count of lean NAFLD patients were slightly higher than those of healthy controls, and the difference was statistically significant ($P<0.05$). Regarding biochemical parameters, lean NAFLD patients had significantly higher levels of AST [21 (15, 29) vs 14 (11, 21) IU/L] and ALT [21 (18, 24) vs 19 (16, 22) IU/L]. Besides, there was a substantial difference between the GGT and ALP levels and the healthy control group [GGT 23.0 (16, 39) vs 13 (12, 20) IU/L, ALP 68.0 (57.0, 77.0) vs 60.0 (48.0, 71.0) IU/L, $P<0.001$]. BUN and serum creatinine did not significantly differ between the two groups in terms of renal function ($P > 0.05$). In terms of blood lipids, lean NAFLD patients had plasma levels of TC, TG, and LDL-C that were substantially higher than those of the healthy control group [TC 4.53 (4.04, 5.15) vs 4.33 (3, 73, 4.89) mmol/L, TG 1.74 (1.26, 1.74, 4.15). 2.50) vs 1.07 (0.68, 1.49) mmol/L, LDL-C 2.57 (2.19, 3.19) vs 2.50 (2.08, 3.01) mmol/L, all $P < 0.01$], while HDL-C levels were significantly reduced [1.08 (0.95, 1.27) vs 1.23 (1.06, 1.50) mmol/L, $P<0.001$]. FBG and SUA were substantially higher in NAFLD patients [FBG 5.17 (4.82, 5.65) vs 4.98 (4.74, 5, 31) mmol/L; SUA 301 (260, 361) vs 267 (227, 318) μmol/L, $P<0.01$]. Lean NAFLD patients showed significantly higher TyG and FLI compared to healthy controls [TyG 8.90 (8.60, 9.32) vs 8.35 (8.01, 8.76), FLI 17.92 (12.07, 28.83) vs 8.62 (4.86, 15.06), both $P < 0.001$]. The SII index showed a slight increase, but the difference was not statistically significant ($P = 0.091$, Table 1).

Correlation Between TyG Index and NAFLD and Its Predictors in Lean Population

As shown in Table 2, the TyG index was strongly positively associated with waist circumference (r=0.161), ALT (r=0.277), AST (r=0.232), SUA (r=0.358) and FLI (r=0.770, Table 2). The restricted cubic splines regression model revealed that the risk of NAFLD among lean populations increased linearly with increasing TyG index (*P* for non-linearity=0.200, Figure 2).

Association of Lean NAFLD with TyG

The associations between TyG index and the risk of lean NAFLD were analyzed using the logistic regression model. In the unadjusted model, TyG were positively correlated with lean NAFLD risk (OR=5.89, 95% CI: 3.49, 9.93, $P<0.001$). The positive correlations between TyG and lean NAFLD risk remained unchanged in the partly adjusted model 2 (OR=5.76, 95% CI: 3.99, 8.47, $P<0.001$) and fully adjusted model 3 (OR=2.99, 95% CI: 1.94, 4.67, $P=0.002$). No

Table 2 Correlations Between the TyG Index and NAFLD and Its Predictors in Lean Population

Variables	Correlation Coefficient	*P* value
BMI (kg/m^2)	0.028	0.635
WC (cm)	0.161	0.005
ALT (IU/L)	0.277	<0.001
AST (IU/L)	0.232	<0.001
SUA (μmol/L)	0.358	<0.001
FLI	0.770	<0.001

Abbreviations:: BMI body mass index, WC waist circumference, ALT alanine aminotransferase, AST aspartate aminotransferase, SUA serum uric acid, FLI fatty liver index.

multicollinearity was found among the significant predictors, with a kappa value of 10.637. In the fully adjusted model, the TyG index demonstrated a significant correlation with the risk of lean NAFLD when analyzed as a nominal variable (Q1 as the reference). The results revealed a progressive increase in risk associated with the TyG index: Q3 had an OR of 2.65 (95% CI: 0.84, 11.75, *P*=0.134); and Q4 had an OR of 5.92 (95% CI: 1.96, 25.77, *P*=0.005). The *P* value for trend was 0.037 (Table 3).

Diagnostic Value of TyG in NAFLD Detection Among Lean Populations

The ROC curve for the ability of TyG index to predict the risk of lean NAFLD is shown in Figure 3. The AUC was 0.851 (95% CI: 0.815, 0.886), and the ideal cut-off value of TyG was 8.42, with a diagnostic specificity of 70.2% and a sensitivity of 88.9% (Figure 3). The AUC of TyG was comparable to the FLI (AUC = 0.762, 95% CI: 0.706 to 0.818), with a *P* value of 0.756 by DeLong's test (Figure S3).

Discussion

In this cross-sectional study, 99 patients with lean NAFLD were enrolled based on abdominal ultrasound and BMI, and 198 healthy controls were propensity score matched. After the PS match, there were no significant differences in age, gender, BMI and waist circumference between the two groups. Compared with the control group, SBP and DBP of lean

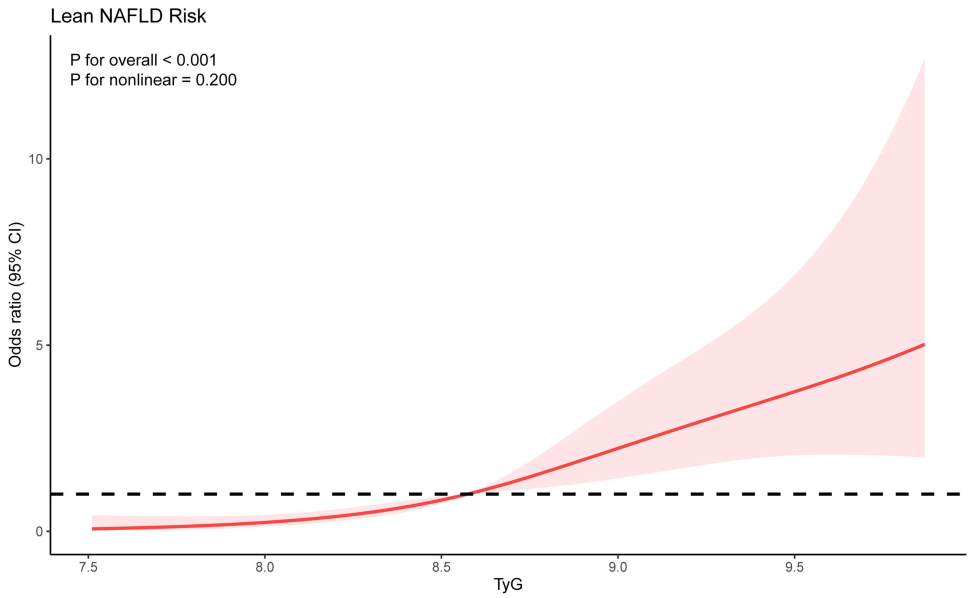

Figure 2 Restrictive cubic spline modelling of the association between NAFLD and TyG index among lean populations. Red area, 95% CI. Model was adjusted for gender, age, BMI and waist circumference.

Table 3 Logistic Regression for Risk of Lean NAFLD

Variable	Model 1			Model 2			Model 3		
	OR (95% CI)	*P* value	*P* for Trend	OR (95% CI)	*P* value	*P* for Trend	OR (95% CI)	*P* value	*P* for Trend
TyG[a]	5.89 (3.49, 9.93)	<0.001		5.76 (3.99–8.47)	<0.001		2.99 (1.94–4.67)	<0.001	
Quartile[b]			<0.001			<0.001			0.037
Q1 (n=75)	Ref.			Ref.			Ref.		
Q2 (n=74)	4.33 (1.50, 12.46)	0.007		0.63 (0.08–3.85)	0.617		0.50 (0.07–3.10)	0.459	
Q3 (n=74)	9.02 (3.25, 25.03)	<0.001		4.69 (1.53–20.45)	0.016		2.65 (0.84–11.75)	0.134	
Q4 (n=74)	23.00 (8.28, 63.89)	<0.001		19.04 (6.74–79.91)	<0.001		5.92 (1.96–25.77)	0.005	

Notes: Model 1: unadjusted, Model 2: adjusted for age, gender, BMI, Model 3: adjusted for age, sex, BMI, DBP, WC, lymphocyte, HDL-C, LDL-C, ALT and SUA. [a]TyG index as continuous variable. [b]TyG quartile: Q1(6.95, 8.14), Q2(8.14, 8.57), Q3(8.57, 8.94), Q4(8.94, 11.23).

NAFLD patients were increased, the hemoglobin concentration, neutrophil, monocyte and lymphocyte counts were slightly higher than those of healthy controls, and the levels of ALT, AST, GGT and ALP were significantly increased. Regarding glucolipid metabolism, plasma TC, TG, LDL-C, SUA and FBG were considerably higher in lean NAFLD patients than in healthy controls, while HDL-C was significantly lower. Compared to the healthy control group, the index of TyG and FLI was significantly increased in patients with lean NAFLD. Further analysis showed that the TyG index was independently correlated with the risk of lean NAFLD and showed a dose-response relationship. The TyG index has a better diagnostic value for lean NAFLD with an AUC of 0.851, and the specificity and sensitivity were of 70.2% and 88.9%, respectively.

The obesity pandemic has led to a sharp rise in the incidence of NAFLD, and the global prevalence of NAFLD in adults is over 25%.[19] Obesity and overweight have a strong correlation with the risk of NAFLD. According to reports, over 70% of individuals who are overweight or obese have NAFLD, and more than a third of them have developed steatohepatitis.[20] Nonetheless, a sizable fraction of NAFLD patients continue to fall within the normal BMI range. According to reports, about a fifth of patients with a BMI of less than 23 kg/m^2 are classified as lean NAFLD, and up to 40% of individuals with NAFLD are nonobese.[2] Even in the lean population, more than 10% of people suffer from

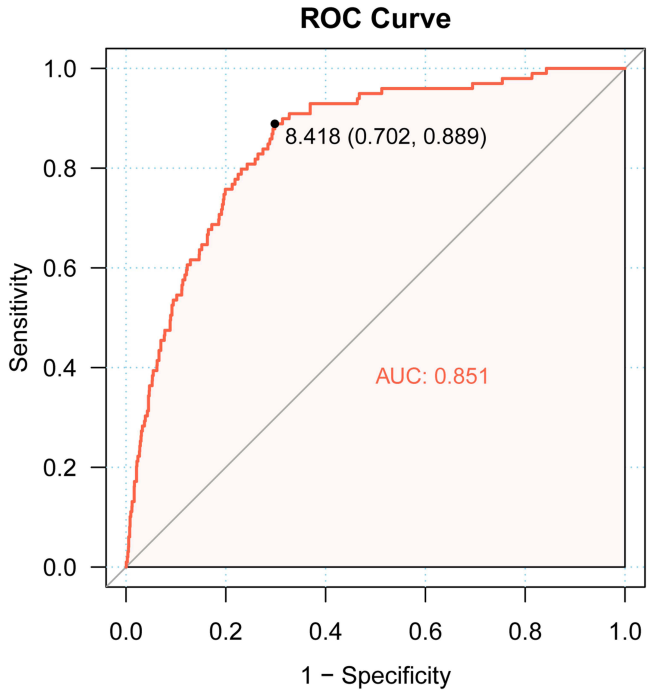

Figure 3 Receiver operating characteristic curves of TyG.

NAFLD.[4] This proportion is even higher in East Asian or middle age groups.[9] Lean NAFLD patients have relatively moderate metabolic abnormalities and are less likely to have diabetes, hypertension, abdominal obesity, and metabolic syndrome together than overweight or obese NAFLD patients.[4,9] Our research revealed that lean NAFLD patients had significantly higher arterial blood pressure, hemoglobin concentration, liver transaminase, TC, TG, LDL-C, SUA, and FBG than healthy controls, even after controlling for age, sex, BMI, and waist circumference. HDL-C, however, was much lower. Additionally, this agrees with the findings of a different recent study.[21] The above results suggest that lean NAFLD patients continue to have a higher prevalence of glucolipid metabolism disorders, which puts them at risk for CVD. Studies have even shown that the all-cause mortality of lean NAFLD patients is higher than that of non-lean NAFLD patients.[11]

An increasing number of studies have shown that NAFLD is an independent risk factor for CVD and the risk of cardiovascular morbidity and mortality is significantly higher than patients without NAFLD.[22] Because of the strong association between NAFLD and obesity and diabetes, the cardiovascular risk of patients with NAFLD is often attributed to obesity and the associated disorders of glucolipid metabolism. However, after adjusting for BMI, waist circumference and diabetes, the overall risk ratio decreases in most studies but still remains significant.[8] A significant proportion of lean NAFLD patients may still develop advanced steatohepatitis, liver fibrosis, and even hepatocellular carcinoma, and metabolic comorbidities related to CVD and liver-related death independent of obesity.[23] This suggests that the increased cardiovascular risk caused in NAFLD is independent of obesity and IR, and that low-level chronic inflammation and genetic variation may also play an important role in NAFLD.[24,25] Currently, the long-term CVD risk of lean NAFLD and its pathophysiology have not received enough attention and in-depth research. Our study found that the TyG index, as a great surrogate maker of IR, was significantly increased in lean NAFLD patients, while the SII index showed no significant difference between the two groups, regardless of whether PS matched or not, suggests that IR rather than systemic inflammation may play a more important role in lean NAFLD patients.

Currently, lean individuals in the general population are not recommended to undergo routine screening for NAFLD,[15] so lean NAFLD can easily be missed during health examinations. The FLI index is considered a good diagnostic tool for NAFLD screening, which was calculated using a sophisticated formula based on TG, BMI, GGT and waist circumference, and showed a high consistent correlation with NAFLD in different ethnic or geographical populations.[17,21] In some studies of healthy populations, the diagnosis of NAFLD is often based on the FLI index (eg FLI>60).[26] However, the measurement of the FIL index requires TG and liver function tests, the calculation of which is costly and complex, thus limiting its application in clinical practice. Second, FLI requires measurement of BMI and waist circumference, which are closely related to obesity, especially abdominal obesity, and therefore its predictive value is likely weakened in lean NAFLD. Hsu et al[21] included 4000 lean subjects in the health checkups and found that lean NAFLD patients (BMI < 24 kg/m^2) could be easily distinguished when FLI was adopted as the optimal cut-off value of 15, but the sensitivity was only 61.58% and the specificity was 77.37%. In contrast, the TyG index only requires fasting blood glucose and TG values, which is more economical and relatively simple to calculate, and therefore more suitable for promotion and application in grassroots communities or economically underdeveloped areas. In addition, our study found that the TyG index was significantly correlated with the risk of lean NAFLD, with a diagnostic sensitivity of 88.9%. This is important for the early detection of NAFLD and more helpful in lean populations and in reducing missed diagnoses. Finally, the TyG index can well reflect the degree of IR of the whole body, which is closer to the pathophysiology of lean NAFLD and reflects the severity of the disease.

This study also had several limitations. First, this study is a cross-sectional survey at a single center, and the participants are exclusively Han Chinese and long-term residents of Xi'an. Given the ethnic and regional differences, caution should be exercised when extrapolating research findings. Second, the subjects were all from the health checkups population of our hospital, which may have a selective bias. Third, this study was unable to carefully determine participants' history of diabetes and alcohol consumption, and the diagnosis of NAFLD only relied on abdominal ultrasound instead of liver biopsy for histopathological diagnosis. Finally, the correlation between TyG index and lean NAFLD severity has not been investigated. Therefore, further research is needed to verify our results here.

Conclusion

Together, our results confirmed that lean NAFLD patients still have significant disturbances in glucolipid metabolism, and their blood pressure, lipids and uric acid levels are significantly elevated. The TyG index was significantly associated with an increased risk of lean NAFLD in the health screening population and had high diagnostic efficacy with a sensitivity approaching 90%. The TyG index offers further advantages in screening NAFLD in lean populations and is expected to be promoted and applied in economically underdeveloped areas.

Data Sharing Statement

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

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 declare that they have no competing interests.

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