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Research Article

Triglyceride Glucose Index is Associated with Ultrasonographic Fatty Liver Indicator in Children and Adolescents with Non-alcoholic Fatty Liver Disease

Bitgyeol Kim, Hye Young Jin, Jong Seo Yoon, Eu Seon Noh, Il Tae Hwang
Department of Pediatrics, Kangdong Sacred Heart hospital, Hallym University College of Medicine, Seoul, Korea

What is already known on this topic?
Triglyceride glucose index has been shown to be a reliable surrogate marker for insulin resistance and non-alcoholic fatty liver disease in adults. The usefulness of this index as a predictive marker for the development and severity of non-alcoholic fatty liver disease in children and adolescents is unknown.

What this study adds?
The triglyceride glucose index could be a useful tool predicting severity of non-alcoholic fatty liver disease and determining the need for a liver biopsy.

Abstract
Objective: Non-alcoholic fatty liver disease (NAFLD) is defined as chronic hepatic steatosis and is becoming prevalent along with the increasing trend of obesity in children and adolescents. A non-invasive and reliable tool is needed to differentiate non-alcoholic steatohepatitis (NASH) from simple steatosis. This study evaluates the association between the triglyceride glucose (TyG) index and the ultrasonographic fatty liver indicator (US-FLI), and the possibility of using the TyG index for prediction of severity of pediatric NAFLD.
Methods: One hundred twenty one patients who were diagnosed with NAFLD by ultrasonography were included. They were categorized into 3 groups according to body mass index (BMI). Ninety two were obese, and 19 and 10 were overweight and normal weight, respectively.
Results: The homeostatic model assessment for insulin resistance (HOMA-IR) was highest in the group with obesity (P=0.044). The TyG index and US-FLI did not differ significantly among the 3 BMI groups (P=0.186). Fourteen (11.6 %) of the 121 patients had US-FLI ≥ 6, in whom the BMI-SDS and TyG index were higher (P=0.017, P=0.004), whereas HOMA-IR did not differ significantly from the group with US-FLI < 6 (P=0.366). US-FLI was associated with BMI-SDS and the TyG index. TyG index was significantly associated with US-FLI after adjustment for BMI-SDS. The cut-off value for the TyG index for predicting US-FLI ≥ 6 was 8.91, with an area under the curve of 0.785.
Conclusion: TyG index was associated with the degree of hepatic steatosis, suggesting that it might be a useful tool for predicting the severity of pediatric NAFLD.
Keywords: Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, triglyceride glucose index

Il Tae Hwang, Department of Pediatrics, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, 150, Seongan-ro, Gangdong-gu, Seoul, 05355, Republic of Korea
+82-2-2224-2257
ithwang83@kdh.or.kr
08.02.2024
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0000-0002-3885-4322

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive fat accumulation in the liver and can occur at various severities, from simple steatosis to fibrosis and liver cirrhosis. The incidence of NAFLD is increasing along with the worldwide increase of obesity in children (1). The prevalence of NAFLD increased from 8.2% in 2009 to 12.1% in 2018 in Korea (2,3). The prevalence of NAFLD diagnosed on ultrasonography was 11.2% in a study of Korean children and adolescents (4). Some studies reported that the prevalence of obesity in childhood and adolescence increased during the COVID-19 pandemic due to reduced physical activity and increased sedentary time (5,6,7). The prevalence of obesity increased from 11.5% in 2019 to 12.7% in 2020 in a nationwide study of Korean adolescents (8). Obesity in youth can be accompanied by metabolic alterations such as insulin resistance and metabolic syndrome (9,10). Insulin resistance and dyslipidemia are strongly associated with the pathogenesis of NAFLD (11), which can be divided into nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH) based on histology (12). NASH is defined when steatosis is accompanied by inflammation and hepatocyte damage proved by a histological examination, and it could progress toward cirrhosis, even in children (13,14). Thus, early discrimination of NASH from benign simple steatosis in obese children suspected to have NAFLD is crucial. Non-invasive and reliable tools to predict the severity of NAFLD in children are needed, given the increase of obesity and NAFLD in children, because liver biopsy is limited for young patients. Biomarkers of hepatic inflammation, oxidative stress, hepatic apoptosis, and fibrosis have been suggested; however, they are not easily measurable for clinical use (15). Ultrasonography is a convenient, widely available, and non-invasive modality. A non-invasive, semi-quantitative ultrasonographic fatty liver indicator (US-FLI) was recently suggested as a method for predicting hepatitis in patients with NAFLD and shown to correlate with histopathologic severity in adults (16). However, screening asymptomatic individuals with ultrasonography is not recommended. Therefore, simple indices based on laboratory findings or anthropometric data have been proposed to detect NAFLD. The triglyceride glucose (TyG) index was suggested as hyperglycemia, hyperinsulinemia, and hypertriglyceridemia are linked with triglyceride (TG) accumulation in hepatocytes and development of NAFLD. The TyG index has been shown to be a reliable surrogate marker for insulin resistance and NAFLD in adults (17,18). Evaluation of the usefulness of this index as a predictive marker for the development and severity of NAFLD in children and adolescents is needed. Therefore, this study evaluates the association between the TyG index and clinical parameters, including the US-FLI, and the usefulness of the TyG index for detecting the severity in pediatric NAFLD patients.

Materials and Methods

Patients

Subjects who were diagnosed with NAFLD were enrolled in this study after they visited the pediatric endocrinologic clinic between January 2021 and May 2022. NAFLD was suspected when alanine aminotransferase (ALT) was higher than 26 IU/L for males and 22 IU/L for females (19). Abdominal ultrasonography was performed by a single experienced radiologist, and the US-FLI score was determined. Subjects with a US-FLI score of at least 2 accompanied by elevated ALT were diagnosed with NAFLD. NAFLD was diagnosed in the absence of a known etiology of hepatitis such as viral hepatitis, Wilson disease, autoimmune hepatitis, or drug-induced hepatitis. Furthermore, subjects in this study with a US-FLI score of 6 or greater were suspected of having NASH (20).

Weight and height were obtained, and body mass index (BMI) was calculated as body weight (kg)/height (m^2). The enrolled subjects were divided into 3 groups (obesity, overweight, normal weight) according to BMI, with obesity defined as BMI ≥ 95th percentile on sex- and age-adjusted charts (21,22). Patients with BMI between the 85th and 95th percentiles were categorized as overweight. The rest of the subjects composed the normal weight group. Ninety two were obese, and 19 and 10 were overweight and normal weight, respectively. Severe obesity was defined as BMI above 99th percentile. Sex maturation ratings (SMR) of patients were described based on Tanner classification.

Venous samples for biochemical testing were obtained after a fast of at least 8 hours. Aspartate transaminase (AST), ALT, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG were measured using an automatic analyzer (Hitachi 7600, Hitachi, Tokyo, Japan). Serum insulin level was measured using a Wizard 1470 gamma counter (PerkinElmer). Non-HDL-C concentration was calculated as total cholesterol – HDL-C. The TyG index was calculated using the following formula: Ln[fasting TG (mg/dL) X fasting glucose (mg/dL)/2]. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as the product of the fasting insulin level (μU/mL) and the fasting glucose level (mmol/L), divided by 22.5. The HbA1c level was measured using high-performance liquid chromatography. Prediabetes and diabetes were defined as an HbA1c level of 5.7% to 6.4% and ≥ 6.5%, respectively (23). US-FLI was scored based on a published report as mild/moderate (score 2) or severe (score 3) by the intensity of liver/kidney contrast. Additional criteria included the presence (score 1 each) of posterior attenuation of the ultrasound beam, vessel blurring, difficult visualization of the gallbladder wall, difficult visualization of the diaphragm, and areas of focal sparing (16). The US-FLI was determined by summing all scores for a total range from 2 to 8 in cases of NAFLD (16).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA). Independent t-tests and one-way ANOVAs were performed to compare the means of clinical parameters according to US-FLI and BMI, respectively. Fisher's exact test was performed when analyzing categorical parameters such as sex. Associations between US-FLI and clinical variables were analyzed using simple and multiple regression analyses. A receiver operating characteristics (ROC) analysis was performed to obtain cut-off values and the area under the curve for the variables. A P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The clinical and biochemical characteristics of the study population according to BMI are shown in Table 1. Ninety-two of the 121 subjects with NAFLD were obese, and 19 and 10 subjects were overweight and normal weight, respectively. Eighty-three (68.6 %) of the 121 subjects were male. AST and ALT were higher in the groups with overweight or obesity than in the normal weight group (P=0.009, P=0.041). Biochemical parameters, fasting glucose, insulin, and lipid profiles other than high sensitivity C reactive protein and uric acid did not differ significantly among the 3 groups. HOMA-IR was highest in the group with obesity (P=0.044). The TyG index and US-FLI did not differ significantly among the 3 BMI groups (P=0.186). Two (10.5%) of the 19 subjects with overweight and 12 (13.0%) of the 92 subjects with obesity had US-FLI ≥ 6. Among 92 patients with obesity, 62 (67.4%) had severe obesity. The patients with severe obesity had higher US-FLI compared to the rest of patients with obesity (4.26 ± 1.20 vs 3.6 ± 1.22, P=0.008). Among 83 male patients, 65 presented pubertal sign with SMR 2 stage or above. The 65 male patients with pubertal sign showed higher HOMA-IR (P<0.001) and TyG index (P=0.009) in spite of similar BMI-SDS. US-FLI tended to be higher in patients with pubertal sign (4.08 ± 1.30 vs 3.56 ± 1.10, P=0.069). Among 38 female patients, 9 were prepubertal. The age of 29 female patients with SMR 2 stage or above ranged from 8.3 to 18.6 years, 11 of 29 were under 10 years of age. Four patients had type 2 diabetes, with the level of HbA1c ranging from 6.6–12.3%. Their BMI-SDS ranged from 2.43-4.74. All 4 of the subjects with diabetes had US-FLI ≥ 6. Sixteen patients had prediabetes; with HbA1c in the range of 5.7–6.2%, and 1 of them had US-FLI ≥ 6.

Clinical characteristics of subjects suspected of NASH (according to US-FLI ≥ 6)

The enrolled subjects were divided into 2 groups according to a US-FLI cut-off level of 6. Table 2 shows the clinical characteristics of the resulting groups. The US-FLI scores of the 2 respective groups were 3.7 ± 1.0 and 6.1 ± 0.4. Fourteen (11.6 %) of the 121 patients with NAFLD had US-FLI ≥ 6, and they were older (P=0.007) and had higher BMI-standard deviation scores (SDS) than the subjects in the other group (P=0.017). The levels of AST, ALT, and HbA1c tended to be higher in the group with US-FLI ≥ 6 than in the other group. Biochemical data, such as glucose, insulin, and lipid profile, did not differ significantly between the groups (Table 2). The TyG index was significantly higher in the group with US-FLI ≥ 6 (P=0.004), but HOMA-IR did not differ significantly between the groups (P=0.366). Simple linear regression analysis showed that US-FLI was associated with BMI-SDS, AST and ALT levels, HOMA-IR, and the TyG index (Table 3). However, the TyG index was the only variable that was significantly associated with US-FLI after adjustment for BMI-SDS.

Clinical parameters for predicting US-FLI ≥ 6

The cut-off values of 5 parameters (BMI-SDS, AST, ALT, HOMA-IR, TyG index) that could be used to predict US-FLI ≥ 6 are shown in Table 4. The cut-off value of HOMA-IR was 2.61 and had high sensitivity but low specificity. The cut-off values of BMI-SDS and the TyG index were 3.2 and 8.91, respectively. The ROC curves of the 5 parameters are depicted in Figure 1. The area under the curve (AUC) for the 5 parameters is shown in Table 4. The TyG index had the highest AUC score.

Discussion

This study evaluated the link between the TyG index and the degree of fatty infiltration in the liver to enable us to predict the severity of NAFLD using the TyG index in children and adolescents. Generally, screening for NAFLD should be considered for all children with obesity or overweight with risk factors such as central adiposity, insulin resistance, pre-diabetes, dyslipidemia, or family history of NAFLD/NASH (12). Currently, ALT is widely used to screen for NAFLD. The normal cut-off value for ALT can differ depending on the studied cohort. The 95th percentile level for ALT was 24.1 U/L for male children and 17.7 U/L for female children in a study using KNHANES 2010–2015 data (24). However, the serum ALT level can increase as a consequence of some acute diseases, and it does not exactly reflect the extent of fatty infiltration. In this study, the AST and ALT levels correlated with the US-FLI in a simple linear regression analysis. However, the adjusted β values were not significantly associated with US-FLI. On the other hand, the odds ratio of the TyG index for detecting NAFLD was higher than that of liver enzymes in children (25). In addition, the TyG index was associated with the US-FLI in a multiple linear regression analysis conducted in the present study, suggesting that the TyG index could be used to predict the severity of NAFLD.

A liver biopsy is the gold standard for diagnosing the severity of NAFLD. However, liver biopsy is a painful and invasive procedure that can produce complications such as infection or hemorrhage. Furthermore, a small biopsied sample of liver tissue might not represent the overall liver, and histologic findings of pediatric NASH can be different from those of adult NASH (26). The optimal timing of liver biopsies remains controversial, and no clear indication for liver biopsies has been established. Candidate criteria for immediate liver biopsy in pediatric NAFLD patients were suggested: young age, highly increased serum AST or ALT, very severe insulin resistance, suspected comorbidity or other chronic liver disease, and a family history of NAFLD (27). The European Society for Paediatric Gastroenterology Hepatology and Nutrition panel recommended that liver biopsy be performed after considering differential diagnoses and the risk of disease progression to liver cirrhosis (28). The North American Society for Pediatric Gastroenterology guideline also recommends liver biopsy in children with an increased risk of NASH or advanced fibrosis (12).

The US-FLI score was used to predict the severity of NAFLD in this study. Ultrasonography is non-invasive, widely available, and well tolerated as a first-line imaging study. However, interobserver and intraobserver variability and lack of objective quantitative analyses are limitations. Generally, ultrasonographic findings are classified using a 4-grade scale (normal, mild, moderate, and severe) (29). Despite those limitations, ultrasonographically quantified fat is associated with metabolic disturbances, and the histologic extent of steatosis correlates with a NASH diagnosis, suggesting that ultrasonographic score could be used to predict the severity of NAFLD (30,31). The US-FLI, a semi-quantitative ultrasonographic score, reflects the severity of hepatosteatosis and correlates with liver histology other than fibrosis, so it can help clinicians when selecting patients for liver biopsy (16). In addition, the US-FLI score was associated with liver enzymes; the waist-to-height ratio; and uric acid, adiponectin, and cytokeratin 18 levels in a pediatric study (20). A US-FLI score > 6 was suggested to indicate a relatively high risk for hepatitis, with a 71.4% positive predicted value(20).

We demonstrated an association between the TyG index and the degree of hepatic steatosis, indicating that the TyG index is a simple and cost-effective tool for predicting severe hepatic steatosis and considering liver biopsy in children and adolescents. Pediatric NAFLD can progress to clinically severe conditions such as cirrhosis and might present with an aggressive phenotype in the young population with obesity (32). In addition, severe phenotypes are expected to be more likely to progress to cirrhosis (33). All children and adolescents with obesity or overweight should receive lifestyle intervention counseling, and screening for NAFLD should be considered for early detection. If ALT is above the normal range, calculating the TyG index is helpful for identifying NAFLD and predicting the severity of steatosis, which could lead to more intensive lifestyle interventions. Modified TyG indices combine the TyG index with obesity-related parameters and have been reported to be superior to the TyG index for detecting NAFLD (4,34,35). Associations between other indices and the severity of hepatic steatosis need to be investigated.

Study limitations

This study has some limitations. First, we used ultrasonographic data to identify the patients suspected of having NASH. The data presented in this study was obtained retrospectively. Waist circumferences were not available in most patients although waist circumference better reflects abdominal obesity. Second, we used cross-sectional data from only Korean children and adolescents. Genetic predisposition could strongly affect the development of NAFLD. Third, this study included the NAFLD patients with relatively low or moderate severity considering the ages and follow-up periods of enrolled patients. Thus, the number of subjects with US-FLI score ≥ 6 was small. Nevertheless, few studies have investigated the association between the semi-quantitative US-FLI score and the TyG index, and our results suggest the usefulness of the TyG index in children and adolescents. Given the increasing number of children and adolescents with NAFLD, further longitudinal investigations that use non-invasive tools to evaluate NAFLD severity and response to treatment are required.

Conclusion

Pediatric NAFLD presents asymptomatic but could progress to fibrosis and cirrhosis. Thus, early recognition and proper intervention are required. No non-invasive modalities have been validated for assessing the severity of pediatric NAFLD until now. The TyG index could be a useful tool for predicting the severity of pediatric NAFLD and determining the need for a liver biopsy, as well as for detecting NAFLD in children and adolescents. Further research is needed to develop non-invasive indices or discover biomarkers that accurately reflect the progression or improvement of pediatric NAFLD.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea (IRB No. 2021-12-007). Our study was exempt from the requirement of informed consent because of the retrospective nature of the study and the anonymity of the clinical data.

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Competing interest

The authors certify that they do not have any financial or non-financial associations that might pose a conflict of interest in connection with the submitted article.

Author Contribution

Conceptualization: Jin HY, Hwang IT
Investigation: Kim B, Yoon JS, Jin HY, Noh ES
Original draft Writing: Kim B, Jin HY
Review and Editing: Kim B, Jin HY, Noh ES, Yoon JS, Hwang IT

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Figure 1. Ability of clinical variables to detect US-FLI ≥6, as shown by ROC analysis. The TyG index had the highest AUC score

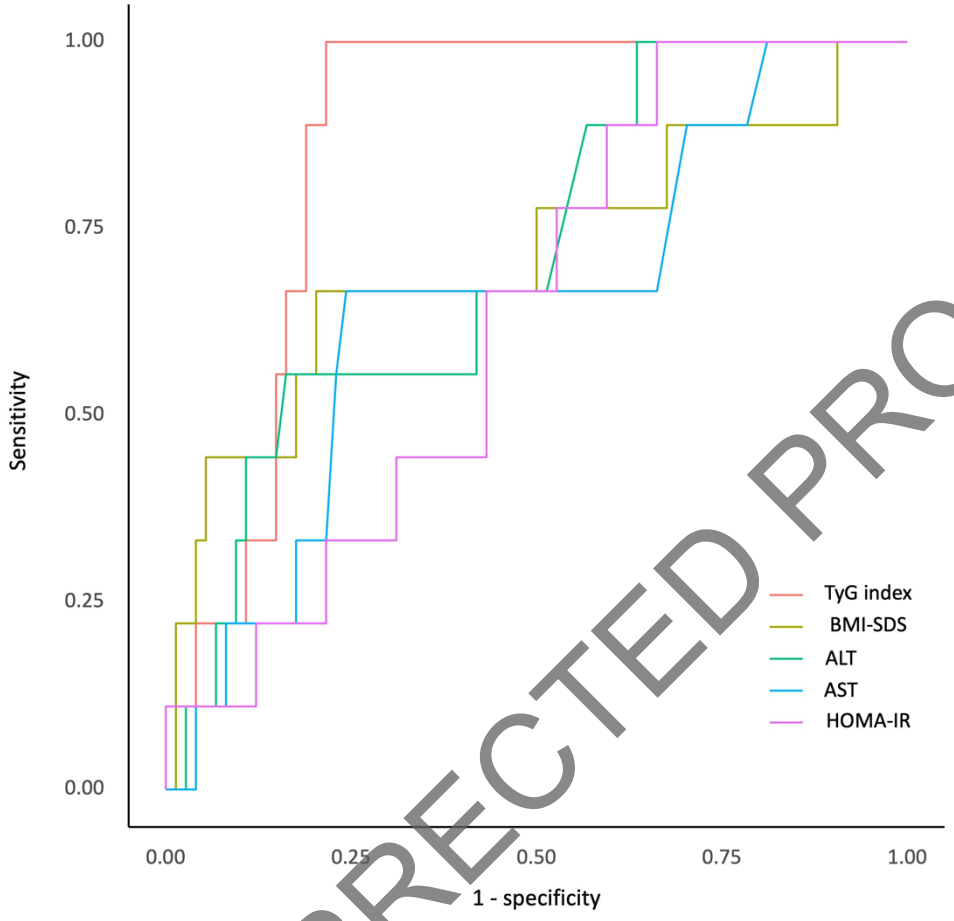

Table 1. Clinical and biochemical characteristics of the study population according to BMI
BMI, body mass index; SDS, standard deviation score; AST, aspartate transaminase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; hsCRP, high-sensitivity C reactive protein; Non-HDL-C, non-high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; TyG index, triglyceride glucose index; US-FLI, ultrasonographic fatty liver indicator

	Normal (n=10)	Overweight (n=19)	Obese (n=92)	*P*
Sex (M/F)	10/0	13/6	60/32	0.067
Age, years	11.7 ± 0.8	11.1 ± 1.4	11.4 ± 2.4	0.372
BMI, kg/m^2	21.3 ± 1.4	23.3 ± 1.6	28.0 ± 3.9	<0.001
BMI-SDS	0.7 ± 0.4	1.5 ± 0.2	2.8 ± 0.8	<0.001
AST, IU/L	42.8 ± 8.1	58.2 ± 37.7	55.7 ± 31.6	0.009
ALT, IU/L	66.3 ± 23.9	104.9 ± 81.1	89.0 ± 52.7	0.041
Glucose, mg/dL	94.5 ± 11.1	98.1 ± 9.6	101.9 ± 29.2	0.363
Uric acid, mg/dL	5.6 ± 1.0	5.7 ± 0.8	6.4 ± 1.4	0.015
Insulin, µU/mL	10.0 ± 5.1	13.9 ± 6.3	17.3 ± 11.3	0.056
HbA1c, %	5.2 ± 0.3	5.4 ± 0.1	5.7 ± 1.0	0.055
TC, mg/dL	159.3 ± 31.2	180.3 ± 35.7	178.0 ± 31.5	0.215
HDL-C, mg/dL	57.2 ± 19.8	53.9 ± 15.8	47.1 ± 9.7	0.15
LDL-C, mg/dL	92.9 ± 27.2	107.7 ± 29.0	111.4 ± 22.9	0.218
TG, mg/dL	103.8 ± 61.4	115.6 ± 61.2	141.4 ± 79.7	0.19
hsCRP, mg/L	0.4 ± 0.1	2.0 ± 2.3	2.3 ± 2.7	<0.001
Non-HDL-C, mg/dL	104.1 ± 33.2	128.7 ± 42.9	132.0 ± 29.8	0.113
HOMA-IR	2.4 ± 1.3	3.4 ± 1.7	4.4 ± 3.1	0.044
TyG index	8.3 ± 0.7	8.5 ± 0.7	8.7 ± 0.5	0.186
US-FLI	3.4 ± 1.2	3.8 ± 1.3	4.0 ± 1.2	0.269
US-FLI≥6 (%)	0 (0)	2 (10.5)	12 (13.0)	0.704

Table 2. Clinical and biochemical characteristics of the study population according to US-FLI

	US-FLI <6 (n=107)	US-FLI≥6 (n=14)	*P*
US-FLI	3.7 ± 1.0	6.1 ± 0.4	<0.001
Sex (M/F)	72/35	11/3	0.545
Age, years	11.1 ± 2.0	13.4 ± 2.6	0.007
BMI, kg/m^2	26.2 ± 3.8	30.7 ± 5.3	0.008
BMI-SDS	2.3 ± 0.9	3.2 ± 1.2	0.017
AST, IU/L	53.0 ± 29.9	70.5 ± 39.2	0.128
ALT, IU/L	85.4 ± 54.7	121.6 ± 63.7	0.06
Glucose, mg/dL	96.9 ± 8.6	129.1 ± 67.4	0.111
Uric acid, mg/dL	6.1 ± 1.2	7.3 ± 1.5	0.011
Insulin, µU/mL	16.6 ± 11.2	15.0 ± 4.5	0.43
HbA1c, %	5.5 ± 0.3	7.0 ± 2.3	0.081
TC, mg/dL	176.6 ± 32.3	177.9 ± 33.6	0.888
HDL-C, mg/dL	49.5 ± 12.2	44.6 ± 10.4	0.141
LDL-C, mg/dL	109.1 ± 24.5	111.7 ± 24.6	0.727
TG, mg/dL	128.4 ± 72.7	180.3 ± 90.4	0.068
hsCRP	2.2 ± 2.7	1.3 ± 0.6	0.041
Non-HDL-C, mg/dL	128.4 ± 32.3	136.5 ± 36.8	0.449
HOMA-IR	4.0 ± 2.7	5.4 ± 4.3	0.366
TyG index	8.6 ± 0.5	9.2 ± 0.6	0.004

US-FLI, ultrasonographic fatty liver indicator; BMI, body mass index; SDS, standard deviation score; AST, aspartate transaminase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; hsCRP, high-sensitivity C reactive protein; Non-HDL-C, non-high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; TyG index, triglyceride glucose index

Table 3. Associations between US-FLI and clinical and biochemical variables in a linear regression analysis

	β	95% CI	*P*	Adjusted β	95% CI	*P*
BMI-SDS	0.41	0.2-0.62	<0.001	0.27	0-0.53	0.05
AST, IU/L	0.01	0-0.02	0.013	-0.01	-0.02-0.01	0.334
ALT, IU/L	0.01	0-0.01	<0.001	0.01	0-0.01	0.127
HOMA-IR	0.09	0-0.18	0.048	0.02	-0.08-0.12	0.708
TyG index	0.65	0.25-1.05	0.002	0.54	0.04-1.04	0.037

US-FLI, ultrasonographic fatty liver indicator; BMI, body mass index; SDS, standard deviation scores; AST, aspartate transaminase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment for insulin resistance; TyG index, triglyceride glucose index

Table 4. Cut-off values and areas under the ROC curves for predicting US-FLI ≥ 6

ROC, receiver operating characteristics; US-FLI, ultrasonographic fatty liver indicator; AUC, area under the curve; BMI, body mass index; SDS, standard deviation score; AST, aspartate transaminase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment for insulin resistance; TyG index, triglyceride glucose index

	Cut-off values	AUC	Sensitivity/specificity, %
BMI-SDS	3.21	0.712 (0.539-0.885)	64/85
AST, IU/L	59.5	0.632 (0.457-0.807)	57/76
ALT, IU/L	126.5	0.690 (0.531-0.849)	57/84
HOMA-IR	2.61	0.634 (0.469-0.798)	100/34
TyG index	8.91	0.785 (0.659-0.911)	85/72