

## Original Article



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### Conflict of Interest

The author has no financial conflicts of interest.

# Significance of Triglyceride-to-High-Density Lipoprotein Cholesterol Ratio in Children with Non-Alcoholic Fatty Liver Disease

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## ABSTRACT

**Purpose:** Nonalcoholic fatty liver disease (NAFLD) is associated with obesity and metabolic syndrome. This study evaluated the significance of markers such as the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio and TG-glucose (TyG) indices in a group of patients with NAFLD.

**Methods:** We retrospectively analyzed the data of patients aged 5–18 years diagnosed with NAFLD between January 2014 and January 2021.

**Results:** Among the 151 patients with NAFLD, 79.5% were found to be obese, and the mean TG/HDL-C ratio ( $3.78 \pm 2.54$  vs.  $3.13 \pm 2.24$ ) and TyG index ( $4.69 \pm 0.28$  vs.  $4.56 \pm 0.30$ ) were slightly higher in patients with obesity compared to those without obesity. Patients with severe hepatic steatosis had a significantly higher mean TG/HDL-C ratio ( $4.11 \pm 2.16$  vs.  $3.11 \pm 2.30$ ,  $p=0.035$ ) than those with mild to moderate steatosis. Severe hepatic steatosis grade was defined as an area under the receiver operating characteristic curve of the TG/HDL-C ratio of 0.760 (95% confidence interval, 0.544–0.875), with an optimal cutoff value of 3.37.

**Conclusion:** A high TG/HDL-C ratio is associated with severe hepatic steatosis and diabetes mellitus in children with NAFLD. Measurement of this ratio can help clinicians in identifying patients and targeting them for treatment and follow-up.

**Keywords:** Non-alcoholic fatty liver disease; Pediatrics; Triglyceride to high-density lipoprotein cholesterol ratio; Triglyceride-glucose index; Marker

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of hepatic diseases that has been increasing rapidly and is associated with metabolic disorders such as obesity, dyslipidemia, and insulin resistance (IR) [1]. Moreover, the prevalence of obesity is increasing and is associated with a wide range of serious health complications, including metabolic syndrome and IR [2,3]. Adult studies have shown that the triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio is an accurate predictor of IR and metabolic syndrome [4,5].

Another simple index, the TG-glucose (TyG) index, which is calculated using fasting TG and glucose measurements, has also been proposed as a low-cost marker of IR [6,7]. These

markers are advantageous because they are easy to use and non-invasive. However, studies investigating the effectiveness of these indices in children with NAFLD are scarce. To date, noninvasive biomarkers such as blood tests have been proposed to identify advanced fibrosis in the liver or combined complications [8].

Therefore, we aimed to evaluate the significance of simple indices such as the TG/HDL-C ratio and the TyG index in pediatric patients with NAFLD and determine their relationships with the metabolic condition and grade of hepatic steatosis.

## MATERIALS AND METHODS

We analyzed the data of patients aged 5–18 years who were diagnosed with NAFLD between January 2014 and January 2021. Patients with laboratory or clinical evidence suggesting or confirming underlying chronic liver disease (e.g., viral hepatitis, autoimmune hepatitis, Wilson disease, or other liver diseases) were excluded. A trained technician measured body height and weight, and body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). After calculating the BMI, age- and sex-dependent z-scores were also evaluated. Laboratory tests for total cholesterol, TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and albumin were conducted.

### Characterizations

Obesity was defined as a BMI  $\geq$ 95th percentile for sex and age [9]. Two methods were used to confirm NAFLD: 1) a single pediatric radiologist reviewed abdominal ultrasound, and bright or hyperechoic lesions on liver imaging were considered a positive diagnosis, and 2) an ALT level of  $\geq$ 30 IU/L [10]. Diabetes mellitus (DM) was defined as either a fasting plasma glucose level of  $\geq$ 126 mg/dL, a 2-hour glucose tolerance test result of  $\geq$ 200 mg/dL, or typical symptoms of diabetes and a random plasma glucose level  $\geq$ 200 mg/dL or HbA1c  $\geq$ 6.5% [11]. Dyslipidemia was defined using the cut-off levels of TC  $\geq$ 200 mg/dL, LDL-C  $\geq$ 130 mg/dL, HDL-C  $<$ 40 mg/dL, TG  $\geq$ 130 mg/dL (age  $\geq$ 10 years) or  $\geq$ 100 mg/dL (age  $\leq$ 9 years) [12], and the TyG index was calculated as  $\ln$  [TG (mg/dL)  $\times$  fasting glucose (mg/dL)/2] [13]. The levels of steatosis were classified with sonographic findings as follows: “mild; the echotexture of the liver is normal” (grade I), “moderate; a slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and of the portal vein wall” (grade II), or “severe; a moderate increase of liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm” (grade III) [14].

### Statistical methods

Continuous data were expressed as mean  $\pm$  standard deviation, and comparisons were made using the Mann-Whitney U-test or Student's *t*-test. Discrete data were expressed as numbers and percentages and compared using Fisher's exact or chi-square tests. We used the odds ratio for logistic regression models to evaluate the factors associated with the severe hepatic steatosis grade. Receiver operating characteristic (ROC) curve analysis was used to determine the relationship between hepatic steatosis grade and TG/HDL-C ratio. ROC curves were plotted to illustrate the trade-off between specificity and sensitivity to identify adjusted cutoff values and 95% confidence intervals (CIs). Statistical significance was set at  $p < 0.05$ . Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Co.).

### Ethical considerations

This retrospective analysis was approved by the Institutional Review Board of Chungnam National University Hospital and conducted in accordance with the Declaration of Helsinki (IRB number: 2021-04-105). Informed consent was waived due to the retrospective nature of this study.

## RESULTS

Of the 151 patients with NAFLD, 121 (80.1%) were male, and the overall mean age was 12.22±3.07 years.

**Table 1** presents the characteristics of all the patients in relation to obesity. Obesity was confirmed in 79.5% (120/151) of patients, and the mean TG/HDL-C ratio (3.78±2.54 vs. 3.13±2.24) and mean TyG index (4.69±0.28 vs. 4.56±0.30) were slightly higher in patients with obesity than in those without obesity, although significant differences were not observed. Other laboratory and sonographic findings did not differ between the two groups.

**Table 2** shows the characteristics of patients in relation to the hepatic steatosis grade. The patients with severe hepatic steatosis were older (13.6 vs. 11.8 years,  $p=0.001$ ) and more obese (BMI z-score: 3.85 vs. 2.05,  $p=0.013$ ) than the mild to moderate group. The mean TG/HDL-C ratio was significantly higher for the severe hepatic steatosis group of patients (4.11±2.16) than for the mild to moderate group (3.11±2.30,  $p=0.035$ ). The mean TyG index was also higher for the severe hepatic steatosis group (4.75±0.26) than for the mild to moderate group (4.52±0.30,  $p=0.055$ ), although no significant difference was observed. Except for HDL-C levels, other laboratory findings were not different between the two groups.

**Table 1.** Clinical and laboratory characteristics of NAFLD patients in relation to obesity

Variable	Total (n=151)	Obesity (n=120)	Non-obesity (n=31)	p-value
Age (yr)	12.22±3.07	11.32±2.90	14.21±2.59	0.117
Male	121 (80.1)	98 (81.7)	22 (71.0)	0.244
BMI z-score	3.16±1.18	3.71±1.66	1.14±0.57	0.025
Family history of DM and/or dyslipidemia	9 (6.0)	8 (6.7)	1 (3.2)	0.414
AST (IU/L)	55.91±35.57	56.24±34.70	54.77±39.36	0.372
ALT (IU/L)	101.48±63.65	102.73±63.12	95.54±66.52	0.203
Albumin (g/dL)	4.45±0.27	4.43±0.26	4.53±0.28	0.690
Total bilirubin (mg/dL)	0.75±0.80	0.75±0.88	0.77±0.33	0.437
Fasting glucose (mg/dL)	98.13±27.52	101.52±33.72	97.25±25.74	0.311
Total cholesterol (mg/dL)	178.56±31.29	191.43±33.92	175.45±29.95	0.762
LDL-C (mg/dL)	111.72±32.84	132.52±40.81	107.37±29.44	0.146
HDL-C (mg/dL)	46.55±14.25	42.59±13.81	47.52±14.27	0.205
TG (mg/dL)	136.23±67.84	136.28±69.08	135.18±62.24	0.163
Presence of DM and/or dyslipidemia	54 (35.8)	43 (35.8)	11 (35.5)	0.573
Hepatic steatosis				0.281
Mild	64 (42.4)	49 (40.8)	15 (48.4)	
Moderate	51 (33.8)	40 (33.3)	11 (35.5)	
Severe	36 (23.8)	31 (25.9)	5 (16.1)	
TG/HDL-C ratio	3.34±2.30	3.78±2.54	3.13±2.24	0.078
TyG index	4.66±0.29	4.69±0.28	4.56±0.30	0.153

Values are presented as mean±standard deviation or number (%).

NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, DM: diabetes mellitus, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, TyG: TG-glucose.

\*TyG index was calculated as  $\ln [TG (mg/dL) \times \text{fasting glucose} (mg/dL)]/2$ .

**Table 2.** Clinical and laboratory characteristics of NAFLD patients in relation to hepatic steatosis grade

Variable	Severe (n=36)	Mild to moderate (n=115)	p-value
Age (yr)	13.62±2.58	11.83±3.09	0.001
Male	33 (91.7)	88 (76.5)	0.034
BMI z-score	3.85±1.41	2.05±0.43	0.013
Family history of DM and/or dyslipidemia	2 (5.6)	7 (6.1)	0.634
AST (IU/L)	57.47±38.15	55.46±34.89	0.252
ALT (IU/L)	99.28±54.57	102.17±55.47	0.153
Albumin (g/dL)	4.42±0.28	4.46±0.26	0.430
Total bilirubin (mg/dL)	0.81±0.42	0.73±0.89	0.217
Fasting glucose (mg/dL)	102.42±28.74	96.77±27.11	0.110
Total cholesterol (mg/dL)	179.65±30.47	175.26±33.96	0.132
LDL-C (mg/dL)	115.24±31.46	110.58±33.44	0.125
HDL-C (mg/dL)	40.28±10.40	48.36±13.72	0.021
TG (mg/dL)	148.66±74.31	132.17±65.51	0.120
Presence of DM and/or dyslipidemia	17 (47.2)	37 (32.2)	0.075
TG/HDL-C ratio	4.11±2.16	3.11±2.30	0.035
TyG index	4.75±0.26	4.52±0.30	0.055

Values are presented as mean±standard deviation or number (%).

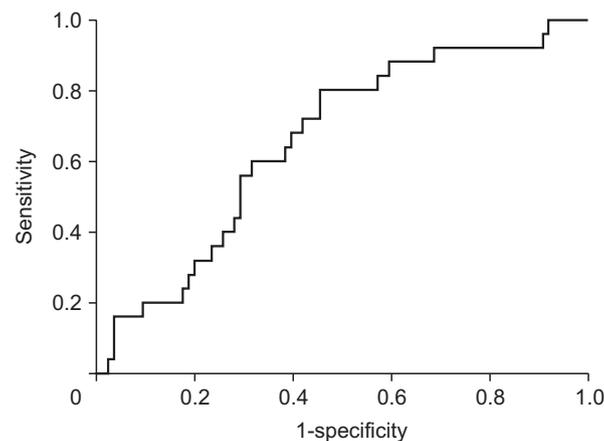
NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, DM: diabetes mellitus, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, TyG: TG-glucose.

\*TyG index was calculated as  $\ln [TG (mg/dL) \times \text{fasting glucose} (mg/dL) / 2]$ .

**Fig. 1** shows the ROC curves for the prediction models used to identify patients with severe hepatic steatosis. To identify the grade of severe hepatic steatosis, the area under the curve of ROC for the TG/HDL-C ratio was defined as 0.760 (95% CI, 0.544–0.875). The sensitivity and specificity were 75.0% and 65.9%, respectively, and the optimal cutoff TG/HDL-C ratio was 3.37.

After determining the cutoff level, the patients were divided into two groups: those with an elevated TG/HDL-C ratio ( $\geq 3.37$ ) and those with a ratio of  $< 3.37$ . **Table 3** shows the characteristics of patients in relation to their TG/HDL-C ratios. Higher total cholesterol levels were observed in participants with a higher TG/HDL-C ratio than in those with a lower TG/HDL-C ratio. In addition, a TG/HDL-C of  $\geq 3.37$  was closely correlated with the presence of DM and/or dyslipidemia.

Univariate analysis found that older age, male sex, higher BMI z-scores and TG/HDL-C ratios, and lower HDL-C levels were associated with severe hepatic steatosis in patients with NAFLD.



**Fig. 1.** Receiver operating characteristic curves as predictive models for differentiating subjects with severe hepatic steatosis.

**Table 3.** Clinical and metabolic characteristics of NAFLD patients in relation to the TG/HDL-C ratio

Variable	TG/HDL-C ratio $\geq 3.37$ (n=65)	TG/HDL-C ratio $< 3.37$ (n=86)	p-value
Age (yr)	13.19 $\pm$ 2.78	11.69 $\pm$ 2.80	0.754
Male	49 (75.4)	72 (83.7)	0.180
BMI z-score	3.59 $\pm$ 1.31	1.98 $\pm$ 0.62	0.045
Family history of DM and/or dyslipidemia	6 (9.2)	3 (3.5)	0.227
AST (IU/L)	57.88 $\pm$ 37.89	57.42 $\pm$ 36.22	0.731
ALT (IU/L)	106.81 $\pm$ 66.02	106.42 $\pm$ 67.47	0.804
Albumin (g/dL)	4.41 $\pm$ 0.30	4.47 $\pm$ 0.24	0.195
Total bilirubin (mg/dL)	0.90 $\pm$ 1.32	0.71 $\pm$ 0.32	0.132
Fasting glucose (mg/dL)	101.21 $\pm$ 34.95	96.56 $\pm$ 26.58	0.412
Total cholesterol (mg/dL)	193.46 $\pm$ 37.18	171.77 $\pm$ 25.43	0.001
LDL-C (mg/dL)	123.00 $\pm$ 34.18	102.29 $\pm$ 29.54	0.165
HDL-C (mg/dL)	37.08 $\pm$ 6.52	54.02 $\pm$ 14.46	$< 0.001$
TG (mg/dL)	194.29 $\pm$ 54.53	90.96 $\pm$ 35.78	0.005
Presence of DM and/or dyslipidemia	36 (55.4)	18 (20.9)	$< 0.001$
Hepatic steatosis			0.042
Mild	19 (29.2)	45 (52.3)	
Moderate	24 (36.9)	27 (31.4)	
Severe	22 (33.9)	14 (16.3)	

Values are presented as mean $\pm$ standard deviation or number (%).

NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, DM: diabetes mellitus, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride.

**Table 4.** Factors associated with severe hepatic steatosis grade in NAFLD patients by univariate and multivariate analyses

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value*
Age (yr)	1.19 (1.099–2.306)	0.035	1.09 (0.898–1.335)	0.173
Male	1.27 (0.959–5.876)	0.048	1.58 (1.142–4.876)	0.058
BMI z-score	1.435 (0.976–3.632)	0.035	1.14 (0.976–1.530)	0.045
HDL-C (mg/dL)	0.747 (0.447–2.125)	0.025	0.685 (0.352–1.529)	0.035
TG/HDL-C ratio	2.37 (0.993–4.539)	0.030	2.89 (0.822–5.233)	0.033

NAFLD: non-alcoholic fatty liver disease, OR: odds ratio, CI: confidence interval, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride.

\*Adjusted for age, sex.

In the multivariate analysis, higher BMI z-scores, TG/HDL-C ratios, and lower HDL-C levels were positively correlated with severe hepatic steatosis. **Table 4** shows the related factors for the grade of severe hepatic steatosis.

## DISCUSSION

In this study, we evaluated the significance of two markers (the TG/HDL-C ratio and TyG index) and found that a higher TG/HDL-C ratio was significantly associated with metabolic conditions in children with NAFLD. Therefore, we conclude that the TG/HDL-C ratio is a potential biomarker for severe hepatic steatosis and a screening tool for a higher risk of metabolic syndrome among children with NAFLD.

Recently, the effectiveness of these markers for diagnosing NAFLD has been studied in adults. Chen et al. [15] reported that TG/HDL-C was an independent predictive risk factor for NAFLD, especially among people without obesity and with normal lipid levels, and Zhang et al. [16] demonstrated the TyG index outperformed the ALT test in identifying NAFLD, and the inclusion of TyG index to ALT in the test protocol increased the specificity for detecting

subjects at risk for NAFLD. Furthermore, the TyG index positively correlated with the severity of hepatic steatosis and the presence of liver fibrosis in NAFLD [17]. The association between these markers and NAFLD may be explained by IR. High TG levels can cause elevated levels of free fatty acids, leading to hepatic lipotoxicity, which in turn leads to metabolic interference and cellular stress responses. When combined with hyperglycemia, these conditions lead to islet  $\beta$ -cell dysfunction and IR [18].

In our study, no significant differences were noted in liver function tests and other lipid profiles, except HDL-C levels, according to the hepatic steatosis grade. The association between liver function tests and hepatic steatosis grade is controversial, and another study reported no correlation between hepatic steatosis grade and liver function tests, which is similar to the results of our study [19,20].

Previous studies have been conducted to calculate the cutoff values of TG/HDL-C and establish their association with metabolic conditions. A Korean study [21] reported a TG/HDL-C ratio of 3.3 as a useful marker of metabolic syndrome in adolescents, while another Asian study [22] reported that children with obesity and IR had a significantly higher TG/HDL-C ratio of 2.48. In addition, western studies found that a high TG/HDL-C ratio with a cut-off point of approximately 2.3 was a predictor of metabolic syndrome [23,24]. In this study, we found that a TG/HDL-C ratio of  $\geq 3.37$  was a simple marker for predicting metabolic conditions and severe hepatic steatosis among children with NAFLD.

Our study had several limitations. First, the sample size was too small to allow definitive conclusions; in particular, the number of patients included in the severe hepatic steatosis group was relatively small. Therefore, a larger cohort study is required to confirm our findings. Second, the retrospective study design may have affected the analyzed variables. Third, we did not perform MR-based techniques or liver biopsy to quantify the degree of steatosis; however, MR-based techniques are not widely available, and in the case of liver biopsy, parents are reluctant to perform this because of their invasiveness. Despite these limitations, our study proposes a simple marker that can be used in patients with NAFLD.

We found that a high TG/HDL-C ratio was associated with severe hepatic steatosis, diabetes DM, and/or dyslipidemia in children with NAFLD. The measurement of this ratio can help clinicians identify patients who require targeted treatment, management, and follow-up.

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