

Original Article



A Nomogram for Predicting Non-Alcoholic Fatty Liver Disease in Obese Children

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Conflict of Interest

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ABSTRACT

Purpose: Non-alcoholic fatty liver disease (NAFLD) ranges in severity from simple steatosis to steatohepatitis. Early detection of NAFLD is important for preventing the disease from progressing to become an irreversible end-stage liver disease. We developed a nomogram that allows for non-invasive screening for NAFLD in obese children.

Methods: Anthropometric and laboratory data of 180 patients from our pediatric obesity clinic were collected. Diagnoses of NAFLD were based on abdominal ultrasonographic findings. The nomogram was constructed using predictors from a multivariate analysis of NAFLD risk factors.

Results: The subjects were divided into non-NAFLD (n=67) and NAFLD groups (n=113). Factors, including sex, body mass index, abdominal circumference, blood pressure, insulin resistance, and levels of aspartate aminotransferase, alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ GT), uric acid, triglycerides, and insulin, were significantly different between the two groups (all $p < 0.05$) as determined using homeostasis model assessment of insulin resistance (HOMA-IR). In our multivariate logistic regression analysis, elevated serum ALT, γ GT, and triglyceride levels were significantly related to NAFLD development. The nomogram was established using γ GT, uric acid, triglycerides, HOMA-IR, and ALT as predictors of NAFLD probability.

Conclusion: The newly developed nomogram may help predict NAFLD risk in obese children. The nomogram may also allow for early NAFLD diagnosis without the need for invasive liver biopsy or expensive liver imaging, and may also allow clinicians to intervene early to prevent the progression of NAFLD to become a more advanced liver disease.

Keywords: Obesity; Non-alcoholic fatty liver disease; Nomograms; Children

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in both, adults and children [1,2]. Since childhood obesity is a growing problem, NAFLD has rapidly become an important cause of chronic liver disease in children and adolescents [3]. The early stages of NAFLD do not usually cause lasting harm; however, the more severe non-alcoholic steatohepatitis may progress to cirrhosis and end-stage liver disease later in life [4]. The early

detection of NAFLD may, therefore, help prevent the progression of NAFLD to end-stage liver disease [5,6]. However, most patients with NAFLD are nonsymptomatic or experience nonspecific symptoms such as fatigue, malaise, and abdominal discomfort, making the early diagnosis of NAFLD difficult [7].

The rate at which children with obesity are screened for NAFLD appears to vary widely among different practitioners and institutions, primarily due to the lack of guidelines regarding pediatric obesity-related comorbidities [8]. Generally, diagnostic procedures include clinical signs and symptoms, various anthropometric parameters, and laboratory and radiological imaging tests [9,10]. Although several of these markers are commonly used to evaluate a patient with suspected NAFLD, none seem to have a high enough specificity or sensitivity to exclude another potential liver diseases. Because liver function test results can be within the normal range for patients with NAFLD, they also may not be sensitive enough to serve as screening tests. Liver ultrasonography (USG) is potentially more sensitive, but is expensive and operator-dependent (and thus reliant on subjective interpretation). The gold standard for diagnosing and assessing NAFLD severity is liver biopsy [11]. However, the routine use of liver biopsy is not practical because the procedure is invasive and can cause complications. For these reasons, various non-invasive imaging methods such as transient elastography, shear-wave elastography, and magnetic resonance elastography have been introduced to assess liver fibrosis [12]. However, simple screening tools that can be easily used in outpatient settings as a nomogram have not yet been developed, especially for obese children with suspected NAFLD.

The aims of this study were to evaluate the significant risk factors for NAFLD in obese children and to develop a nomogram that predicts the risk of NAFLD using clinical and laboratory obesity markers and obesity-related metabolic abnormalities.

MATERIALS AND METHODS

Subjects

A total of 180 children and adolescents who visited the pediatric obesity clinic at Bundang Hospital at Seoul National University were enrolled in this study. All subjects visited the clinic seeking treatment for obesity. Subjects complaining of any symptoms, with a history of drug/alcohol abuse in the last three months, or with an underlying liver disease such as autoimmune liver disease, metabolic liver disease, Wilson disease, or viral hepatitis were excluded from the study. Subjects underwent abdominal USG and were divided into two groups according to their NAFLD status. USG was performed by a pediatric radiology specialist. NAFLD was diagnosed and classified as involving mild, moderate, and severe steatosis according to a recognized classification system [13]. NAFLD was classified as more severe based on increased hepatic echogenicity, impaired visualization of the hepatic vessels and diaphragm, and poor ultrasonographic penetration of the posterior liver.

This study was approved by the Institutional Review Board of Seoul National University's Bundang Hospital (IRB No. B1604/344-102).

Anthropometric data

The subjects' anthropometric measurements, including weight, height, abdominal circumference (AC), and blood pressure (BP), were recorded. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1 cm. Body mass index (BMI)

was calculated as body weight (kg) divided by the square root of height (m²). BMI percentile was calculated according to the 2007 Korean national growth charts [14]. 'Overweight' was defined as a BMI between the 85th and 95th percentiles for the child's age and sex, and 'obese' was defined as a BMI greater than the 95th percentile. AC was defined as a subject's maximum waist circumference in the standing position as measured by a tapeline. Abdominal obesity was defined as an AC exceeding the 90th percentile for the child's age and sex. BP was measured at least twice in the resting state, and hypertension was defined as repeated BP measurements exceeding the 90th percentile for the child's age and sex.

Laboratory data

Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transpeptidase (γ GT), triglycerides (TG), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting glucose, and insulin levels were measured during the first visit after at least 12 hours of fasting.

Serum levels of AST and ALT were measured using a TBA-200FR NEO automated clinical chemistry analyzer (Toshiba Medical Systems Co., Tokyo, Japan). Levels exceeding 40 IU/L were considered abnormal. Serum levels of γ GT higher than 30 IU/L and uric acid levels higher than 7.0 mg/dL were considered abnormal. Hypertriglyceridemia was defined as a serum TG level of 110 mg/dL or higher. Hypercholesterolemia was defined as a serum cholesterol level of 200 mg/dL or higher. Low HDL cholesterol was defined as a serum HDL cholesterol level of 40 mg/dL or lower. High LDL cholesterol was defined as a serum LDL cholesterol level of 130 mg/dL or higher. Fasting glucose intolerance was defined as a fasting glucose level of 100 mg/dL or higher. Hyperinsulinemia was defined as a fasting insulin level exceeding the 95th percentile for the child's age and sex. Insulin sensitivity was determined using the homeostatic model assessment of insulin resistance [HOMA-IR: (insulin \times glucose)/22.5], and insulin resistance was defined as a HOMA-IR value exceeding 3.0 in children [15].

Diagnosis of metabolic syndrome

Our definition of metabolic syndrome was modified from the criteria set by the USA National Cholesterol Education Program-Adult Treatment Panel III from the National Health and Nutrition Examination Surveys III [16]. According to the modified criteria, metabolic syndrome was diagnosed when a subject met more than three of five characteristics: 1) AC exceeding the 90th percentile for a subject's age and sex; 2) serum TG of 110 mg/dL or more; 3) HDL cholesterol lower than 40 mg/dL; 4) systolic BP or diastolic BP exceeding the 90th percentile for a subject's age and sex; and 5) fasting blood glucose of 100 mg/dL or more, or the presence of diabetes mellitus.

Statistical analysis

The results are expressed as mean \pm standard deviation or as raw values. The data were analyzed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). A Student's *t*-test was used to compare the means of two groups. Pearson's correlation was applied to evaluate the correlation between two variables. Frequency data was analyzed using the Chi-square test. Odds ratios (ORs) and 95% confidence intervals for each variable were obtained using the Chi-square test and logistic regression analysis to evaluate significant risk factors. A *p*-values of less than 0.05 were considered statistically significant.

The nomogram was developed using predictors from the multivariate analysis and significant obesity-related variables from univariate analysis to predict NAFLD risk in children. The

analysis for nomogram development was carried out using R software version 3.0.0 (R Development Core Team, 2013; <http://www.r-project.org>).

RESULTS

Clinical characteristics

A total of 180 patients who visited the obesity clinic were included in the study. Of these, 132 subjects were male (73.3%) and 48 were female (26.7%). The mean age was 12.3±2.5 years, ranging from 6 to 19 years old. The number of NAFLD patients was 113 and the number of non-NAFLD patients was 67.

Table 1 shows the anthropometric characteristics, clinical characteristics, and laboratory test results according to NAFLD status. The NAFLD group had significantly more male patients than the non-NAFLD group (male:female, 92:21 NAFLD vs. 40:27 non-NAFLD, $p=0.001$). The mean age was not significantly different between the two groups ($p=0.707$). The mean BMI was significantly higher in the NAFLD group (27.2±3.9 NAFLD vs. 25.4±2.6 non-NAFLD, $p=0.001$), and the proportion of obese patients was also higher in NAFLD group (69% NAFLD vs. 48% non-NAFLD, $p=0.005$). The mean AC of the NAFLD patients was 86.6±21.1cm, which was significantly larger than the non-NAFLD patients (78.4±23.9 cm, $p=0.018$). The proportion of abdominal obesity was higher in the NAFLD group (86% NAFLD vs. 81% non-NAFLD, $p=0.001$). The mean systolic and diastolic BPs of NAFLD patients were 117.7±33.2 mmHg and 61.5±18.6 mmHg respectively. In non-NAFLD patients, the systolic (92.4±51.0 mmHg) and diastolic (48.6±27.9 mmHg) BPs were significantly lower than the NAFLD group ($p<0.001$).

Table 1. Comparison of clinical features and laboratory results of obese children according to their NAFLD status

Variable	NAFLD (n=113)	Non-NAFLD (n=67)	p-value
Sex (male:female)	92:21	40:27	0.001 [†]
Age (yr)	12.3±2.2	12.4±3.0*	0.707
Weight (kg)	67.0±18.9	59.4±15.4	0.006 [†]
Height (cm)	155.3±13.4	151.6±14.8	0.084 [†]
BMI (kg/m ²)	27.2±3.9	25.4±2.6	0.001 [†]
BMI group (Ow:Ob)	35:78	35:32	0.005 [†]
AC (cm)	86.6±21.1	78.4±23.9	0.018 [†]
AC group (AC <90 p: >90 p*)	16:97	13:54	0.001 [†]
Systolic BP (mmHg)	117.7±33.2	92.4±51.0	<0.001 [†]
Diastolic BP (mmHg)	61.5±18.6	48.6±27.9	<0.001 [†]
BP group (BP <90 p: >90 p*)	70:43	53:14	0.017 [†]
AST (IU/L)	56.8±43.9	24.6±11.8	<0.001 [†]
ALT (IU/L)	112.9±96.1	26.6±25.2	<0.001 [†]
γGT (IU/L)	35.7±28.0	12.0±11.0	<0.001 [†]
Uric acid (mg/dL)	6.4±1.5	5.5±1.3	<0.001 [†]
TG (mg/dL)	133.0±72.1	95.6±57.7	<0.001 [†]
Total cholesterol (mg/dL)	183.5±32.5	177.5±27.5	0.202
HDL-cholesterol (mg/dL)	48.1±14.5	50.7±15.7	0.266
LDL-cholesterol (mg/dL)	94.2±27.1	90.3±26.8	0.350
Fasting glucose (mg/dL)	93.9±11.1	91.2±7.9	0.078
Insulin (μU/mL)	24.5±20.2	17.0±10.6	0.006 [†]
HOMA-IR	5.7±4.9	3.9±2.8	0.006 [†]

Values are presented as number only or mean±standard deviation.

NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, Ow: overweight with BMI between the 85th and 95th percentile, Ob: obese with a BMI ≥95th percentile, AC: abdominal circumference, BP: blood pressure, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGT: γ-glutamyl transpeptidase, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostatic model assessment of insulin resistance.

*AC exceeding 90th percentile for the child's age and sex was defined as abdominal obesity. [†]Hypertension was defined as repeatedly measured BP exceeding 90th percentile for the child's age and sex.

The incidence of hypertension was higher in the NAFLD group (38% NAFLD vs. 21% non-NAFLD, $p=0.017$). Obesity-related biomarkers such as AST, ALT, γ GT, uric acid, TG, insulin, and HOMA-IR were significantly higher in NAFLD patients relative to non-NAFLD patients (all p -values <0.05). Total serum cholesterol, HDL-cholesterol, LDL-cholesterol, and fasting blood glucose levels were not significantly different between the NAFLD and non-NAFLD groups.

Risk factors predicting the presence of NAFLD

The statistically significant variables in the univariate analysis included sex, BMI group, BP group, ALT, γ GT, uric acid, TG, and HOMA-IR. These variables were subjected to multiple logistic regression analysis to predict the presence of NAFLD in obese children (Table 2). We found that high ALT (>40 IU/L, OR 10.78, $p<0.001$), high γ GT (>30 IU/L, OR 6.69, $p=0.031$), and high TG (>110 mg/dL, OR 3.98, $p=0.016$) were significant risk factors for NAFLD in obese children.

The nomogram as a prediction model for NAFLD

Based on our multivariate analysis results, a nomogram was designed to predict the probability of NAFLD using γ GT, uric acid, TG, HOMA-IR, and ALT as predictors. The value of each predictor is assigned a certain point value, which is calculated by drawing a line upwards from the predictor scales to their corresponding point value (Fig. 1). When all the points from each predictor are totaled, a line is drawn downward from the “total points” scale to estimate the risk of NAFLD in children with obesity. The NAFLD nomogram indicates that the probability of NAFLD increases with increasing levels of serum ALT (>40 IU/L), γ GT >30 IU/L, uric acid (≥ 7 mg/dL), TG (≥ 110 mg/dL), and HOMA-IR (≥ 3).

DISCUSSION

In this study, a nomogram was developed to predict the risk of NAFLD in children with obesity. The nomogram consists of several obesity-related biochemical markers, and can be used to diagnose NAFLD before subjecting patients to expensive and time-consuming liver imaging or invasive liver biopsy.

Currently, liver biopsy is considered the gold standard method of diagnosing NAFLD. Biopsy is the only single test that can evaluate the degree of liver steatosis in NAFLD and exclude other liver diseases [17-19]. However, liver biopsy is not an appropriate screening method due to its high cost and invasive nature [20]. Therefore, a less invasive screening method is necessary in order to diagnose NAFLD early and halt its progression to end-stage liver disease.

Table 2. Risk factors predicting the presence of NAFLD in obese children

Variable	Multivariate analysis		
	OR	95% CI	p -value
Sex (male)	1.72	0.49–5.98	0.395
BMI group (BMI >95 p*)	0.79	0.24–2.65	0.708
BP group (BP >90 p*)	1.76	0.47–6.50	0.400
ALT (>40 IU/L)	10.78	2.89–40.20	<0.001
γ GT (>30 IU/L)	6.69	1.19–37.58	0.031
Uric acid (>7.0 mg/dL)	2.86	0.69–11.89	0.149
TG (>110 mg/dL)	3.98	1.29–12.27	0.016
HOMA-IR (>3.0)	1.96	0.58–6.64	0.275

NAFLD: non-alcoholic fatty liver disease, OR: odds ratio, CI: confidence interval, BMI: body mass index, BP: blood pressure, ALT: alanine aminotransferase, γ GT: γ -glutamyl transpeptidase, TG: triglyceride, HOMA-IR: homeostatic model assessment of insulin resistance.

*Hypertension was defined as repeatedly measured BP exceeding 90th percentile for the child's age and sex.

Nomogram Predicting NAFLD in Obese Children

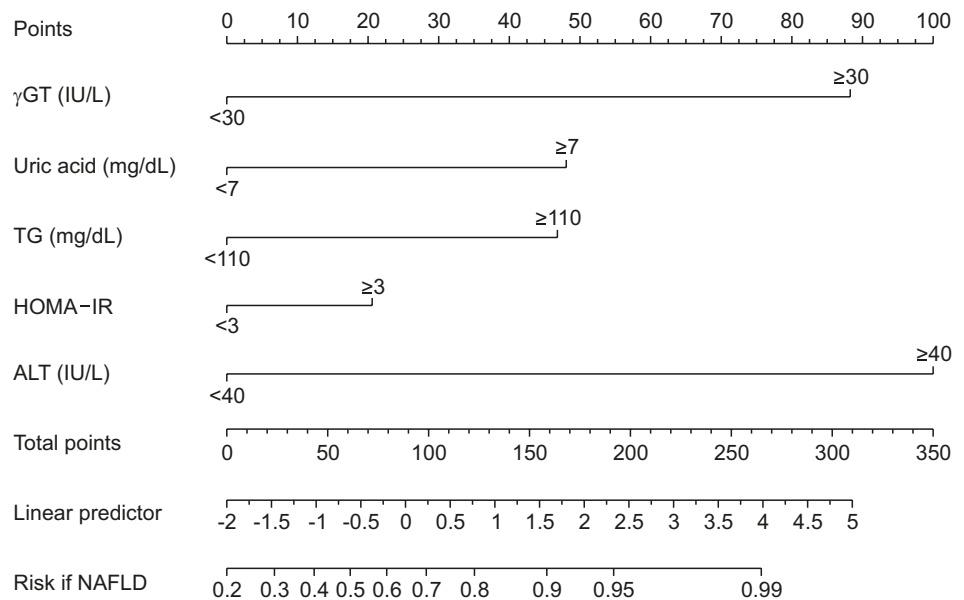


Fig. 1. A nomogram for predicting NAFLD using γ GT, uric acid, TG, HOMA-IR, and ALT as predictors. A line is drawn upward from each category to its corresponding number of points. When all the points are totaled, a line is drawn downward from the "Total points" scale to estimate the risk of NAFLD. γ GT: γ -glutamyl transpeptidase, TG: triglyceride, HOMA-IR: homeostatic model assessment of insulin resistance, ALT: alanine aminotransferase, NAFLD: non-alcoholic fatty liver disease.

Various attempts have been made to predict the presence of NAFLD using several non-invasive serum markers. Booth et al. [21] evaluated the epidemiology of elevated serum concentrations of ALT, GGT, AST, and ALP in Australian adolescents, and found that adverse concentrations of ALT, GGT and AST increased with BMI. These laboratory findings suggest that predicting NAFLD in high-risk populations is possible.

Our study developed a nomogram that can be used to screen for NAFLD in obese children using γ GT, uric acid, TG, HOMA-IR, and ALT as predictors. This nomogram validates a patient's risk score for NAFLD, and can identify patients who should undergo further evaluation. We found that a high ALT level is the most significant risk factor for NAFLD. In clinical practice, serum ALT is one of the main liver function tests used to screen for hepatocellular injury and hepatic dysfunction. NAFLD is one of the most important causes of elevated ALT levels, which indicates fatty infiltration of the liver with or without inflammation [22]. However, elevated ALT is not a specific sign of NAFLD, nor is ALT always elevated in NAFLD patients [23,24]. According to our nomogram, a serum ALT level higher than 40 IU/L is worth 100 points, and corresponds to a <0.6 probability of NAFLD. This finding suggests that elevated ALT alone cannot accurately predict the presence of NAFLD in obese children. Therefore, additional markers besides serum aminotransferases are needed to accurately screen for the presence of NAFLD.

Other markers for NAFLD identified in this study included high serum levels of γ GT, uric acid, TG, and HOMA-IR, all of which are commonly evaluated in obese children and adolescents. According to a previous study, increased γ GT is a risk factor for advanced fibrosis in NAFLD, as γ GT levels correlate with levels of the hepatocyte growth factor that stimulates fibrogenesis [25]. In this study, an increased γ GT level was also a significant predictor for NAFLD. A high serum uric acid level is also an independent predictor of NAFLD in obese children [26]. Uric acid has been shown to promote lipid peroxidation, which

could play a major role in the initiation and progression of NAFLD. In our study, an elevated serum uric acid level was a significant predictor of NAFLD and was used in the nomogram. Hypertriglyceridemia and insulin resistance (expressed as HOMA-IR) were the other risk factors for NAFLD identified in this study. Hypertriglyceridemia is the lipid profile most commonly associated with fatty infiltration of the liver [27]. Insulin resistance is an almost universal finding in NAFLD, and may increase free fatty acid delivery and accelerate hepatic fat accumulation while also stimulating anabolic processes along with hyperinsulinemia [28]. Oh et al. [29] suggested that NAFLD severity was highly and significantly correlated with serum insulin levels, HOMA-IR values, and the serum TG levels.

To identify fibrosis in NAFLD patients without using liver biopsy, numerous simple laboratory ratios have been proposed that serve as markers for advanced fibrosis. Elevated AST:ALT ratios are associated with fibrosis in patients with chronic liver disease [30], and several studies have found that AST to ALT ratios increase along with the degree of fibrosis in patients with chronic liver disease (including NAFLD). This correlation may reflect impaired AST clearance by hepatic sinusoidal cells [31]. The AST to platelet ratio index (APRI), which was initially developed as a non-invasive tool to assess liver fibrosis in chronic hepatitis C, may also be a useful non-invasive marker of hepatic fibrosis in NAFLD [32]. Several other laboratory tests and clinical variables may also help increase the predictive value of tests for liver fibrosis. One study validated the NAFLD fibrosis score using six variables (age, hyperglycemia, BMI, platelet count, albumin, and AST/ALT ratio), which successfully identified liver fibrosis and allowed patients to avoid liver biopsy [33]. The FIB-4 score, which is based on age, AST levels, ALT levels, and platelet counts, was originally developed to predict advanced fibrosis in patients co-infected with HCV and HIV [34]. Shah et al. [35] evaluated the utility of the FIB-4 index as a marker of advanced fibrosis in NAFLD, and found that the overall accuracy of FIB 4 was 0.8, based on the AUROC curve. This score was superior to other non-invasive markers of fibrosis.

Screening for NAFLD without performing invasive tests is especially important in pediatric patients because liver biopsy is technically challenging and leads to high rates of complications. However, there are few reliable non-invasive predictors of NAFLD severity. In addition, no reliable clinical guidelines concerning when to perform liver biopsy in children with NAFLD currently exist. A recent retrospective chart review study examined the efficacy of non-invasive hepatic fibrosis predictors, including the AST:ALT ratio, APRI levels, FIB-4 levels, the pediatric NAFLD fibrosis index, and the pediatric NAFLD fibrosis score [36]. They found that these non-invasive fibrosis markers did not adequately predict fibrosis. More accurate scoring systems should therefore be developed to predict the risk of fibrosis in pediatric NAFLD patients.

Our study has some limitations. Firstly, NAFLD was diagnosed based on abdominal USG results and not by liver histopathologic results. Because liver biopsy is the gold standard method for diagnosing NAFLD, our diagnostic methods may have led to inaccuracies. However, it is almost impossible to perform liver biopsies in large numbers of pediatric patients in outpatient settings. Our nomogram could be an important screening tool for NAFLD, and help refer obese children who are at high risk of NAFLD for liver biopsy. Secondly, our patients may not represent the general pediatric population, as our subjects were patients in an obesity clinic. Because we did not include normal-weight children (who have the lowest risk of NAFLD) as controls, it is not clear if our NAFLD predictors are equally applicable to the general population. Further study is needed to verify this nomogram in a prospective large-group study with normal control subjects.

In conclusion, we present a newly developed nomogram for the non-invasive NAFLD screening in obese pediatric patients. This nomogram may help detect NAFLD early before subjecting patients to invasive liver biopsy or expensive liver imaging procedures. The nomogram may also allow physicians to begin early interventions and prevent the progression of NAFLD to more severe liver disease.

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