Role of Fatty Liver Index and Metabolic Factors in the Prediction of Nonalcoholic Fatty Liver Disease in a Lean Population Receiving Health Checkup

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OBJECTIVES: **Some metabolic factors and noninvasive markers, including fatty liver index (FLI), are used to predict nonalcoholic fatty liver disease (NAFLD) in obese patients. Despite the increasing prevalence of NAFLD in lean patients (lean-NAFLD), the risk factors and predictors are not well determined in this population. We investigated factors associated with lean-NAFLD and validated their predictive ability.**

METHODS: **From 9,293 examinees who underwent routine health checkups, we enrolled 4,000, aged ≥20 years, with a body mass index <24 kg/m² in our lean-NAFLD study population. NAFLD diagnoses were made according to the patients' histories, laboratory values, and sonographic criteria. Clinical variables, serum sugar, lipid, and liver profiles were evaluated using multiple logistic regression analysis. The predictive ability and optimal cutoff values for NAFLD were determined according to the area under the receiver operating characteristic curve.**

RESULTS: **Overall, 18.5% (n = 740) of the lean population had NAFLD. Male sex, body mass index, body fat mass, fasting plasma glucose, uric acid, alanine aminotransferase, triglyceride, and FLI values were associated with NAFLD. FLI had the best discriminative ability to predict lean-NAFLD compared to the other biochemical markers. We further used the Youden index test and found an optimum cut-off value for FLI of 15 with the highest discriminant ability than other values.**

DISCUSSION: **The prevalence of lean-NAFLD was not low. FLI was superior to other predictors including sex, liver function, and other metabolic factors, in the prediction of lean-NAFLD. FLI may be considered an easy to use, noninvasive marker to screen for lean-NAFLD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A43

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has well-known associations with obesity and metabolic syndrome, and has emerged as a salient public health issue worldwide. Recent results from a systematic review suggested that lean and obese patients with NAFLD shared altered metabolic and cardiovascular profiles (1). Patients with NAFLD, irrespective of whether they are lean or obese, have similar risks of cardiovascular diseases (2) and related mortality (3,4), hepatocellular carcinoma (5,6), extrahepatic cancers (7), and other liver disease complications (8).

Although there is a lower prevalence of NAFLD in the lean (lean-NAFLD) patient population than in the obese patient population, a gradient of increasing prevalence in lean-NAFLD was noted (9). In addition, lean-NAFLD patients share a similar metabolic milieu with those who are obese, which warrants clinicians' attention (10). Prevalence rates in the United States were approximately 7% and 28% in lean and obese patients, respectively, according to the National Health and Nutrition Examination Survey III (11). In general, body mass indexes (BMIs) in Asians are lower than those in Westerners. However, the

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prevalence of lean-NAFLD varies from 7% to 19% across different Asian countries (12,13). Genetic predisposition and regional heterogeneity have been reported to be 2 important factors attributable for the development of lean-NAFLD (12). Therefore, we suspected that lean-NAFLD would show different clinical characteristics in Asia.

Lean people with hypertension, hypertriglyceridemia, high fasting plasma glucose (FPG) levels, and high homoeostatic model assessment–insulin resistance (HOMR) indices have an increased risk of developing NAFLD (1). However, the utility of metabolic factors, such as the HOMR index, are limited in clinical practice. Liver biopsy is the gold standard for diagnosing NAFLD; however, it is rather invasive. Bedogni et al. (14) developed the fatty liver index (FLI), which accurately separates patients with NAFLD. Yang et al. (15) also suggested that FLI was a reliable noninvasive predictor of NAFLD in both Asian and Western populations. The relationship between NAFLD and individual metabolic syndrome component values or liver enzyme levels has been widely investigated (1). However, there is a degree of uncertainty with validating FLI and metabolic factors with respect to their ability to predict lean-NAFLD, especially in general Asian populations. Thus, we conducted a retrospective study and aimed to explore the prevalence and associated factors of lean-NAFLD in a population of patients attending routine health checkups in southern Taiwan. Additionally, the roles of FLI and metabolic factors in the prediction of lean-NAFLD were also validated.

METHODS

Study population

In this retrospective study, we reviewed the records of 9,293 examinees who underwent routine health checkups at the health examination center in Kaohsiung Veterans General Hospital from January 1, 2016 to December 31, 2016. Based on the study exclusion criteria, we excluded 2,119 examinees with at least one of the following: (i) significant consumption of alcohol, defined as >20 g/d for men and >10 g/d for women, according to the National Health and Nutrition Examination Survey III criteria (16); (ii) usage of medications reported to cause severe liver damage in the previous 6 months; (iii) liver cirrhosis (defined by ultrasonographic criteria) (17); (iv) chronic hepatitis B or C (defined by history, serum hepatitis B surface antigen, and anti-hepatitis C antibodies); (v) malignant liver cancer; and (vi) no ultrasonographic examination included in the health checkup data. Of the remaining 7,174 examinees, 4,000 examinees with BMI < 24 kg/m^2 were enrolled into the lean patient population for further analysis. The lean patient population was divided into 2 groups according to their NAFLD status: NAFLD and non-NAFLD. NAFLD was defined by an ultrasonographic diagnosis of fatty liver in addition to the history and laboratory findings as mentioned in exclusion criteria. This study was authorized by the Institutional Review Board of the Kaohsiung Veterans General Hospital as No. VGHKS 18-CT9-09. We could not obtain written consent from study patients as the dataset consists of de-identified data for research purposes.

All the participants underwent complete biochemical and blood examinations as well as abdominal ultrasonography. Demographic data, history of current smoking, exercise habits (moderate aerobic activity ≥150 minutes per week or vigorous aerobic ≥75 minutes per week) (18), alcohol intake (number, frequency, and alcohol percentage of drinks per week according to the National Institute on Alcohol Abuse and Alcoholism) (19), and history of comorbidities including cardiovascular disease, diabetes mellitus (DM), hypertension, and dyslipidemia were acquired from questionnaires.

Measurements

The weight, height, and body fat mass of all examinees were measured using the electric impedance method analyzer (X-SCAN PLUS II; Jawon Medical, Gyeongsan-si, South Korea) with the patients minimally clothed and wearing no socks. The examinees' BMI were calculated as weight (kg) divided by height (m) squared. Well-trained examiners used an unstretchable tape measure, without exerting pressure on the body surfaces, to measure all examinees' waist circumferences (WCs) at the umbilical level. These measurements were recorded to the nearest 0.1 cm. A well-trained examiner measured all the anthropometric indices. The abdominal ultrasonographic examinations (GE LOGIQ E9; Chalfont, St. Giles, United Kingdom) for all patients were performed by the same 5 fixed and experienced ultrasonographic technicians. These examinations were performed to determine hepatic fatty infiltration. The measurements were verified by the same 5 experienced senior radiologists with >10 years of experience each. 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 (20).

Serological and biochemical markers

Hematological indicators were measured using hematology analyzers (UniCel DxH 800; Beckman Coulter, Brea, CA). The biochemical indicators included FPG, hemoglobin A1c (HbA1c), serum uric acid (UA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), and alkaline phosphatase. All of these serum biochemical markers were measured using a Hitachi 7600 Automatic Biochemical Analyzer (Hitachi, Tokyo Ibaraki, Japan). The HbA1c was analyzed using a Premier Hb9210 HbA1c Analyzer (Bray, Ireland/Kansas City, MO). Hepatitis B surface antigen was measured by radioimmunoassay kits (Ausria II-125; Abbott Laboratories, North Chicago, IL), and anti-hepatitis C antibody was measured by microparticle enzyme immunoassay (Ax SYM HCV III; Abbott Laboratories). All blood samples were obtained after an 8-hour overnight fast. The FLI was calculated using the following formula:

$$\mathrm{FLI} = \left(\frac{e^{0.953*\log_e(\mathrm{TG}) + 0.139*\mathrm{BMI} + 0.718*\log_e(\mathrm{GGT}) + 0.053*\mathrm{WC} - 15.745}}{1 + e^{0.953*\log_e(\mathrm{TG}) + 0.139*\mathrm{BMI} + 0.718*\log_e(\mathrm{GGT}) + 0.053*\mathrm{WC} - 15.745}} \right) * 100 \quad (21).$$

Statistical analysis

All the statistical analyses were performed using SPSS version 20.0 for Windows (SPSS, Armonk, NY) and MedCalc version 12.7.8 (MedCalc Software, Mariakerke, Belgium). Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. Variability of the demographic characteristics between the NAFLD and non-NAFLD groups were compared using independent *t* tests and χ^2 tests. Variables with statistical significance ($P < 0.05$) in the univariate analysis were included in the binary logistic regression analysis with a forward stepwise method used in the multivariate analysis. The predictive ability and cut-off values for each factor in the prediction of NAFLD were assessed using area under the receiver operator characteristic (AUROC) curves. AUROC between 0.7 and 0.9 was regarded as moderate accuracy according to Greiner et al. (22) A *P*-value <0.05 was considered statistically significant. Youden index and the discriminant ability at each cut-off value for FLI were used to determine the optimal cut-off value for FLI to diagnose lean-NAFLD. The discriminant ability is the average of the sensitivity and specificity at each cut-off value. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were used as performance measures.

RESULTS

Demographic characteristics

Of the 4,000 lean examinees, 740 (18.5%) participants had NAFLD. The severity of NAFLD as assessed by ultrasonography was mild, moderate, and severe in 87.9% (n = 650), 9.7% (n = 72), and 2.4% (n = 18), respectively. As shown in Table 1, patients in the NAFLD group were older, with higher BMIs, higher body fat masses, and larger WCs than those in the non-NAFLD group. Comorbidities including cardiovascular disease, hypertension, DM, and dyslipidemia as well as a smoking history were more frequent in the NAFLD group than in the non-NAFLD group. As shown in Table 2, the NAFLD group also had higher FPG, HbA1c, TC, low-density lipoprotein, TG, UA, AST, ALT, alkaline phosphatase, GGT, and FLI levels, but lower HDL levels than those in the non-NAFLD group.

Factors associated with NAFLD in the lean population

Significant variables including age, male sex, comorbidities, smoking history, and biochemical indicators identified in the univariate analysis were selected for the binary logistic regression analysis. Since FLI is calculated using the combination of BMI, WC, serum TG, and GGT levels, we applied 3 models to the logistic regression analysis to minimize the potential confounding effects of these parameters. In model I, we selected age, sex, body fat mass, BMI and WC, hypertension history, smoking status, FPG, HbA1c, AST, ALT, UA, TC, TG, HDL, and GGT, but

Table 1. Demographic characteristics of the lean patient population (N = 4,000) with and without NAFLD

	Without NAFLD, n = 3,260	With NAFLD, n = 740	*P* value
Age (yr)	46.39 ± 11.49	49.92 ± 10.80	<0.001[a]
BMI (kg/m^2)	20.99 ± 1.89	22.05 ± 1.56	<0.001[a]
Body fat mass (kg)	22.18 ± 5.50	23.38 ± 5.02	0.012[a]
WC (cm)	75.82 ± 6.71	79.87 ± 6.28	<0.001[a]
Sex, n (%)			<0.001[a]
Female	2,197 (67.4)	347 (46.9)	
Male	1,063 (32.6)	393 (53.1)	
Education level, n (%)			0.593
No schooling or elementary school education	204 (13.3)	35 (11.2)	
High school education	255 (16.6)	53 (16.9)	
College or graduate school education	1,074 (70.1)	225 (71.9)	
Personal history, n (%)			
Cardiovascular disease	252 (15.6)	107 (29.3)	<0.001[a]
Hypertension	178 (5.5)	92 (12.4)	<0.001[a]
DM	54 (1.7)	42 (5.7)	<0.001[a]
Dyslipidemia	113 (3.5)	70 (9.5)	<0.001[a]
Social habits, n (%)			
Current smokers (yes)	334 (10.4)	98 (13.4)	0.020[a]
Exercise habit (yes)	277 (8.5)	58 (7.8)	0.558
Alcohol drinking (yes)	1,163 (36.3)	273 (37.3)	0.580

BMI, body mass index; DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; WC, waist circumference.
[a]Represents significance.

Table 2. Laboratory data of the lean patient population (n = 4,000) with and without NAFLD

	Without NAFLD, N = 3,260	With NAFLD, N = 740	*P* value
FPG (mg/dL)	90.04 ± 13.11	97.15 ± 20.15	<0.001[a]
HbA1c (%)	5.59 ± 0.58	5.83 ± 0.76	<0.001[a]
TC (mg/dL)	194.97 ± 34.41	201.29 ± 37.92	<0.001[a]
HDL-C (mg/dL)	59.30 ± 13.60	51.87 ± 13.73	<0.001[a]
LDL-C (mg/dL)	103.33 ± 26.94	109.25 ± 28.67	<0.001[a]
TG (mg/dL)	91.30 ± 53.31	145.79 ± 110.90	<0.001[a]
UA (mg/dL)	5.10 ± 1.27	5.77 ± 1.44	<0.001[a]
AST (U/L)	20.86 ± 7.22	24.42 ± 17.58	<0.001[a]
ALT (U/L)	19.69 ± 11.09	27.83 ± 17.58	<0.001[a]
ALP (U/L)	59.39 ± 18.88	65.32 ± 17.26	<0.001[a]
Total bilirubin (mg/dL)	0.81 ± 0.37	0.83 ± 0.38	0.098
GGT (U/L)	27.28 ± 0.87	79.63 ± 5.47	0.001[a]
FLI	11.74 ± 12.04	26.29 ± 19.81	<0.001[a]

Data are expressed as means ± SD.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglyceride; UA, uric acid.
[a]Represents significance.

not FLI. Model II included the model I variables; however, we used WC in place of BMI. In model III, FLI was included, but all 4 of its components were not entered. According to model I, significant factors associated with lean-NAFLD included BMI, FPG, TG, UA, and ALT. According to model II, the significant factors were male sex, body fat mass, FPG, UA, TG, and ALT. According to model III, the significant factors were male sex, body fat mass, FPG, UA, ALT, and FLI (Table 3).

Validation of FLI to identify ultrasonographic NAFLD and selection of its optimal cut-off value

The discriminative ability of the significant factors related to lean-NAFLD was determined by comparing their AUROC values. Although FLI for diagnosing lean-NAFLD had moderate accuracy (AUROC of 0.76; 95% confidence interval, 0.73–0.78; sensitivity 60.66%; specificity 79.35%), it had the best discriminative ability to predict lean-NAFLD compared to the other biochemical markers (Table 4). Hence, we considered using FLI for identifying ultrasonographic NAFLD.

Following the methodology of several previous studies (22–24), different cut-off values were tested for their ability to diagnose lean-NAFLD using FLI. The percentages of subjects diagnosed as having NAFLD using FLI cut-off value of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, and 75 were 4.9%, 4.0%, 3.3%, 2.7%, 2.3%, 1.9%, 1.5%, 1.2%, 0.9%, 0.8%, 0.7%, 0.3%, 0.3%, 0.2%, and 0.2%, respectively (Table 5).

Although a cut-off value of 5 could rule out NAFLD (based on a sensitivity of 91.53%, negative likelihood ratio: 0.22), and FLI 50 could rule in lean-NAFLD (based on a specificity of 98.40; positive likelihood ratio: 7.07). According to the aforementioned report (25), this polar extreme probability (>90%) might lead to additional unnecessary tests. Therefore, we further used the Youden index test and found an optimum cut-off value of 15 with the highest discriminant ability than other values (sensitivity of 61.58%; specificity of 77.37%). Thus, we considered that this value would be more reasonable for clinical practice.

Furthermore, we applied this FLI to our dataset stratified by age (divided ages into <40, 40–59, ≥60 years), sex, BMI (divided into <18.5 and 18.5–24 kg/m^2), TG (divided into <150 and ≥150 mg/dL) (26), UA (divided into <6 and ≥6 mg/dL) (27), and FPG value (divided into <100, 100–125, and ≥126 mg/dL) (26). We noted higher sensitivity than all study population with age 40–59 and ≥60 years old (sensitivity: 64.3 and 65.6%, respectively), BMI ≥ 18.5 kg/m^2 (sensitivity: 62.8%), FPG = 100–125 and ≥125 mg/dL (sensitivity: 69.4 and 70.0, respectively), and UA ≥ 6 (sensitivity: 79.1%) (see Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A43).

Table 3. Factors associated with lean-nonalcoholic fatty liver disease according to the univariate and multivariate binary logistic regression analyses

	Univariate analysis		Multivariate analysis					
			Model I		Model II		Model III	
Variables	OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Age (yr)	1.027	<0.001[a]						
BMI (kg/m^2)	1.428	<0.001[a]	1.249	<0.001[a]				
WC (cm)	1.099	<0.001[a]						
Sex (male)	2.339	<0.001[a]			2.916	<0.001[a]	2.495	0.002[a]
Body fat mass (kg)	1.043	<0.001[a]			1.121	<0.001[a]	1.109	<0.001[a]
Hypertension	2.459	<0.001[a]						
Smoking status (yes)	1.329	0.021[a]						
FPG (mg/dL)	1.028	<0.001[a]	1.012	0.004[a]	1.012	0.003[a]	1.012	0.006[a]
HbA1c (%)	1.677	<0.001[a]						
TC (mg/dL)	1.005	<0.001[a]						
HDL-C (mg/dL)	0.956	<0.001[a]						
TG (mg/dL)	1.010	<0.001[a]	1.005	<0.001[a]	1.005	<0.001[a]		
UA (mg/dL)	1.435	<0.001[a]	1.244	0.001[a]	1.249	0.002[a]	1.232	0.004[a]
AST (U/L)	1.041	<0.001[a]						
ALT (U/L)	1.046	<0.001[a]	1.023	<0.001[a]	1.028	<0.001[a]	1.109	<0.001[a]
GGT (U/L)	1.011	<0.001[a]						
FLI	1.056	<0.001[a]					1.024	<0.001[a]

Model I: age, sex, body fat mass, BMI and WC, hypertension history, smoking status, FPG, HbA1c, AST, ALT, UA, TC, TG, HDL and GGT, but not FLI.
Mode II: adjusted for age, sex, body fat mass, WC, hypertension, smoking status, FPG, HbA1c, AST, ALT, GGT, UA, TC, TG, HDL, and GGT, but not FLI.
Model III: adjusted for age, sex, body fat mass, hypertension, smoking status, FPG, HbA1c, AST, ALT, UA, TC, HDL, and FLI.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.
[a]Represents significance.

Table 4. Comparison of the AUROC curve among noninvasive markers used for predicting nonalcoholic fatty liver disease in lean patients

All subjects	AUROC	95% CI	SE	*P* value
BMI	0.67	0.65–0.68	0.0107	<0.001[a]
WC	0.67	0.66–0.69	0.0108	<0.001[a]
TC	0.55	0.54–0.57	0.0117	<0.001[a]
Body fat mass	0.55	0.54–0.57	0.0115	<0.001[a]
TG	0.67	0.65–0.68	0.0119	<0.001[a]
FPG	0.64	0.62–0.65	0.0116	<0.001[a]
UA	0.64	0.63–0.66	0.0112	<0.001[a]
HDL-C	0.66	0.65–0.68	0.0116	<0.001[a]
ALT	0.69	0.67–0.70	0.0110	<0.001[a]
GGT	0.69	0.67–0.72	0.0195	<0.001[a]
FLI	0.76	0.73–0.78	0.0188	<0.001[a]

ALT, alanine aminotransferase; AUROC, area under the receiver operating characteristic; BMI, body mass index; CI, confidence interval; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, γ-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.
[a]Represents significance.

DISCUSSION

In this study, we assessed the risk factors associated with lean-NAFLD and refined the new threshold FLI value using data of patients who underwent routine physical examinations. The major findings of our study are as following: (i) the prevalence of NAFLD among lean participants was 18.5%, which is not low; (ii) male sex, higher values for body fat mass, BMI, FPG, UA, TG, ALT, and FLI were all associated with a risk of lean-NAFLD; (iii) we found that FLI ≥ 15 was a reasonable cut-off value for the prediction of lean-NAFLD, especially in those aged ≥40 years, and having FPG ≥ 100 and UA ≥ 6 in clinical practice. The prevalence of NAFLD has been reported to be 10%–40% worldwide. Among Western countries, the rates ranged from approximately 20% to 40% (28) in the United States and approximately 20%–33% in Europe, with even higher rates in diabetic patients (46%–70%) (29,30). The prevalence of lean-NAFLD (BMI < 24 kg/m^2) in this study was 18.5%, which was higher than the prevalence of lean-NAFLD (BMI < 25 kg/m^2) in the United States (about 7%–9%) (31,32). However, higher prevalence rates (approximately 19%–35%) (33–35) of lean-NAFLD in Asia have been reported more recently. Our results were comparable with those of a study conducted in Taiwan (17.9% among subjects with BMI around 17.5–22.4 kg/m^2) (15) and a study conducted in China (18.33% among subjects with BMI < 24 kg/m^2) (36).

Obesity and metabolic syndromes are both well-known factors associated with NAFLD. Expediting body fat expansion and hormone changes in the male population accelerates the production of free fatty acids and adipocytokines. This results in insulin resistance and NAFLD (37). Asians generally have lower BMIs than Westerners, with only 2%–3% of Asians being classified as obese by the current Western criteria (38). In a lean population, Kim et al. (39) demonstrated that their Asian study subjects showed a similar prevalence rate of NAFLD as that for Western people, despite their lower BMIs. Hence, as shown in this study, male sex, body fat mass, and high BMI are still important associated factors for NAFLD, even in the lean population.

Table 5. Evaluation of the series fatty liver index cut-off values

Cutoff value	Sensitivity	Specificity	LR+	LR−	PPV	NPV	Discriminant ability	NAFLD, N (%)
5[a]	91.53	38.50	1.49	0.22	24.5	95.4	65.02	196 (4.9)
10	72.88	63.96	2.02	0.42	30.6	91.5	68.42	161 (4.0)
15[b]	61.58	77.37	2.72	0.50	37.2	90.2	69.48	131 (3.3)
20	50.28	85.73	3.52	0.58	43.4	88.8	68.01	109 (2.7)
25	41.24	89.30	3.85	0.66	45.6	87.5	65.27	90 (2.3)
30[c]	35.03	92.74	4.83	0.70	51.2	86.8	63.89	74 (1.9)
35	26.55	94.59	4.91	0.78	51.6	85.5	60.57	58 (1.5)
40	21.47	95.69	4.99	0.82	52.1	84.8	58.58	46 (1.2)
45	16.95	96.92	5.51	0.86	54.5	84.3	56.94	37 (0.9)
50[a]	11.30	98.40	7.07	0.90	60.6	83.6	54.85	31 (0.8)
55	7.34	98.65	5.43	0.94	54.2	83.0	53.00	26 (0.7)
60[c]	4.52	99.02	4.59	0.96	50.0	82.6	51.77	17 (0.3)
65	2.82	99.26	3.83	0.98	45.5	82.4	51.04	10 (0.3)
70	2.26	99.38	3.67	0.98	44.4	82.4	50.82	7 (0.2)
75	1.13	99.63	3.06	0.99	40.0	82.2	50.38	6 (0.2)

LR−, negative likelihood ratio; LR+, positive likelihood ratio; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value.
[a]Represents suitable cut-off values for ruling in and ruling out lean-NAFLD.
[b]Represents suitable cut-off values for high-risk lean-NAFLD by the Youden test in this study.
[c]Represents suitable cut-off values according to the Bedogni method (14).

Conversely, metabolic factors including FPG, UA, TG, and ALT levels were associated with lean-NAFLD in our study. Previous studies have substantiated the link between NAFLD and metabolic factors including hypertriglyceridemia (40), elevated FPG (40,41), and hyperuricemia (42), as well as increased liver enzymes including ALT (43) and GGT (44). These findings are in line with our findings, despite the absence of obesity. Lean people with metabolic aberrances are still at risk for NAFLD.

The lean-NAFLD phenomenon could be explained by variations in the fat distribution among Asian populations. Asian people tend to have greater central obesity and visceral adiposity, despite having normal BMIs (38,45). Additionally, visceral adipose tissue is attributed to insulin resistance and pronounced lipolysis. Consequently, deteriorated glucose and lipid metabolism can lead to NAFLD (46). Visceral adipose tissue has greater lipolytic activity than subcutaneous adipose tissue, which results in fatty acids being delivered to the liver directly. Induction of lipolysis and increased delivery of lipids to the liver worsens insulin resistance in the liver. This aggravates dyslipidemia by increasing TG synthesis (47). Furthermore, Lanaspa et al. (48) concluded that hyperuricemia could produce oxygen-free radical stress and aggravate inflammation (49), which engenders the progression of fatty liver disease. Finally, higher serum ALT and GGT were correlated with intrahepatic oxidative stress and steatosis (50). Hence, as shown in this study, patients with lean-NAFLD had a higher incidence of comorbidities including cardiovascular disease, hypertension, DM, and dyslipidemia than did lean patients without NAFLD.

Our findings support that FLI is a predictor of lean-NAFLD and is superior to other noninvasive markers. Although the positive predictive value of 38.3% in this study was low, it was affected by the low prevalence of NAFLD in our study population. Our findings were comparable to those of previous studies that referred to FLI as a feasible indicator of ultrasonographic NAFLD (51,52). Our results revealed the cut-off value of FLI $<$ 5 for ruling out lean-NAFLD and FLI $>$ 50 for ruling in lean-NAFLD. However, the cut-off value identified in this study is lower than that reported in previous study of Western populations (14). This could be explained by the low BMI and low WC in our study group, as well as by the presence of central adiposity in the lean Asian population (53). The cut-off values for WC and BMI among Asians were disparate due to different ethnicities, dietary habits, and environmental factors (54). Further investigations in larger prospective studies are needed to validate our study results. Owing to the lack of an established nationwide health policy addressing NAFLD, at present, blood testing is more easily accessible and cost-effective than ultrasonography. Hence, for the avoidance of unnecessary tests and clinical practice, we suggest using an FLI value $\geq$15 as a reasonable cut-off value for screening of lean-NAFLD, especially in those lean participants with metabolic disparities such as serum FPG $\geq$ 100 mg/dL and UA $\geq$ 6 mg/dL.

Limitations

There are some limitations to this study. First, we did not use liver biopsy to diagnose NAFLD. We also cannot detect NAFLD if there is less than 33% fat in the liver and with lower BMI because of the limitations of the ultrasound technique. Moreover, ultrasound findings are operator-dependent and less precise for detecting mild NAFLD. However, in this study, the procedures were performed and verified by a fixed single group of experienced technicians and radiologists, thus decreasing this potential bias dramatically. Second, FLI did not detect advanced fibrosis and steatohepatitis in the original study. Hence, we excluded those patients who had liver cirrhosis history or ultrasonographic detected liver cirrhosis at the beginning of the study, and we used FLI for the prediction of NAFLD rather than steatohepatitis or advanced fibrosis in the lean population. Third, we used BMI $<$ 24 kg/m^2 as the cut-off value for defining the lean population in both men and women. These criteria were chosen in accordance with a previous study in Asia.[56] However, the bias inherent to the potential presence of sexual dimorphism could not be avoided. Future research is needed to identify truly independent and quantitative markers of steatosis between the sexes. Fourth, we did not obtain insulin resistance and HOMR index data, which were previously reported to be robustly correlated with NAFLD. We also did not check serum insulin levels routinely. A prospective study to verify the FLI value and testing another index for this low prevalence but potentially at-risk population may be needed in the future.

Altogether, FLI was superior to liver function parameters, some metabolic factors, and sex for predicting lean-NAFLD. In addition, the FLI is a relatively easy parameter to evaluate and is a cost-effective, noninvasive marker to screen for NAFLD in lean populations, especially those who have metabolic discrepancies.

CONFLICTS OF INTEREST

Guarantor of the article: Hsien-Chung Yu, MD.

Specific author contributions: C.-L.H. and H.-C.Y.: collected data, draft and revised the manuscript. C.-L.H., K.-H.L., and H.-C.Y.: participated in planning the study design, analyzed and interpreted the data. F.-Z.W. and Y.-H.C.: helped with the statistical analyses and interpreted the data. P.-C.W., Y.-H.C., C.-S.C., W.-H.W., and G.-Y.M.: assisted with collecting data and reviewing the database. All authors have read and approved the final draft submitted.

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Study Highlights

WHAT IS KNOWN

- ✓ Prevalence of NAFLD is increasing among lean population worldwide.
- ✓ NAFLD is an independent risk factor for comorbid metabolic conditions irrespective of patient BMI.
- ✓ The FLI could be considered a marker to screen for lean-NAFLD.

WHAT IS NEW HERE

- ✓ Overall, 18.5% of the lean population in one institution at Southern Taiwan had NAFLD.
- ✓ Lean-NAFLD was associated with male sex, BMI, body fat mass, liver function, and metabolic factors.
- ✓ FLI eclipsed other noninvasive metabolic factors at predicting lean-NAFLD.

TRANSLATIONAL IMPACT

- ✓ The FLI bring a better foundation to identify lean-NAFLD.
- ✓ The FLI have a potential to reduce unnecessary screenings.
- ✓ For a greater clinical impact we may expand the use of FLI and other parameters to identify lean-NAFLD in the future.

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