

RESEARCH ARTICLE

# External Validation of Fatty Liver Index for Identifying Ultrasonographic Fatty Liver in a Large-Scale Cross-Sectional Study in Taiwan

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## Abstract

### Background and Aims

The fatty liver index (FLI) is an algorithm involving the waist circumference, body mass index, and serum levels of triglyceride and gamma-glutamyl transferase to identify fatty liver. Although some studies have attempted to validate the FLI, few studies have been conducted for external validation among Asians. We attempted to validate FLI to predict ultrasonographic fatty liver in Taiwanese subjects.

### Methods

We enrolled consecutive subjects who received health check-up services at the Taipei Veterans General Hospital from 2002 to 2009. Ultrasonography was applied to diagnose fatty liver. The ability of the FLI to detect ultrasonographic fatty liver was assessed by analyzing the area under the receiver operating characteristic (AUROC) curve.

### Results

Among the 29,797 subjects enrolled in this study, fatty liver was diagnosed in 44.5% of the population. Subjects with ultrasonographic fatty liver had a significantly higher FLI than those without fatty liver by multivariate analysis (odds ratio 1.045; 95% confidence interval, CI 1.044–1.047,  $p < 0.001$ ). Moreover, FLI had the best discriminative ability to identify patients with ultrasonographic fatty liver (AUROC: 0.827, 95% confidence interval, 0.822–0.831). An FLI  $< 25$  (negative likelihood ratio (LR–) 0.32) for males and  $< 10$  (LR– 0.26) for

design, data collection and analysis, decision to publish, or preparation of the manuscript.

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females rule out ultrasonographic fatty liver. Moreover, an FLI  $\geq 35$  (positive likelihood ratio (LR+) 3.12) for males and  $\geq 20$  (LR+ 4.43) for females rule in ultrasonographic fatty liver.

## Conclusions

FLI could accurately identify ultrasonographic fatty liver in a large-scale population in Taiwan but with lower cut-off value than the Western population. Meanwhile the cut-off value was lower in females than in males.

## Introduction

Fatty liver disease has become an emerging public health concern because its prevalence and incidence rates have rapidly increased in recent decades [1,2]. With different study populations and diagnostic tools, the prevalence rate of fatty liver disease has been reported to be 10–35% in the United States. Fatty liver is correlated with metabolic factors such as central obesity, insulin resistance, arterial hypertension, and hypertriglyceridemia [3,4]. Due to the Westernization of diet and lifestyle and the aging population, the prevalence rate of fatty liver is also increasing in Asian countries. Large population-based surveys in China, Japan, Korea, and Taiwan indicate that the prevalence of fatty liver disease now stands at 12% to 51% in population subgroups, depending on age, gender, ethnicity, and social-economic status [2,5–7].

Moreover, fatty liver disease is now the leading cause of abnormal liver biochemistry tests in the primary care setting worldwide [8]. The clinic-pathological spectrum of fatty liver disease ranges from simple steatosis to steatohepatitis, which may progress to liver cirrhosis and hepatocellular carcinoma (HCC) [9]. The prevalence of fatty liver-related cirrhosis has markedly increased in recent years as the underlying liver disease among patients undergoing transplants for HCC in the United States [10,11]. Welzel et al. further demonstrated that diabetes and/or obesity had the largest population-attributable fractions of HCC, with a value of 36.6% [12]. This rate is significantly higher than that of viral hepatitis, suggesting a dominant role of fatty liver and metabolic disorders for hepatic carcinogenesis.

Most subjects with fatty liver do not have specific symptoms, especially at the early stage, which limits prevention and early detection of fatty liver disease [13]. Liver biopsy is regarded as the gold standard for quantification of liver steatosis in fatty liver disease [14]. However, it is not routinely performed because it is an invasive procedure with a significant degree of sampling error. Hence, the diagnosis of fatty liver in the population studies is usually made by ultrasonography [9]. More sensitive techniques, including magnetic resonance imaging and spectroscopy, are hindered by expense and unfeasibility for large populations [15].

Bedogni et al. established a formula to calculate the fatty liver index (FLI) based on triglycerides (TG), body mass index (BMI), gamma-glutamyltransferase (GGT), and waist circumference (WC) to predict ultrasonographic fatty liver in an Italian cohort [16]. This simple and non-invasive algorithm has excellent discriminative ability to detect ultrasonographic fatty liver disease. Nevertheless, few studies have been conducted for the external validation of FLI in Asians thus far [17]. We attempted to validate FLI for the prediction of ultrasonographic fatty liver in Taiwanese subjects and compared FLI with lipid accumulation products (LAP) which is recently considered as a good marker of liver steatosis [18]. We also attempted to determine the optimal cut-off levels of FLI in detecting ultrasonographic fatty liver and stratified them by gender.

## Materials and Methods

### Study population

There were 34,346 consecutive examinees receiving health check-up services at the Taipei Veterans General Hospital from 2002 to 2009. Subjects who had chronic hepatitis C virus (HCV) infection ( $n = 819$ ), chronic hepatitis B virus (HBV) infection ( $n = 3,642$ ), and dual HBV/HCV infections ( $n = 88$ ) were excluded. The remaining 29,797 subjects were included in the final analysis.

All of the subjects underwent a complete clinical evaluation, laboratory examination and abdominal ultrasonography. BMI was calculated by the division of the body weight in kilograms by the square of body height in meters. In this study, all ultrasonography were performed by five senior doctors with more than 10 years of experience and fatty liver was diagnosed according to the criteria from the American Gastroenterology Association including (1) a diffuse hyperechoic echotexture, (2) increased liver echotexture compared with the kidneys, (3) vascular blurring, and (4) deep attenuation [19]. One recent meta-analysis conducted by Hernaez and colleagues showed that ultrasonography had reliable and accurate detection of fatty liver [20]. Moreover, Dasarathy demonstrated that the increased hepato-renal contrast and bright liver were able to identify the presence of  $\geq 20\%$  area of involvement with fat with a sensitivity of 96.4% and a specificity of 97.8% [21]. The study followed the standards of the Declaration of Helsinki and has been approved by the Institutional Review Board (IRB) of the Taipei Veterans General Hospital. As the dataset used in this study is consisted of de-identified data from a retrospective cohort, the written informed consents from the subjects who receiving physical check-up services were waived by the approval of the IRB.

### Biochemical and serologic markers

Venous blood samples were collected after an overnight fast. Radio-immunoassay (Abbott Laboratories, North Chicago, IL, USA) was used to test serum HBV surface antigen (HBsAg), and second-generation enzyme immunoassay (Abbott Laboratories) was used to test antibody to HCV (anti-HCV). The Roche/Hitachi Modular Analytics System (Roche Diagnostics GmbH, Mannheim, Germany) was utilized to measure serum biochemical markers. FLI was calculated using the following formula:  $FLI = (e^{0.953 \cdot \log_e(TG)} + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot WC - 15.745) / (1 + e^{0.953 \cdot \log_e(TG)} + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot WC - 15.745) \cdot 100$  [16]. LAP was calculated with formula:  $LAP = (\text{waist circumference (cm)} - 58) \times \text{triglycerides (mmol/l)}$  [18].

### Statistical analysis

Pearson's chi-squared analysis and Student t-test analysis were performed to compare categorical and continuous variables between subjects with and without ultrasonographic fatty liver. Variables with statistical significance ( $P < 0.05$ ) or proximate to it ( $P < 0.1$ ) in univariate analysis were further included in multivariate analysis using a logistic regression model with the forward stepwise selection procedure. The performance of serum markers in diagnosing ultrasonographic fatty liver was examined using the area under the receiver operator characteristic (AUROC) curves. The AUROC was expressed as plots of the test sensitivity vs. 1—specificity. The sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), positive predictive value (PPV), and negative predictive value (NPV) were also assessed. A P value of  $< 0.05$  was considered to be statistically significant. All statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

**Table 1. Comparison of demographic characteristics between subjects with and without ultrasonographic fatty liver.**

	All (n = 29797)	Without fatty liver (n = 16542)	With fatty liver (n = 13255)	P
Age, years	52.2±13.3	50.9±14.1	53.9±11.9	<0.001
Sex, (M/F) (%)	16098/13699 (54.0%/46.0%)	7388/9154 (44.7%/55.3%)	8710/4545 (65.7%/34.3%)	<0.001
BMI, kg/m <sup>2</sup>	23.82±3.58	22.32±2.90	25.68±3.47	<0.001
WC, cm	83.8±1.3	79.5±9.0	89.1±9.3	<0.001
SBP, mmHg	124.3±18.6	121.1±18.5	128.2±18.0	<0.001
DBP, mmHg	77.5±14.3	75.3±11.6	80.4±16.6	<0.001
Fasting Glucose, mg/dL	95.5±24.8	90.7±19.1	101.6±29.3	<0.001
Cholesterol, mg/dL	199.2±37.0	194.0±36.0	205.0±37.5	<0.001
LDL, mg/dL	125.3±32.9	120.5±31.7	131.4±33.2	<0.001
HDL, mg/dL	53.7±15.0	58.2±15.5	48.1±12.3	<0.001
TG, mg/dL	130.4±88.1	101.0±57.2	167.1±104.6	<0.001
ALT, U/L	27.0±22.2	21.2±17.2	34.3±25.3	<0.001
AST, U/L	23.1±13.2	21.1±11.4	25.5±14.8	<0.001
GGT, IU/L	24.8±36.8	20.0±33.9	30.8±39.4	<0.001
Platelet, 1000/mm <sup>3</sup>	249.83±60.33	247.62±60.90	252.56±59.50	<0.001
FLI	27.23±19.50	15.61±16.27	41.75±24.58	<0.001
LAP	32.29±12.55	26.58±10.24	30.42±11.47	<0.001

Continuous variables are expressed as mean ± standard deviation

Abbreviations: M, male; F, female; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; FLI, fatty liver index; LAP, lipid accumulation products

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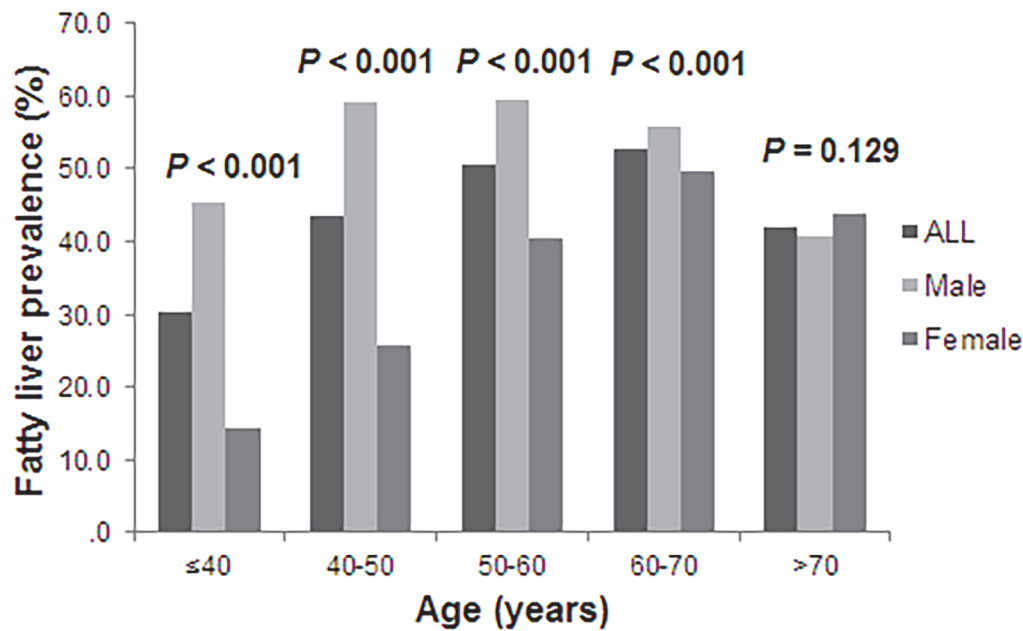
## Results

### Demographic characteristics of study subjects

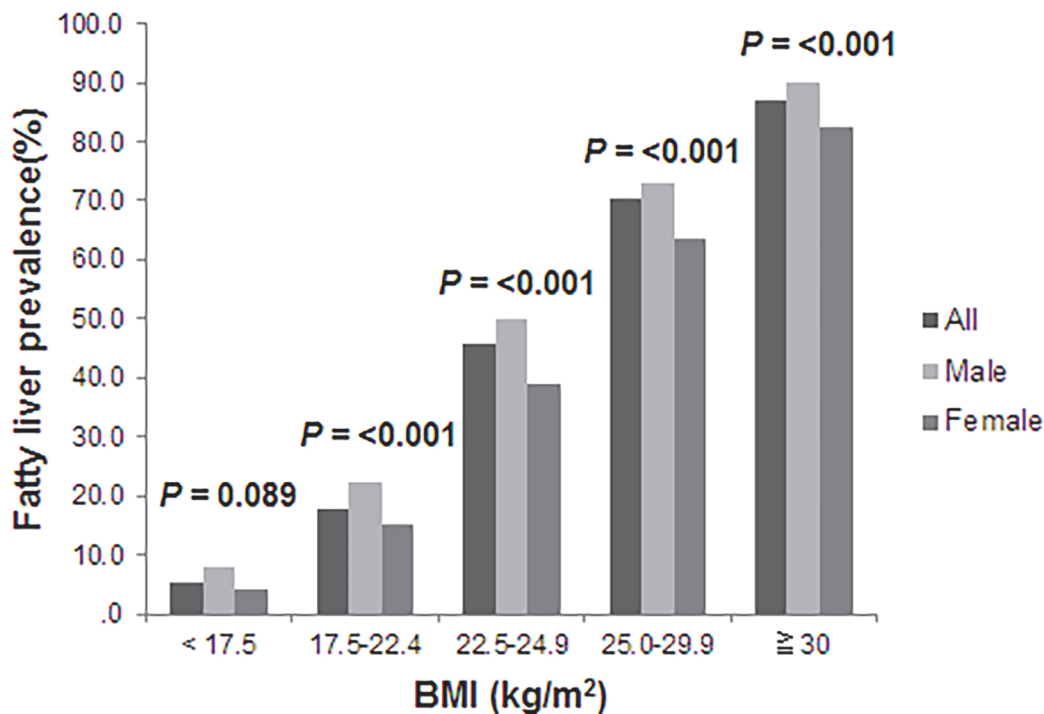
Among the 29,797 subjects that were enrolled in this study, the mean age was 52.2 years, and 54.0% were male. Fatty liver was diagnosed by ultrasonography in 44.5% of the whole population. As summarized in [Table 1](#), compared to subjects without ultrasonographic fatty liver, those with fatty liver tended to be older and male, and they had higher BMI, larger WC, higher systolic and diastolic blood pressure (BP), higher levels of fasting glucose, cholesterol, low density lipoprotein (LDL), TG, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and GGT, higher platelet counts, and higher FLI, but lower high-density lipoprotein (HDL) levels according to univariate analysis.

Compared to females, male subjects were older, and they had higher BMI, larger WC, higher systolic and diastolic BP, higher levels of fasting glucose, LDL, TG, ALT, AST, and GGT, but lower platelet counts, serum cholesterol, and HDL levels ([S1 Table](#)). Moreover, male subjects had a significantly higher rate of fatty liver diagnosed by ultrasonography (54.1% vs. 33.2%,  $p < 0.001$ ) and higher FLI (mean ± standard deviation, 35.35 ± 24.68 vs. 17.70 ± 19.70,  $p < 0.001$ ) than female subjects. When stratified by age and BMI, the prevalence rates of ultrasonographic fatty liver were significantly higher in male subjects than in females in most of the age populations except those who were older than 70 years or those with BMI < 17.5 kg/m<sup>2</sup> ([Fig. 1](#) and [S2 Table](#)).

A



B



**Fig 1. Comparison of the prevalence rate of ultrasonographic fatty liver between male and female subjects. (A)** Comparison of ultrasonographic fatty liver prevalence rate between male and female subjects stratified by age. **(B)** Comparison of ultrasonographic fatty liver prevalence rate between male and female subjects stratified by body mass index.

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**Table 2. Factors associated with ultrasonographic fatty liver in different populations by multivariate analysis in model I.**

	Odds Ratio	95% Confidence level	P value
<b>All subjects</b>			
Age, years	1.007	1.004–1.009	<0.0001
Fasting glucose, mg/dL	1.009	1.007–1.010	<0.0001
LDL, mg/dL	1.006	1.005–1.007	<0.0001
ALT, U/L	1.017	1.015–1.020	<0.0001
Platelet, 1000/mm <sup>3</sup>	1.002	1.002–1.003	<0.0001
HDL, mg/dL	0.980	0.978–0.983	<0.0001
FLI	1.045	1.044–1.047	<0.0001
<b>Females</b>			
Age, years	1.013	1.009–1.018	<0.0001
Fasting glucose, mg/dL	1.011	1.008–1.013	<0.0001
LDL, mg/dL	1.006	1.005–1.008	<0.0001
ALT, U/L	1.016	1.013–1.020	<0.0001
Platelet, 1000/mm <sup>3</sup>	1.003	1.002–1.004	<0.0001
HDL, mg/dL	0.978	0.975–0.981	<0.0001
FLI	1.053	1.050–1.056	<0.0001
<b>Males</b>			
Fasting glucose, mg/dL	1.007	1.009–1.009	<0.0001
LDL, mg/dL	1.005	1.004–1.006	<0.0001
ALT, U/L	1.018	1.015–1.021	<0.0001
Platelet, 1000/mm <sup>3</sup>	1.002	1.001–1.002	<0.0001
HDL, mg/dL	0.982	0.979–0.985	<0.0001
FLI	1.043	1.041–1.045	<0.0001

Abbreviations: SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; ALT, alanine aminotransferase; FLI, fatty liver index

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## Factors associated with ultrasonographic fatty liver in different populations by multivariate analysis

As FLI is calculated by the combination of BMI, WC, serum TG, and GGT levels, we applied two models in multivariate analysis to minimize the potential confounding effects of these parameters. In model I, FLI was enrolled, but its 4 components were not entered into multivariate analysis. In model II, we selected BMI, WC, TG, and GGT for the multivariate analysis, but not FLI.

As shown in [Table 2](#), the multivariate analysis in model I demonstrated that older age, higher fasting glucose, LDL, and ALT levels, higher platelet counts, higher FLI, and low HDL levels were the independent risk factors correlated with ultrasonographic fatty liver in the whole population. In model II, higher BMI, WC, higher fasting glucose, LDL, TG, GGT levels, and lower HDL levels were associated with ultrasonographic fatty liver in multivariate analysis ([S3 Table](#)). The results were similar when the analyses were stratified by gender in both model I and model II. This indicated that FLI and its components were all critical factors for determining ultrasonographic fatty liver, irrespective of gender.

**Table 3. Comparison of AUROCs among non-invasive markers for predicting ultrasonographic fatty liver.**

	AUROC	95% CI	Standard error	P value
<b>All subjects</b>				
FLI	0.827	0.822–0.831	0.002	<0.0001
LAP	0.806	0.801–0.811	0.003	<0.0001
BMI	0.787	0.782–0.791	0.003	<0.0001
WC	0.777	0.771–0.782	0.003	<0.0001
ALT	0.741	0.735–0.746	0.003	<0.0001
GGT	0.715	0.710–0.720	0.003	<0.0001
Fasting glucose	0.663	0.658–0.669	0.003	<0.0001
Cholesterol	0.582	0.575–0.588	0.003	<0.0001
TG	0.755	0.750–0.761	0.003	<0.0001
HDL	0.702	0.696–0.708	0.003	<0.0001
LDL	0.597	0.591–0.604	0.003	<0.0001
<b>Female</b>				
FLI	0.827	0.820–0.834	0.004	<0.0001
LAP	0.794	0.786–0.802	0.004	<0.0001
BMI	0.786	0.778–0.794	0.004	<0.0001
WC	0.762	0.754–0.770	0.004	<0.0001
ALT	0.717	0.708–0.726	0.005	<0.0001
GGT	0.708	0.699–0.717	0.005	<0.0001
Fasting glucose	0.708	0.698–0.717	0.005	<0.0001
Cholesterol	0.599	0.589–0.609	0.005	<0.0001
TG	0.759	0.750–0.767	0.004	<0.0001
HDL	0.690	0.681–0.700	0.005	<0.0001
LDL	0.622	0.613–0.632	0.005	<0.0001
<b>Male</b>				
FLI	0.800	0.793–0.806	0.003	<0.0001
LAP	0.785	0.778–0.792	0.004	<0.0001
BMI	0.760	0.752–0.767	0.004	<0.0001
WC	0.754	0.746–0.761	0.004	<0.0001
ALT	0.725	0.717–0.732	0.004	<0.0001
GGT	0.675	0.667–0.683	0.004	<0.0001
Fasting glucose	0.616	0.607–0.625	0.004	<0.0001
TG	0.720	0.712–0.728	0.004	<0.0001
Cholesterol	0.581	0.572–0.590	0.004	<0.0001
HDL	0.657	0.649–0.664	0.004	<0.0001
LDL	0.572	0.563–0.581	0.005	<0.0001

Abbreviations: AUROC: area under the receiver operating characteristic; CI: confidence interval; FLI: fatty liver index; LAP, lipid accumulation products; BMI, body mass index; GGT, gamma-glutamyl transferase; TG: triglyceride; WC, waist circumference; ALT: alanine aminotransferase; LDL: low-density lipoprotein

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### Validation of FLI for identifying ultrasonographic fatty liver and selection of its optimal cut-off value

Subsequently, we compared the discriminative ability to identify ultrasonographic fatty liver among FLI and other clinical non-invasive markers by comparing their AUROCs. As depicted in [Table 3](#), FLI had the highest AUROC with a value of 0.827 (95% confidence interval, CI



**Table 4. Selecting the optimal cut-off value of FLI in identifying ultrasonographic fatty liver stratified by gender.**

Cut-off	Sensitivity (%)	Specificity (%)	LR+	LR-	DOR	PPV (%)	NPV (%)
<b>Female</b>							
05	91.79	43.84	1.63	0.19	8.57	44.8	91.5
<b>10</b>	<b>81.9</b>	<b>68.4</b>	<b>2.59</b>	<b>0.26</b>	<b>9.96</b>	<b>56.3</b>	<b>88.4</b>
15	71.8	79.5	3.50	0.35	10	63.5	87.6
<b>20</b>	<b>62.0</b>	<b>86.0</b>	<b>4.43</b>	<b>0.44</b>	<b>10.06</b>	<b>68.7</b>	<b>82.0</b>
25	53.9	90.3	5.55	0.51	10.88	73.3	79.7
30	46.2	93.0	6.63	0.58	11.43	76.6	77.7
35	39.4	94.7	7.42	0.64	11.59	78.7	75.9
40	33.7	96.2	8.86	0.69	12.84	81.5	74.5
45	27.8	97.2	9.85	0.74	13.31	83.1	73.1
50	22.8	97.9	10.79	0.79	13.65	84.4	71.9
55	18.8	98.5	12.84	0.82	15.65	86.4	71.0
60	15.1	99.0	12.85	0.86	14.94	88.1	70.0
<b>Male</b>							
05	99.04	12.67	1.13	0.07	16.14	54.2	91.7
10	96.3	30.7	1.38	0.13	10.61	62.0	86.4
15	90.9	45.7	1.68	0.20	8.4	66.4	81.0
20	85.3	57.5	2.01	0.26	7.73	70.3	76.9
<b>25</b>	<b>78.5</b>	<b>67.0</b>	<b>2.38</b>	<b>0.32</b>	<b>7.43</b>	<b>73.7</b>	<b>72.5</b>
30	71.1	74.5	2.78	0.39	7.12	76.6	68.6
<b>35</b>	<b>63.0</b>	<b>79.8</b>	<b>3.12</b>	<b>0.46</b>	<b>6.78</b>	<b>78.6</b>	<b>64.6</b>
40	56.1	84.1	3.53	0.52	6.78	80.6	61.9
45	49.2	84.8	4.03	0.58	6.94	82.6	59.5
50	42.5	90.7	4.55	0.63	7.22	84.3	57.2
55	36.6	92.9	5.08	0.69	7.36	85.7	55.2
60	30.5	94.8	5.83	0.73	7.98	87.3	53.6

Abbreviations: LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; DOR: diagnostic odd ratios

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0.822–0.831) in comparison to other single markers, such as BMI, LAP, GGT, TG, WC, ALT, fasting glucose, cholesterol, LDL and HDL. When analyses were stratified by gender, the AUR-OCs of FLI in predicting ultrasonographic fatty liver were 0.827 (95% CI 0.820–0.834) and 0.800 (95% CI 0.793–0.806) for females and males, respectively. They were both higher than those of the other markers, suggesting FLI had the best discriminative ability to predict ultrasonographic fatty liver compared to other non-invasive markers in both genders.

As shown in Table 4, by using Bedogni’s method [16], the two cut-off points for the males are FLI <25 (Sensitivity 78.5%, Specificity 67.0%, LR+ 2.38, LR- 0.32) for exclusion and FLI ≥35 (Sensitivity 63.0%, Specificity 79.8%, LR+ 3.12, LR-: 0.46) for inclusion of ultrasonographic fatty liver. For the females, the two cut-off values are FLI <10 (Sensitivity 81.9%, Specificity 68.4%, LR+ 2.59, LR- 0.26) to rule out ultrasonographic fatty liver and FLI ≥20 (Sensitivity 62.0%, Specificity 86.0%, LR+ 4.43, LR- 0.44) to rule in ultrasonographic fatty liver, respectively.

## Discussion

With the growing epidemic of obesity, the prevalence rates of fatty liver have increased in both Eastern and Western countries [7,8]. Previous studies conducted in Western countries



demonstrated that the risk factors of fatty liver disease include age, gender, and metabolic factors, such as central obesity, higher BMI, elevated fasting blood glucose, insulin, TG, and cholesterol, and lower HDL levels [9,22]. Our study also validates that Asian subjects are at risk of ultrasonographic fatty liver disease if they possess these metabolic aberrances.

Although Asians have a significantly lower BMI compared to other ethnic populations, they have a surprisingly high prevalence rate of fatty liver disease [23]. Moreover, Asian people have a significantly higher incidence of metabolic syndrome than other ethnic groups with similar BMI [24]. This may be due to the more central adiposity and visceral fat deposition in Asian subjects [23]. In our study, fatty liver was diagnosed by ultrasonography in 44.5% of patients who received physical check-up in a single medical center from Taiwan. Notably, the prevalence rates of ultrasonographic fatty liver were 5.2% and 17.9% for subjects with BMIs of  $<17.5 \text{ kg/m}^2$  and  $17.5\text{--}22.4 \text{ kg/m}^2$ , respectively. This suggests that fatty liver disease is not uncommon in non-obese Asian subjects [23]. They may progress to steatohepatitis, cirrhosis, and even HCC if not diagnosed promptly. Moreover, previous studies have demonstrated that the development of HCC in patients with hepatic steatosis can occur in the absence of liver cirrhosis [25]. Consequently, the development of a feasible non-invasive screening marker is needed to identify high-risk groups of patients with fatty liver in non-obese populations, who are easily overlooked if there is a lack of clinical suspicion.

Fatty liver is not only a hepatic manifestation of metabolic syndrome, but it could also promote the development of metabolic-related extra-hepatic complications like cardiovascular disease (CVD), type 2 diabetes, chronic kidney disease, hypothyroidism, polycystic ovarian syndrome, osteoporosis, and colorectal cancer [1,9,26]. Notably, a growing body of evidence shows that patients with fatty liver disease have a significantly higher risk of CVD compared to general populations of the same age and gender [27,28]. Although CVD and fatty liver disease share similar risk factors, such as insulin resistance and central adiposity, fatty liver disease is independently associated with the presence of CVD [26]. This may be due to the increased inflammatory cytokines, insulin resistance, and free fatty acid promoted by the expanded and inflamed visceral fat mass in patients with fatty liver [27]. It highlights the critical role of fatty liver in determining the prognoses of subjects with metabolic syndrome. Hence, there is an urgent need to identify well-validated, quantitative, cost-effective, and non-invasive methods for the evaluation of fatty liver disease in clinical practice as well as epidemiological and clinical research.

FLI is a feasible marker that involves four clinical available parameters, and it is easily calculated in an office setting. It has been proven to correlate well with fatty liver diagnosed by ultrasonography [16]. Moreover, one study conducted with a large middle-aged non-diabetic European population demonstrated that FLI was correlated with insulin resistance, coronary heart disease, and early atherosclerosis [29]. Calori et al. further showed that FLI was associated with all-cause, hepatic-related, cardiovascular disease-related, and cancer mortality [30]. This suggests that FLI could be applied not only for screening fatty liver disease, but also for identifying high-risk groups of subjects for metabolic and cardiovascular disorders, which are critical public health issues that are worthy of concern. However, due to variations in ethnicity, dietary, and environmental factors, the cut-off for waist and BMI is different for Asian people [31]. Thus, FLI needs to be validated when used in a different population. Our study confirmed the significance of FLI as an indicator of ultrasonographic fatty liver and its close link to metabolic syndrome. It had better discriminative ability for identifying ultrasonographic fatty liver than other serum markers and could therefore be recommended for Asian subjects.

In our cohort, male subjects had a higher rate of ultrasonographic fatty liver compared to the female population in most subgroup analyses. There are several mechanisms that might explain this phenomenon. First, male subjects had higher BMI and showed more metabolic

derangement, which are both important determinants of fatty liver disease. Second, in comparison to females, male subjects had more accelerating visceral adipose tissue expansion with the increase of age, which in turn facilitates the development of insulin resistance and fatty liver by the production of free fatty acid and adipocytokines [32]. Third, it is speculated that estrogen could suppress visceral adipose tissue and TG accumulation [33]. One recent study showed that estrogen receptor ligands reduced hepatic TG levels through the inhibition of liver X receptor transcriptional activity in a mouse model [34]. For the female population, the risk of obesity and metabolic syndrome markedly increase after menopause, implying a protective role of estrogen in the development of fatty liver disease [35]. This may explain the differences in the prevalence rate of ultrasonographic fatty liver in both genders decreasing after post-menopausal age in our cohort (Fig. 1A). Moreover, females had a similar prevalence rate of ultrasonographic fatty liver compared to males in subjects who were older than 70 years.

Compared to the cut-off values proposed by Bedogni et al., our findings were lower for both genders [16]. According to the metabolic syndrome criteria from the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, the cut-off values of WC, which is a major component of FLI, are set lower for Asian female subjects (80 cm) and for males (90 cm), respectively [31,32]. This might explain the lower cut-off values of FLI in our cohort, especially in female subjects. Another possible mechanism is the more central adiposity and higher incidence of fatty liver in non-obese Asians compared to the Western populations [24]. Nevertheless, further prospective studies are still needed to validate this result.

This study has a number of limitations that are worth noting. First, the study population had a higher socio-economic status, and subjects could afford the expense of a physical check-up, so the prevalence rate of ultrasonographic fatty liver may be higher than that of the general population. Second, some liver-related diseases, such as alcohol consumption, medication use, autoimmune liver disease, congenital liver disease, diabetes mellitus and hyperlipidemia were not documented in the study. Nevertheless, previous studies showed that these factors may only have a small effect on the result [36,37]. For example, Chen et al. demonstrated that the etiology of elevated serum ALT level due to alcohol consumption is as low as 0.8% in a Taiwanese community study [38]. Besides, from a National Health Interview Survey in Taiwan, there were 1.82% of the young adults and 4.82% of the middle-aged adults in Taiwan drank alcohol on a daily basis with the corresponding estimates for probable alcoholism were 2.40% and 2.27%, respectively [39]. This suggests that alcohol consumption only plays a very minor role in the development of fatty liver in Taiwan. Third, we adopted ultrasonography as a diagnostic tool for fatty liver. Its sensitivity decreased with while hepatic steatosis is less than 20%. It might result in underestimation of the rate of fatty liver disease. Although ultrasonography was performed by five 10-year-experience senior doctors with the same criteria, the inter-observation and intra-observation variations were unavailable due to the retrospective study design. Nevertheless, the strengths of this study are the large sample size and the detailed biochemistry data which provide robust data for the external validation of FLI in predicting ultrasonographic fatty liver in Asian subjects.

In conclusion, FLI could accurately identify ultrasonographic fatty liver in a large-scale population in Taiwan but the optimal cut-off values are lower than the Western people. Besides, the cut-off value was also noted lower in females. For the males, the optimal cut-off values are the  $FLI < 25$  to rule out and  $FLI \geq 35$  to rule in ultrasonographic fatty liver. For the females,  $FLI < 10$  for exclusion and  $FLI \geq 20$  for inclusion of ultrasonographic fatty liver are chosen.

## Supporting Information

**S1 Table. Comparison of demographic characteristics between male and female subjects.**  
(DOCX)

**S2 Table. Comparison of prevalence rates of ultrasonographic fatty liver between male and female subjects stratified by body mass index.**  
(DOCX)

**S3 Table. Factors associated with ultrasonographic fatty liver in different populations by multivariate analysis in model II.**  
(DOCX)

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## Author Contributions

Conceived and designed the experiments: YCW TIH YHH HIY CWS SDL. Performed the experiments: BLY WCW KCF YCW CWS. Analyzed the data: BLY WCW HIY CWS. Contributed reagents/materials/analysis tools: YCW HCL FYL JCW SDL. Wrote the paper: BLY WCW CWS.

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