Prediction and validation of nonalcoholic fatty liver disease by fatty liver index in a Japanese population

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Abstract. Fatty liver index (FLI) calculated by using body mass index (BMI), waist circumference and levels of γ-glutamyl transferase and triglycerides is a non-invasive predictor of nonalcoholic fatty liver disease (NAFLD). The original study in Italy showed that the cutoff level for prediction of NAFLD was FLI ≥60. However, the sex difference in FLI was not taken into consideration, and it is unclear whether the cutoff value can be applied to other races. We investigated the cutoff value of FLI for prediction of NAFLD determined by abdominal ultrasonography using receiver operating characteristic curve analyses in 14,471 Japanese subjects (men/women: 9,240/5,231; mean age: 48 ± 9 years). There was a significant interaction between sex and FLI for detection of NAFLD (p < 0.001). The cutoff values of FLI in men and women were 35.1 (area under the curve [AUC]: 0.82) and 15.6 (AUC: 0.91), respectively. When the subjects were divided by the absence and presence of obesity (BMI ≥25), there was a significant interaction between FLI and obesity for detection of NAFLD in women (p < 0.001) but not in men (p = 0.679). The cutoff values of FLI in non-obese/obese men and women were 22.6/52.6 and 11.2/33.2, respectively. In conclusion, the cutoff value of FLI for prediction of NAFLD in Japanese individuals was lower than that in the original study, and there is a significant sex difference. The simple and useful cutoff values in Japanese men and women are FLI ≥35 (non-obese/obese: 23/53) and FLI ≥16 (non-obese/obese: 11/33), respectively.

Key words: Nonalcoholic fatty liver disease (NAFLD), Fatty liver index, Non-invasive test, Validation

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disease and is closely related to obesity and lifestyle-related diseases [1, 2]. The frequency of NAFLD in adult subjects who received health examinations has been reported to be 9–30% in Japan [3] and has been increasing in recent years [4]. It has been shown that NAFLD is common even in lean subjects [5], and the prevalence of non-obese NAFLD patients with body mass index (BMI) >25 was approximately 15% in annual health checkup examinations in Japan [6]. NAFLD is a multisystem disease affecting extra-hepatic organs and regulatory pathways [7] in association with increased risks of insulin resistance [8], type 2 diabetes mellitus [9], hypertension [10], cardiovascular disease [11] and chronic kidney disease [12] as well as the development of liver cirrhosis [13] and liver cancer [14]. It is noteworthy that a new concept of metabolic dysfunction-associated fatty liver disease (MAFLD) has recently been proposed regardless of alcohol consumption [15].

In epidemiological studies, several non-invasive biochemical indicators are used for the diagnosis of NAFLD/MAFLD. Among the biomarkers, fatty liver index (FLI), which is calculated by using BMI, waist circumference (WC) and levels of γ-glutamyl transferase (γ-GTP) and triglycerides, was originally reported in Italy as an index for prediction of fatty liver detected by abdominal ultrasonography, and the cutoff value was reported to be FLI ≥60 [16]. The ability of FLI to predict fatty liver has been verified, and its usefulness has been reported in several countries [17-23] as well as in Japan [24] (Supplementary Table S1). However, the sex difference in FLI level was not taken into consideration in most of the studies [17-21, 24] despite the fact that there is a sex difference in the level of FLI [22, 23].
Furthermore, it is not clear whether categorization of FLI using FLI ≥60 is optimal because of the possibility of a racial difference in cutoff levels of FLI for diagnosis of NAFLD [16-24]. Since Asians have lower BMI and WC than those in other ethnic groups [25], their own FLI cutoff values for identification of fatty liver would be necessary. It has been reported that the cutoff level of FLI for diagnosis of NAFLD seems to be lower in Asians than in Europeans: FLI ≥30 in China [18] and FLI ≥60 in Italy [16]. However, the subjects were not divided by sex in either of those studies. These findings indicate that there are racial and sex differences in cutoff levels of FLI for diagnosis of NAFLD. To the best of our knowledge, the sex difference in the FLI value for diagnosis of NAFLD was considered in only two studies performed in Taiwan. One study showed that the cutoff levels in men (n = 16,098) and women (n = 13,699) were FLI ≥35 and FLI ≥20, respectively [22]. The other study showed that the cutoff levels in men (n = 424) and women (n = 947) were FLI ≥20 and FLI ≥10, respectively [23]. Since the cutoff values have varied even in a same country, we investigated prediction and validation of NAFLD, which is defined by abdominal ultrasonography, exclusion of excess alcohol consumption and absence of viral hepatitis, by FLI in a large number of Japanese subjects divided by sex in the present study.

**Methods**

**Study subjects**

All of the subjects who received annual health examinations at Keijinkai Maruyama Clinic, Sapporo, Japan in 2006 were enrolled in this registry (n = 28,990) [26, 27]. A self-administered questionnaire survey was performed to obtain information on smoking habit, alcohol drinking habit and use of drugs for diabetes mellitus, hypertension and dyslipidemia. A flow chart of the study participants is shown in Fig. 1. Exclusion criteria were subjects with hepatitis B surface antigen positive, hepatitis C antibody positive and excess alcohol consumption (alcohol equivalent: ≥30 g/day for men, ≥20 g/day for women) and subjects with the absence of data for abdominal ultrasonography and components of FLI calculation including BMI, WC and levels of γ-GTP and triglycerides. After prespecified exclusion, a total of 14,471 Japanese subjects (men/women: 9,466/6,499) were finally recruited in the present study. The study conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval of the institutional ethical committee of Sapporo Medical University (Number: 30-2-32). Written informed consent was obtained from all of the subjects.

**Measurements**

Medical examinations, blood pressure measurements and samplings of urine and blood were performed after an overnight fast. Body height and weight were measured in light clothing without shoes, and BMI was calculated as body weight in kilograms divided by height in meters squared. FLI was calculated using the algorithm reported by Bedogni et al. [16]: FLI = (a × ln(triglycerides) + 0.139 × BMI + 0.718 × ln(γ-GTP) + 0.053 × WC – 15.745) × 100. The FIB-4 index, a marker of hepatic fibrosis, was calculated by the following formula: age (years) × aspartate aminotransferase (AST; U/L)/(platelet count [10⁹/L] × alanine aminotransferase [ALT; U/L]¹/²) [28].

NAFLD was diagnosed by the presence of fatty liver determined by abdominal ultrasonography in the recruited subjects who had no findings of viral hepatitis and no excess alcohol consumption. Obesity was defined as BMI ≥25. Diabetes mellitus was diagnosed in accordance with the guideline of the American Diabetes Association [29]: fasting plasma glucose ≥126 mg/dL,
hemoglobin A1c ≥6.5% or self-reported use of anti-diabetic drugs. Hypertension was diagnosed as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or self-reported use of anti-hypertensive drugs. Dyslipidemia was diagnosed as low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL, triglycerides ≥150 mg/dL or self-reported use of anti-dyslipidemic drugs.

Abdominal ultrasonography
Abdominal ultrasonography was performed using SSA-250A or SSA-340A (Toshiba Medical, Otawara, Japan) by 10 well-experienced echographers with at least 5 years of experience who were trained by gastroenterologists with more than 5 years of experience. Fatty liver was determined by any findings of high-intensity bright liver, hepato-renal contrast, vascular obscuration and deep attenuation in the liver [30, 31]. The images and the presence of hepatic steatosis were independently reviewed by certified gastroenterologists who were blinded to clinical data.

Statistical analysis
Numeric variables are expressed as means ± standard deviation (SD) for parameters with normal distributions and as medians (interquartile ranges) for parameters with skewed distributions. The distribution of each parameter was tested for its normality using the Shapiro-Wilk W test. Comparison between two groups was done with Mann-Whitney’s U test. Intergroup differences of demographic parameters were tested by the chi-square test. Logistic regression analysis after adjustment of sex was performed to identify subjects with NAFLD using FLI, and the interaction between sex and FLI for the presence of NAFLD was also investigated. The ability of FLI, BMI, WC, triglycerides, γ-GTP, AST, ALT or FIB-4 index to predict NAFLD by 5-value intervals of FLI is shown in Table 2. Both men and women with NAFLD were older and had significantly larger BMI and WC, higher systolic and diastolic blood pressures and pulse rate, higher frequencies of obesity, hypertension, diabetes mellitus, and dyslipidemia and higher levels of hemoglobin, platelet count, albumin, uric acid, ALT, γ-GTP, fasting plasma glucose, hemoglobin A1c, total cholesterol, LDL cholesterol, triglycerides, and FLI and lower levels of eGFR, HDL cholesterol and FIB-4 index than did those without NAFLD.

Prediction and validation of NAFLD by biomarkers
Logistic regression analysis after adjustment of sex showed that FLI was an independent determinant of NAFLD, and there was a significant interaction between FLI and sex for the presence of NAFLD (p < 0.001). Therefore, further analyses for prediction of NAFLD using FLI as well as its related parameters including BMI, WC, triglycerides, γ-GTP, ALT, AST and FIB-4 index were investigated in subjects divided by sex.

ROC curve analyses showed that the cutoff values of FLI for prediction of NAFLD in men (Fig. 2A) and women (Fig. 2B) were 35.1 (sensitivity/specificity: 76.7%/71.3%; AUC [95% CI]: 0.82 [0.81–0.83]; positive predictive value (PPV) [95% CI]: 70.1% [68.8–71.4]; negative predictive value (NPV) [95% CI]: 77.7 [76.4–78.9]; positive likelihood ratio (LR+) [95% CI]: 2.67 [2.55–2.80]; negative likelihood value (LR−) [95% CI]: 0.33 [0.31–0.35]) and 15.6 (sensitivity/specificity: 85.2%/81.4%; AUC [95% CI]: 0.91 [0.90–0.92]; PPV [95% CI]: 46.8 [44.3–49.4]; NPV [95% CI]: 96.6 [96.0–97.2]; LR+ [95% CI]: 4.58 [4.28–4.90]; LR− [95% CI]: 0.182 [0.16–0.21]), respectively. The diagnostic accuracy of FLI to predict NAFLD by 5-value intervals of FLI is shown in Supplementary Table S2. When values of FLI in men and women were 35 and 15, respectively, levels of Youden’s index were highest in both sexes.

The cutoff values of components of FLI calculation, including BMI, WC, triglycerides and γ-GTP, as well as the related markers, including AST, ALT and FIB-4 index, are shown in Table 3. The AUCs of FLI in both men and women were the highest among those of the biomarkers.

Results
Characteristics of the study subjects
Basal characteristics of the recruited subjects are shown in Table 1. NAFLD was found in 5,166 subjects (35.7%, men/women: 4,322 [46.8%]/844 [16.1%]). Components of FLI calculation, including BMI, WC, γ-GTP and triglycerides, were significantly higher in men than in women. FLI level was significantly higher in men (median [interquartile ranges]: 36 [18–60]) than in women (7 [4–19]). FIB-4 index was significantly higher in men than in women. The frequency of current smoking habit was higher in men than in women.

Basal characteristics of the included subjects with and without NAFLD are shown in Table 2. Both men and women with NAFLD were older and had significantly larger BMI and WC, higher systolic and diastolic blood pressures and pulse rate, higher frequencies of obesity, hypertension, diabetes mellitus, and dyslipidemia and higher levels of hemoglobin, platelet count, albumin, uric acid, ALT, γ-GTP, fasting plasma glucose, hemoglobin A1c, total cholesterol, LDL cholesterol, triglycerides, and FLI and lower levels of eGFR, HDL cholesterol and FIB-4 index than did those without NAFLD.
Prediction and validation of NAFLD by FLI in non-obese and obese subjects

As subgroup analyses, the subjects were divided by the absence and presence of obesity (BMI ≥25). Basal characteristics of men and women in the subgroup analysis are shown in Supplementary Table S3 and Supplementary Table S4, respectively. There was a significant interaction between FLI and obesity for detection of NAFLD in women \( (p < 0.001) \) but not in men \( (p = 0.679) \). The cutoff values of FLI for prediction of NAFLD in non-obese and obese men were 22.6 (sensitivity/specificity: 71.4%/65.9%, AUC [95% CI]: 0.75 [0.74–0.77]) and 52.6 (sensitivity/specificity: 69.6%/67.0%, AUC [95% CI]: 0.74 [0.73–0.76]), respectively (Table 4). On the other hand, the cutoff values of FLI for prediction of NAFLD in non-obese and obese women were 11.2 (sensitivity/specificity: 78.2%/80.7%, AUC [95% CI]: 0.86 [0.84–0.88]) and 33.2 (sensitivity/specificity: 75.9%/68.2%, AUC [95% CI]: 0.78 [0.76–0.81]), respectively (Table 4).

Table 1 Characteristics of recruited subjects \( (n = 14,471) \)

| Variable                        | All \( (n = 14,471) \) | Men \( (n = 9,240) \) | Women \( (n = 5,231) \) | \( p \)  |
|---------------------------------|------------------------|-----------------------|-------------------------|--------|
| Age (years)                     | 48 ± 9                 | 49 ± 9                | 47 ± 9                  | <0.001 |
| Body mass index                 | 23 ± 3                 | 24 ± 3                | 22 ± 3                  | <0.001 |
| Waist circumference (cm)        | 84 ± 9                 | 86 ± 9                | 79 ± 9                  | <0.001 |
| Systolic blood pressure (mmHg)  | 117 ± 17               | 120 ± 16              | 111 ± 16                | <0.001 |
| Diastolic blood pressure (mmHg) | 75 ± 11                | 77 ± 11               | 70 ± 11                 | <0.001 |
| Pulse rate (beats/min)          | 63 ± 9                 | 63 ± 9                | 64 ± 9                  | <0.001 |
| Current smoking habit           | 4,729 (34.0)           | 3,842 (43.5)          | 887 (17.5)              | <0.001 |

Comorbidity

| Variable                      | All \( (n = 14,471) \) | Men \( (n = 9,240) \) | Women \( (n = 5,231) \) | \( p \)  |
|-------------------------------|------------------------|-----------------------|-------------------------|--------|
| NAFLD                         | 5,166 (35.7)           | 4,322 (46.8)          | 844 (16.1)              | <0.001 |
| Obesity*                      | 5,342 (36.9)           | 4,273 (46.2)          | 1,069 (20.4)            | <0.001 |
| Hypertension                  | 2,631 (18.2)           | 2,040 (22.1)          | 591 (11.3)              | <0.001 |
| Diabetes mellitus             | 844 (5.8)              | 742 (8.0)             | 102 (1.9)               | <0.001 |
| Dyslipidemia                  | 3,558 (24.6)           | 2,246 (24.3)          | 1,312 (25.1)            | 0.306  |

Biochemical data

| Variable                          | All \( (n = 14,471) \) | Men \( (n = 9,240) \) | Women \( (n = 5,231) \) | \( p \)  |
|-----------------------------------|------------------------|-----------------------|-------------------------|--------|
| Hemoglobin (g/dL)                 | 14.3 ± 1.6             | 15.1 ± 1.1            | 12.9 ± 1.2              | <0.001 |
| Platelet \( (10^4/\mu L) \)       | 23.8 ± 5.2             | 23.3 ± 5.0            | 24.6 ± 5.5              | <0.001 |
| Albumin (g/dL)                    | 4.4 ± 0.2              | 4.4 ± 0.2             | 4.3 ± 0.2               | <0.001 |
| Blood urea nitrogen (mg/dL)       | 14.2 ± 3.5             | 14.7 ± 3.5            | 13.4 ± 3.4              | <0.001 |
| Creatinine (mg/dL)                | 0.73 ± 0.24            | 0.81 ± 0.24           | 0.60 ± 0.18             | <0.001 |
| eGFR (mL/min/1.73 m²)             | 84.6 ± 14.9            | 83.3 ± 14.5           | 86.9 ± 15.4             | <0.001 |
| Uric acid (mg/dL)                 | 5.5 ± 1.4              | 6.1 ± 1.2             | 4.4 ± 1.0               | <0.001 |
| AST (U/L)                         | 21 (18–26)             | 22 (19–28)            | 19 (16–22)              | <0.001 |
| ALT (U/L)                         | 21 (15–31)             | 25 (18–36)            | 15 (12–20)              | <0.001 |
| γ-GTP (U/L)                       | 31 (19–57)             | 42 (27–73)            | 18 (14–27)              | <0.001 |
| FPG (mg/dL)                       | 93 ± 20                | 97 ± 22               | 88 ± 14                 | <0.001 |
| Hemoglobin A1c (%)                | 5.4 ± 0.7              | 5.4 ± 0.8             | 5.2 ± 0.5               | <0.001 |
| Total cholesterol (mg/dL)         | 206 ± 34               | 206 ± 34              | 205 ± 34                | 0.006  |
| LDL cholesterol (mg/dL)           | 125 ± 33               | 127 ± 33              | 120 ± 32                | <0.001 |
| HDL cholesterol (mg/dL)           | 60 ± 16                | 55 ± 14               | 69 ± 15                 | <0.001 |
| Triglycerides (mg/dL)             | 93 (63–138)            | 111 (79–161)          | 67 (50–94)              | <0.001 |
| FIB-4 Index                       | 0.94 (0.73–1.22)       | 0.95 (0.73–1.24)      | 0.93 (0.72–1.19)        | <0.001 |
| FLI                               | 23 (8–50)              | 36 (18–60)            | 7 (4–19)                | <0.001 |

Variables are expressed as number (%), means ± SD or medians (interquartile ranges).

* Body mass index ≥25. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; γ-GTP, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.
Table 2  Characteristics of recruited subjects with and without NAFLD (n = 14,471)

| Variable                      | Men (n = 9,240) | Women (n = 5,231) | P  |
|-------------------------------|----------------|-------------------|----|
| Age (years)                   |                |                   |    |
| NAFLD (-) (n = 4,918)         | 48 ± 10        | 50 ± 9            | <0.001 | 47 ± 9 | 52 ± 9 | <0.001 |
| NAFLD (+) (n = 4,322)         | 23 ± 2         | 26 ± 3            | <0.001 | 21 ± 3 | 26 ± 4 | <0.001 |
| Waist circumference (cm)      | 82 ± 7         | 91 ± 8            | <0.001 | 77 ± 8 | 90 ± 9 | <0.001 |
| Systolic blood pressure (mmHg)| 118 ± 15       | 123 ± 16          | <0.001 | 109 ± 16 | 120 ± 17 | <0.001 |
| Diastolic blood pressure (mmHg)| 55 ± 9        | 77 ± 11           | <0.001 | 69 ± 10 | 76 ± 10 | <0.001 |
| Pulse rate (beats/min)        | 62 ± 9         | 64 ± 9            | <0.001 | 63 ± 9 | 66 ± 9 | <0.001 |
| Current smoking habit         | 2,161 (46.1)   | 1,681 (40.6)      | <0.001 | 751 (17.6) | 136 (16.8) | 0.579 |
| Comorbidity                   |                |                   |    |
| Obesity*                      | 1,260 (25.6)   | 3,013 (69.7)      | <0.001 | 496 (11.3) | 573 (67.9) | <0.001 |
| Hypertension                  | 797 (16.2)     | 1,243 (28.8)      | <0.001 | 354 (8.1) | 237 (28.1) | <0.001 |
| Diabetes mellitus             | 202 (4.1)      | 540 (12.5)        | <0.001 | 37 (0.8) | 65 (7.7) | <0.001 |
| Dyslipidemia                  | 969 (19.7)     | 1,277 (29.5)      | <0.001 | 1,038 (23.7) | 274 (32.5) | <0.001 |
| Biochemical data              |                |                   |    |
| Hemoglobin (g/dL)             | 15.0 ± 1.0     | 15.3 ± 1.1        | <0.001 | 12.8 ± 1.2 | 13.4 ± 1.1 | <0.001 |
| Platelet (10^4/μL)            | 23.2 ± 4.8     | 23.4 ± 5.2        | <0.017 | 24.3 ± 5.3 | 26.4 ± 6.0 | <0.001 |
| Albumin (g/dL)                | 4.4 ± 0.2      | 4.5 ± 0.2         | <0.001 | 4.3 ± 0.2 | 4.3 ± 0.2 | 0.007 |
| Blood urea nitrogen (mg/dL)   | 14.7 ± 3.6     | 14.8 ± 3.4        | <0.001 | 13.3 ± 3.4 | 13.9 ± 3.6 | <0.001 |
| Creatinine (mg/dL)            | 0.81 ± 0.31    | 0.81 ± 0.14       | 0.612 | 0.60 ± 0.19 | 0.59 ± 0.10 | 0.126 |
| eGFR (mL/min/1.73 m²)         | 83.8 ± 14.0    | 82.8 ± 14.9       | 0.001 | 87.1 ± 15.4 | 85.8 ± 15.7 | 0.029 |
| Uric acid (mg/dL)             | 5.9 ± 1.2      | 6.3 ± 1.3         | <0.001 | 4.3 ± 0.9 | 5.0 ± 1.0 | <0.001 |
| AST (U/L)                     | 21 (18–25)     | 25 (20–32)        | <0.001 | 22 (18–27) | 19 (16–22) | <0.001 |
| ALT (U/L)                     | 21 (16–27)     | 33 (24–49)        | <0.001 | 14 (12–18) | 23 (17–34) | <0.001 |
| γ-GTP (U/L)                   | 34 (23–57)     | 53 (34–88)        | <0.001 | 17 (14–24) | 28 (20–44) | <0.001 |
| FPG (mg/dL)                   | 92 ± 16        | 102 ± 27          | <0.001 | 86 ± 12 | 96 ± 20 | <0.001 |
| Hemoglobin A1c (%)            | 5.2 ± 0.6      | 5.6 ± 1.0         | <0.001 | 5.2 ± 0.5 | 5.6 ± 0.8 | <0.001 |
| Total cholesterol (mg/dL)     | 201 ± 33       | 213 ± 35          | <0.001 | 202 ± 34 | 218 ± 35 | <0.001 |
| LDL cholesterol (mg/dL)       | 122 ± 31       | 134 ± 33          | <0.001 | 117 ± 31 | 138 ± 32 | <0.001 |
| HDL cholesterol (mg/dL)       | 59 ± 15        | 52 ± 12           | <0.001 | 71 ± 15 | 59 ± 13 | <0.001 |
| Triglycerides (mg/dL)         | 94 (68–131)    | 136 (99–192)      | <0.001 | 62 (47–85) | 107 (77–146) | <0.001 |
| FIB-4 Index                   | 0.95 (0.74–1.26)| 0.94 (0.72–1.23) | 0.046 | 0.93 (0.73–1.20) | 0.92 (0.70–1.16) | 0.019 |
| FLI                           | 22 (11–38)     | 56 (36–77)        | <0.001 | 6 (3–12) | 38 (21–60) | <0.001 |

Variables are expressed as number (%), means ± SD or medians (interquartile ranges).

* Body mass index ≥25. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; FPG, fasting plasma glucose; γ-GTP, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

Discussion

To the best of our knowledge, we showed for the first time that the cutoff values of FLI for prediction of NAFLD determined by abdominal ultrasonography in Japanese men and women were 35.1 and 15.6, respectively. There was a significant interaction between sex and FLI for detection of NAFLD (p < 0.001), suggesting that there is a significant sex difference in the cutoff value of FLI for prediction of NAFLD. As shown in Supplementary Table S1, possible racial and sex differences in FLI for the cutoff level have been reported. A previous study using Asians in China showed that the cutoff value was FLI ≥30, but the sex difference was not taken into consideration [18]. A study in Taiwan showed that the cutoff values in men (n = 16,098) and women (n = 13,699) were FLI ≥35 and FLI ≥20, respectively [22]. Another study in Taiwan also showed that the
Fig. 2 Prediction of fatty liver by FLI.
A, B. Receiver operating characteristic (ROC) curves of fatty liver index (FLI) to predict nonalcoholic fatty liver disease determined by abdominal ultrasonography in men (A) and women (B). AUC, area under the curve; CI, confidence interval.

### Table 3 Cutoff values of parameters for prediction of NAFLD

|       | Men (n = 9,240) |          |          | Women (n = 5,231) |          |          |
|-------|----------------|----------|----------|------------------|----------|----------|
|       | Cutoff | AUC      | 95% CI   | Sensitivity (%)  | Specificity (%) | Cutoff | AUC      | 95% CI   | Sensitivity (%)  | Specificity (%) |
| FLI   | 35.1   | 0.82     | 0.81–0.83 | 76.7             | 71.3      | 15.6    | 0.91     | 0.90–0.92 | 85.2             | 81.4      |
| Body mass index | 25     | 0.80     | 0.79–0.81 | 63.9             | 79.5      | 24      | 0.88     | 0.87–0.89 | 75.6             | 85.1      |
| Waist circumference (cm) | 86.8   | 0.80     | 0.79–0.81 | 70.0             | 75.0      | 83.2    | 0.87     | 0.86–0.88 | 79.1             | 79.3      |
| Triglycerides (mg/dL) | 111    | 0.71     | 0.70–0.72 | 67.1             | 63.6      | 76      | 0.79     | 0.77–0.80 | 77.0             | 66.3      |
| γ-GTP (U/L) | 41     | 0.67     | 0.66–0.68 | 66.1             | 60.3      | 20      | 0.75     | 0.73–0.77 | 78.1             | 62.3      |
| AST (U/L) | 24     | 0.68     | 0.67–0.69 | 57.4             | 68.8      | 22      | 0.69     | 0.67–0.71 | 52.8             | 75.7      |
| ALT (U/L) | 27     | 0.77     | 0.76–0.78 | 66.5             | 73.1      | 19      | 0.81     | 0.79–0.82 | 70.7             | 75.0      |
| FIB-4 Index | 0.69   | 0.51     | 0.50–0.52 | 22.3             | 80.3      | 0.64    | 0.53     | 0.50–0.55 | 86.2             | 20.0      |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; FLI, fatty liver index; γ-GTP, γ-glutamyl transpeptidase; NAFLD, nonalcoholic fatty liver disease.

### Table 4 Cutoff values of FLI for prediction of NAFLD in non-obese and obese subjects

|       |          |          |          |          |          |          |          |          |
|-------|----------|----------|----------|----------|----------|----------|----------|----------|
|       | n       | Cutoff   | AUC      | 95% CI   | Sensitivity (%)  | Specificity (%) |
| Men   |          |          |          |          |          |          |          |          |
| Non-obese | 4,967   | 22.6     | 0.75     | 0.74–0.77 | 71.4       | 65.9     |
| Obese  | 4,273    | 52.6     | 0.74     | 0.73–0.76 | 69.6       | 67.0     |
| Women  |          |          |          |          |          |          |          |          |
| Non-obese | 4,162   | 11.2     | 0.86     | 0.84–0.88 | 78.2       | 80.7     |
| Obese  | 1,069    | 33.2     | 0.78     | 0.76–0.81 | 75.9       | 68.3     |

AUC, area under the curve; CI, confidence interval; FLI, fatty liver index; NAFLD, nonalcoholic fatty liver disease.
cutoff values in men \(n = 424\) and women \(n = 947\) were FLI \(\geq 20\) and FLI \(\geq 10\), respectively \[23\]. The cutoff values of FLI for prediction of NAFLD obtained in Asian individuals in those studies \[22, 23\] as well as the present study were obviously lower than that in the original study (FLI \(\geq 60\)) \[16\]. Setting cutoff values of FLI in different races and sexes is essential for predicting NAFLD.

NAFLD is common in not only obese subjects but also lean subjects \[5\], and the incidence of NAFLD has been increasing even in lean individuals in recent years \[34\]. In Asia, 15–20\% of subjects with NAFLD were reported to be non-obese subjects \[6, 35, 36\]. Lean patients with NAFLD have been reported to require medical attention due to the same unhealthy metabolic environment as that for obese patients with NAFLD \[37, 38\]. The usefulness of FLI for detection of NAFLD in lean subjects has also been reported \[39, 40\] (Supplementary Table S1). A study in Taiwan showed that the cutoff value for prediction of NAFLD in lean subjects with BMI <24 was FLI \(\geq 15\) \[39\]. Another study in China also showed that the cutoff value for prediction of NAFLD in lean subjects with BMI <23 and normal WC (<90 cm for men and <80 cm for women) was FLI \(\geq 25.2\) \[40\]. In the present study, when divided by the absence and presence of obesity (BMI \(\geq 25\)), the cutoff values of FLI in non-obese/obese subjects in men and women were 22.6/52.6 and 11.2/33.2, respectively. The ability of FLI to predict NAFLD may be useful in both non-obese and obese subjects, though there was a significant interaction between FLI and obesity for detection of NAFLD in women \((p < 0.001)\) but not in men \((p = 0.679)\) in the present study.

It has been reported that detection of fatty liver by abdominal ultrasonography is difficult when fat content in the liver is less than 30\% \[41, 42\], though performance of new equipment is improving nowadays. Therefore, FLI may not be suitable for detection of fatty liver at an early stage. However, FLI is a non-invasive, inexpensive and convenient indicator that is useful for identification of patients with NAFLD. Calculating FLI may trigger early efforts to prevent metabolic complications in patients with NAFLD. On the other hand, a new concept of fatty liver associated with metabolic disorders has recently been proposed as MAFLD, and FLI has been recommend as a biomarker for detection of fatty liver \[15\]. There have been several studies showing that FLI is associated with the development of hypertension \[43, 44\], diabetes mellitus \[45, 46\], chronic kidney disease \[47, 48\], heart failure \[49\] and cardiovascular disease \[50, 51\]. Determination of the cutoff value of FLI will make it easier to find several NAFLD-associated diseases.

The present study has some limitations. First, since the study subjects had a yearly health check-up at a single urban clinic, the possibility of sample selection bias cannot be ruled out. Second, since diagnosis of hepatic steatosis was performed by abdominal ultrasonography but not by liver biopsy, the pathological severity of hepatic steatosis was not taken into consideration. Third, since the amount of alcohol consumption was obtained by a questionnaire, it may not reflect the accurate amount. Forth, since recruited subjects were recipients of annual health examinations, most of the subjects would be apparently healthy. However, among a total of 14,471 subjects (men/women: 9,240/5,231), the numbers of men and women with a high level of FIB-4 index \((\geq 1.3)\) as a possible risk for hepatic fibrosis \[52, 53\] in the non-NAFLD group were 1,090 \((11.8\%)\) and 817 \((15.6\%)\), respectively. Since it has been reported that NAFLD patients with severe fibrosis have steatosis in less than 30\% of hepatocytes \[54, 55\], diagnosis of NAFLD by FLI may cause false negative results in some patients with NAFLD. Finally, among 28,990 subjects who received health examinations in 2006, hepatitis B surface antigen and hepatitis C antibody were examined in only 15,623 subjects \((53.9\%)\) and 15,051 subjects \((51.9\%)\), respectively. Therefore, some patients with viral hepatitis might have been included in the present study, though the prevalence of hepatitis B \((0.63\%)\) and that of hepatitis C \((0.49\%)\) were reported to be relatively low in the Japanese population \[56, 57\].

In conclusion, the cutoff value of FLI for prediction of NAFLD in Japanese individuals was lower than that in the original study \((FLI \geq 60)\), and there is a significant sex difference. The simple and useful cutoff values for prediction of NAFLD in Japanese men and women are FLI \(\geq 35\) (non-obese/obese: 23/53) and FLI \(\geq 16\) (non-obese/obese: 11/33), respectively.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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