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# Fatty Liver Index as a Simple and Useful Predictor for 10-year Cardiovascular Disease Risks Determined by Framingham Risk Score in the General Korean Population

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## ABSTRACT

**Background & Aims**: The fatty liver index (FLI) is a simple and non-invasive method for the diagnosis of fatty liver disease with an increased risk of cardiovascular disease (CVD) as well as liver-related mortality. We examined the association between FLI and 10-year CVD risk as determined by the Framingham risk score.
**Methods**: This cross-sectional study included 7,240 individuals aged 30 to 69 years who underwent a health examination between 2015 and 2017. The FLI was calculated using an algorithm based on triglyceride, γ-glutamyltransferase, body mass index (BMI), and waist circumference. Multiple linear and logistic regression analyses were performed to assess independent relationships between the FLI and Framingham risk score after adjusting for confounding variables.
**Results**: The overall prevalence of fatty liver disease among study participants as assessed by an FLI ≥ 60 was 19.7%. Compared with non-hepatic steatosis (FLI < 30), the odds ratio (95% confidence interval) for a high Framingham 10-year CVD risk ≥ 10% in individuals with hepatic steatosis (FLI ≥ 60) was 2.56 (1.97–3.33) after adjusting for age, gender, fasting plasma glucose, high-density and low-density lipoprotein cholesterol, blood pressure, C-reactive protein, regular exercise, alcohol-drinking, and current smoking.
**Conclusions**: The FLI was positively and independently associated with a Framingham 10-year CVD risk in the general Korean population. Our findings suggest that the FLI, a simple, useful, and economical index, may be an indicator of CVD events.

**Key words:** fatty liver index – insulin resistance – cardiovascular disease – Framingham risk score.

**Abbreviations**: AFLD: alcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CRP: C-reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; FLD: fatty liver disease; FLI: fatty liver index; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IHD: ischemic heart disease; LDL: low-density lipoprotein; NAFLD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglycerides; WC: waist circumference.

## INTRODUCTION

Fatty liver disease (FLD) includes non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) [1], which are the most common chronic liver diseases encountered in clinical practice [2]. Non-alcoholic fatty liver disease is defined by the accumulation of fat in more than 5% of the liver by weight, with little or no alcohol consumption, and AFLD is developed by consuming greater than 30 g/day of alcohol [3]. Although these forms of FLD are defined in medical terms, with the concept of "dual-etiology fatty liver disease," both NAFLD and AFLD have similar pathophysiology and histological features, from steatosis to cirrhosis [4].

An increasing body of epidemiological evidence suggests that FLD predicts not only liver-related diseases but also cardiovascular disease (CVD), which is a leading cause of premature mortality and a substantial determinant of a lower quality of life [5, 6]. Previous observational studies have been conducted to investigate the link between FLD and incident CVD, but they have shown inconsistent results. A recent study found that NAFLD was not associated with increased incident acute myocardial infarction or stroke after adjusting for established CVD factors [7]. On the other hand, another cohort study concluded that NAFLD was associated with

increased incidence of myocardial infarction independently of established risk factors [8].

Early identification of individuals at higher risk for FLD may allow for the application of preventive strategies that can slow the development and progression of both liver-related diseases and CVD. The traditional diagnosis of FLD requires various techniques such as liver ultrasonography, magnetic resonance, and biopsy. More recently, the fatty liver index (FLI), based on body mass index (BMI), waist circumference (WC), triglycerides (TG), and γ-glutamyltransferase [9], has emerged as a simple and economical alternative for mass screening for hepatic steatosis with reasonable sensitivity and specificity [10].

Although several previous studies have shown an association between FLD and CVD risks, most diagnostic methods of FLD are based on liver ultrasonography, magnetic resonance, or biopsy. These diagnostic tools have limited applicability in general clinical practice. Therefore, we examined the association between FLI and CVD risk in an apparently healthy population as determined by Framingham risk scores.

## METHODS

### Study participants

Volunteers in a retrospective, cross-sectional study underwent medical examinations at the at the Severance Health Promotion Center, Severance Hospital, Yonsei University Health System, in Seoul, Korea, between 2015 and 2017. The study was conducted by the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University College of Medicine. We retrospectively reviewed the medical records of 26,176 participants between the ages of 12 and 92 years. We excluded participants who met one or more of the following criteria: missing anthropometric and questionnaire data; aged < 30 and ≥ 70 years; a positive test for hepatitis B antigens or hepatitis C antibodies; above twice the upper normal limits for aspartate aminotransferase (AST) or alanine aminotransferase (ALT); leukocyte count ≥ 11,000 cells/μL; high sensitive C- reactive protein (CRP) ≥ 10 mg/L; a history of ischemic heart disease, stroke, any cancer, thyroid, respiratory, renal, hepatobiliary, or rheumatologic disease; and failure to fast for 8 h prior to testing. After these exclusions (n=18,936), a total of 7,240 participants aged 30 to 69 years old were included in the final analysis.

### Data collection

Each participant completed a questionnaire about lifestyle and medical history. Self-reported cigarette smoking, alcohol consumption, and physical activity characteristics were extracted from the questionnaires. The smoking statuses were nonsmoker, ex-smoker, and current smoker. Questions regarding alcohol intake included frequency on a weekly basis. Current alcohol consumption was defined as drinking alcoholic beverages two or more times per week. Participants were asked about their physical exercise on a weekly basis, and regular exercise was defined as exercising more than 3 times per week with moderate-to-vigorous intensity. Body mass and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the participants wearing light indoor clothing without shoes. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters (kg/m$^2$). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the patient's right arm with a standard mercury sphygmomanometer (Kensei Industry Co., Ltd. Japan). The presence of hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, taking antihypertensive medication, or diagnosis by a physician. The presence of diabetes was determined as a fasting glucose of 126 mg/dL, glycated hemoglobin (HbA1c) of 6.5% or above, taking antidiabetic medication, or diagnosis by a physician. The presence of dyslipidemia was determined as total cholesterol ≥ 240 mg/dL or low-density lipoprotein (LDL) cholesterol ≥ 160 mg/dL or TG ≥ 150 mg/dL or high-density lipoprotein (HDL) cholesterol < 40 mg/dL in men and < 50 mg/dL in women, taking antidyslipidemic medication, or diagnosis by a physician. Blood samples were obtained after 8 hours of overnight fasting. Leukocyte counts were measured using the ADVIA 2120i Hematology System Clinical (Siemens Healthcare Diagnostic, Inc, NY). Fasting plasma glucose, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, AST, ALT, and CRP were measured with the ADVIA 1800 Clinical Chemistry System (Siemens Healthcare Diagnostic, Inc, NY).

### Fatty liver index

The FLI score was calculated using the algorithm based on TG, γ-glutamyltransferase, BMI, and WC as follows:

$$FLI = (e^{[0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745]})/(1 + e^{[0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745]}) \times 100$$

Possible FLI scores range from 0 to 100, with subjects categorized as having non-hepatic steatosis (FLI < 30) or hepatic steatosis (FLI ≥ 60) [9]. Also, we defined the middle scores (FLI 30–59) as an "intermediate group" in this study.

### 10-year CVD risk

The Framingham risk score is a useful predictor of an individual's risk of experiencing a severe cardiovascular event for the next 10 years. The Framingham risk score prediction algorithm that served as the basis for the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) risk-scoring algorithm used six risk factors, including gender, age, total cholesterol, HDL cholesterol, SBP (points assigned for blood pressure depend on the treatment of hypertension), and smoking status. Table I showed that total scores were obtained by summing the points for each risk factor, and the 10-year CVD risk in percentage was divided by the total points [11]. The estimated risk for 10-year CVD was classified as low (< 10%) and intermediate or high (≥ 10%). A high Framingham 10-year CVD risk score was defined as ≥ 10% in this study.

### Statistical analysis

Normal distribution was evaluated by determining skewness using a Kolmogorov–Smirnov test and AST, ALT, CRP, and Framingham 10-years CVD risk levels had skewed distributions. FLI was categorized as follows: FLI < 30, 30 ≤ FLI ≤ 59, and FLI ≥ 60.

The clinical characteristics of the study population according to categorized FLI groups were compared using

**Table I**. Estimate of 10-year cardiovascular disease risk for men and women

| Men | | Women | |
|---|---|---|---|
| Total points | 10-year risk, % | Total points | 10-year risk, % |
| < 0 | 0 | < 9 | 0 |
| 0–4 | 1 | 9–12 | 1 |
| 5–6 | 2 | 13–14 | 2 |
| 7 | 3 | 15 | 3 |
| 8 | 4 | 16 | 4 |
| 9 | 5 | 17 | 5 |
| 10 | 6 | 18 | 6 |
| 11 | 8 | 19 | 8 |
| 12 | 10 | 20 | 11 |
| 13 | 12 | 21 | 14 |
| 14 | 16 | 22 | 17 |
| 15 | 20 | 23 | 22 |
| 16 | 25 | 24 | 27 |
| ≥ 17 | 30 | ≥ 25 | 30 |

one-way analysis of variance (ANOVA) or a Kruskal–Wallis test for continuous variables according to the normality of distributions and chi-square tests for categorical variables. Continuous data were presented as mean (standard deviation, SD) or median (interquartile range), and categorical data were presented as frequencies. The mean values [standard deviation (SDs)] of Framingham 10-year CVD risk across the categorized FLI per 10 points were evaluated using an ANOVA. The odds ratios (ORs) and 95% confidence intervals (CIs) for high Framingham 10-year CVD risks were calculated across categorized FLI groups using multiple logistic regression analysis after adjusting for confounding variables. All analyses were conducted using SPSS for Windows (version 25.0; IBM, NY, USA). All statistical tests were two-sided, and a $p < 0.05$ was considered statistically significant.

## RESULTS

A flow diagram of the study participants was showed in Fig. 1. The clinical characteristics of the subjects are supplied in Table II. Among the 7,240 subjects, 3,856 were categorized as having non-hepatic steatosis (FLI < 30), 1,955 as intermediated (FLI 30–59), and 1,429 as having hepatic steatosis (FLI ≥ 60). The overall prevalence of FLD as assessed by FLI ≥ 60 was 19.7% in the current study participants. The hepatic steatosis group (FLI ≥ 60) had the highest mean values of BMI, WC, SBP, DBP, fasting plasma glucose, total cholesterol, and leukocyte counts, whereas they had the lowest HDL-cholesterol level. Members of the hepatic steatosis group (FLI ≥ 60) had the highest median values of AST, ALT, CRP, and Framingham 10-year CVD risks. The percentages of current smoking and alcohol-drinking were highest, and hypertension, type 2 diabetes, and dyslipidemia were most prevalent in the hepatic steatosis group (FLI ≥ 60) compared with other groups.

Fig. 2 shows the mean (SD) Framingham 10-year CVD risk according to the categorized FLI per 10 points. The means (SD) of Framingham 10-year CVD risks increased gradually by the categorized FLI per 10 points ($p < 0.001$).

Table III presents the results of multiple logistic regression analysis to assess the independent relationships between FLI and Framingham 10-year CVD risk. Compared with non-hepatic steatosis (FLI < 30), the OR (95% CI) for a Framingham 10-year CVD risk ≥10% in individuals with hepatic steatosis (FLI ≥ 60) was 2.56 (1.97–3.33) after adjusting for age, gender, fasting plasma glucose, HDL cholesterol, LDL cholesterol, SBP,

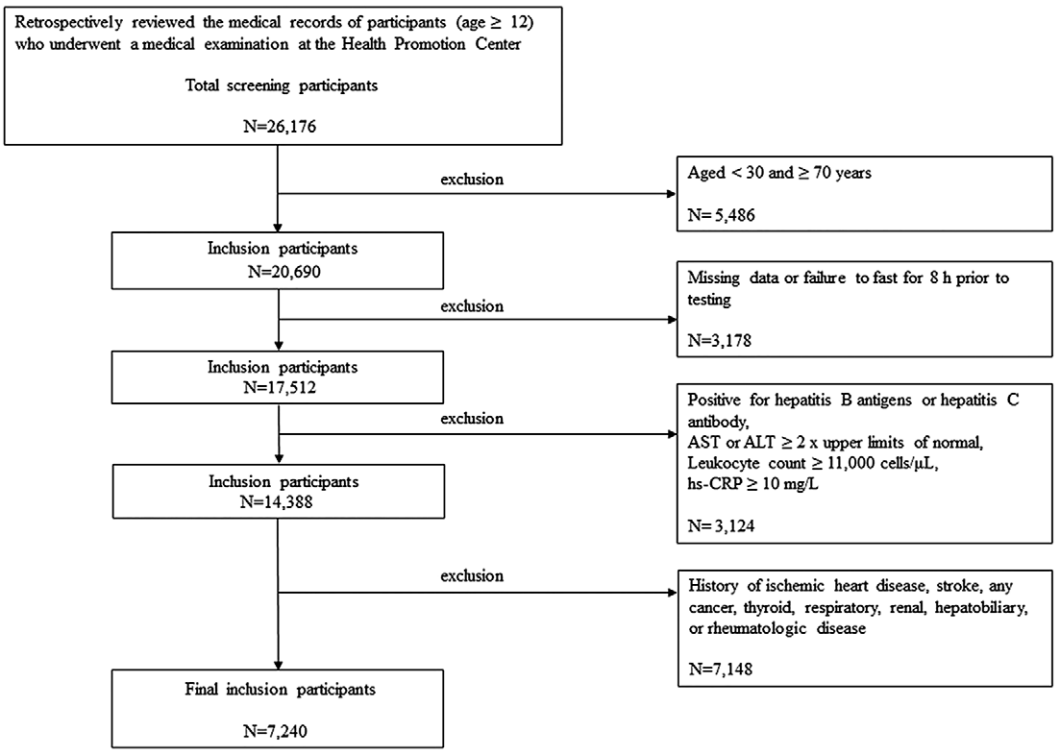


**Fig. 1.** Flow diagram of the study participants.

**Table II.** Clinical characteristics of the study population according to the fatty liver index (FLI)

| | | Fatty liver index (FLI) | | | |
|---|---|---|---|---|---|
| | Total | FLI (< 30) | FLI (30-59) | FLI (≥60) | p-value |
| N | 7,240 | 3,856 | 1,955 | 1,429 | |
| Male (%) | 78.5 | 62.2 | 95.0 | 97.7 | <0.001 |
| Age (year) | 47.8 (9.4) | 46.6 (9.7) | 49.7 (8.9) | 48.3 (8.6) | <0.001 |
| Body mass index (kg/m2) | 24.2 (3.1) | 22.3 (2.1) | 25.2 (1.8) | 27.8 (2.9) | <0.001 |
| Waist circumference (cm) | 83.9 (9.9) | 77.6 (7.3) | 88.1 (5.2) | 95.0 (7.7) | <0.001 |
| Systolic blood pressure (mmHg) | 120.9 (13.5) | 116.5 (12.8) | 123.7 (12.3) | 129.0 (12.0) | <0.001 |
| Diastolic blood pressure (mmHg) | 79.4 (11.2) | 75.5 (10.4) | 82.2 (10.1) | 86.3 (10.0) | <0.001 |
| Fasting plasma glucose (mg/dL) | 100.2 (18.6) | 95.3 (13.6) | 103.4 (18.2) | 109.2 (25.1) | <0.001 |
| Total cholesterol (mg/dL) | 198.0 (34.4) | 192.0 (31.7) | 201.6 (33.4) | 209.3 (39.0) | <0.001 |
| LDL-cholesterol (mg/dL) | 119.3 (32.4) | 113.7 (30.4) | 125.7 (31.3) | 125.5 (36.3) | <0.001 |
| HDL-cholesterol (mg/dL) | 53.2 (13.1) | 58.1 (13.6) | 48.9 (10.5) | 46.1 (9.1) | <0.001 |
| Aspartate aminotransferase (U/L) | 24 (20-29) | 22 (19-26) | 25 (21-30) | 29 (24-37) | <0.001 |
| Alanine aminotransferase (U/L) | 22 (16-32) | 18 (13-23) | 26 (20-36) | 36 (27-50) | <0.001 |
| Leukocyte count (cells/μL) | 5,806 (1,457) | 5,431 (1,357) | 6,056 (1,432) | 6,480 (1,436) | <0.001 |
| C-reactive protein (mg/L) | 0.3 (0.1-0.8) | 0.2 (0.1-0.4) | 0.3 (0.2-0.9) | 0.6 (03-1.6) | <0.001 |
| Framingham 10-years CVD risk (%) | 5 (2-10) | 4 (1-8) | 6 (4-12) | 8 (5-12) | <0.001 |
| Current smoking (%) | 27.1 | 18.9 | 33.5 | 40.4 | <0.001 |
| Alcohol drinking (%)[a] | 65.3 | 59.3 | 69.6 | 75.6 | <0.001 |
| Regular exercise (%)[b] | 58.6 | 61.0 | 59.8 | 50.5 | <0.001 |
| Hypertension (%) | 29.5 | 16.5 | 37.1 | 54.0 | <0.001 |
| Type 2 diabetes (%) | 7.4 | 3.6 | 9.8 | 14.5 | <0.001 |
| Dyslipidemia (%) | 46.6 | 25.2 | 59.4 | 85.7 | <0.001 |

Data are expressed as the mean (SD), median (interquartile range) or percentage. P values were calculated using 1-way ANOVA test, Kruskal-Wallis test and chi-square test. [a]Alcohol drinking ≥two times /week. [b]Regular exercise ≥three times /week.

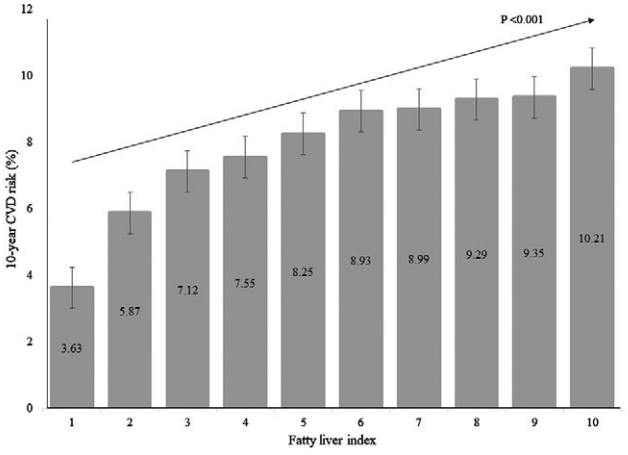


**Fig. 2**. The mean (SD) of the Framingham 10-year CVD risk according to the categorized FLI per 10 points.

DBP, CRP, regular exercise, alcohol-drinking, and current smoking.

## DISCUSSION

In this cross-sectional study, we found that FLI was positively and independently associated with the 10-year CVD risk in the general Korean population. Our findings are consistent with previous results that demonstrated that FLD is positively associated with an increased CVD risk in adult populations [8, 12].

Motamed et al. [12] conducted a study on 2,804 subjects aged 40-74 years from a cohort study of northern Iran. They concluded that individuals with NAFLD had a higher risk of 10-year CVD events than individuals without NAFLD [12]. Moreover, Kim et al. [8] conducted a prospective study involving 3,011,588 subjects with no history of CVD who underwent health examinations in the Korean National Health Insurance System cohort from 2009 to 2011, with a median follow-up period of 6 years. The authors concluded that FLI has a prognostic value for detecting individuals at a higher risk for cardiovascular events [8]. On the other hand, the European cohort study reported that the diagnosis of NAFLD in current routine care of 17.7 million patients appears not to be associated with acute myocardial infarction and stroke risk after adjustment for established cardiovascular risk factors [7]. The difference in results between countries as above may be due to age range, racial characteristics, comorbidities, and sample size of the study populations' racial characteristics.

Although in the previous studies, there has been a large focus on the differentiation between NAFLD and AFLD, it is gradually recognized that a large coincide exists between the two entities [13]. Recent literature reviews reported that NAFLD and AFLD have an overlap in the pathogenic mechanisms

**Table III**. Odds ratios and 95% confidence intervals for high Framingham 10-years CVD risk ≥ 10 % according to fatty liver index

| | Fatty liver index (FLI) | | |
|---|---|---|---|
| | FLI (<30) | FLI (30-59) | FLI (≥60) |
| Unadjusted | 1.00 (reference) | 2.62 (2.32-2.95) | 3.43 (3.01-3.91) |
| Model 1 | 1.00 (reference) | 2.39 (2.06-2.78) | 4.46 (3.77-5.28) |
| Model 2 | 1.00 (reference) | 1.63 (1.38-1.92) | 2.64 (2.17-3.21) |
| Model 3 | 1.00 (reference) | 1.60 (1.28-2.00) | 2.56 (1.97-3.33) |

Model 1: adjusted for age, sex. Model 2: adjusted for age, sex, fasting glucose, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, diastolic blood pressure and C-reactive protein. Model 3: adjusted for age, sex, fasting glucose, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein, regular exercise, alcohol drinking and current smoking.

leading to the trigger of both hepatic inflammation and fibrogenic pathways [4, 14]. Furthermore, moderate and heavy alcohol consumption, obesity, and metabolic dysfunction are synergistic effects on the development of fatty liver disease [15, 16]. Therefore, NAFLD and AFLD frequently coexist in the general clinical setting. Furthermore, a recent international consensus suggested metabolic associated fatty liver disease (MAFLD) as a novel concept [17]. Lin et al. [18] showed that compared with NAFLD, MAFLD is more practical to identify FLD patients associated with a high risk of metabolic disease progression. In these aspects, we wanted to study the concept of "dual-etiology fatty liver disease" without distinguishing between NAFLD and AFLD [4]. We also wanted to report the results by statically adjusting metabolic parameters and lifestyle such as age, BMI, blood pressure, fasting plasma glucose, lipid profile, regular exercise, alcohol-drinking, and current smoking.

Several potential mechanisms may explain the positive relationships between the FLD and 10-year CVD risk. NAFLD is now regarded as a hepatic manifestation of metabolic syndrome [19]. Insulin resistance, the core feature of metabolic syndrome, may lead to the development of systemic chronic low-grade inflammation [20]. In this respect, subclinical inflammation can promote adverse CVD events mediated by coronary artery atherosclerosis. This pathway can be triggered by a pro-inflammatory protein complex and cytokines, such as nuclear factor-kB, interleukin-1, interleukin-6, and tumor necrosis factor-α [21]. Additionally, insulin resistance can alter lipid metabolism, decrease HDL cholesterol, and increase triglycerides and fatty acids in the liver [22]. In these cascades, oxidative stress triggered by accumulated adipose tissue in the liver may play a key role in endothelial dysfunction, leading to the accumulation of oxidized LDL cholesterol in the sub-intimal wall [23].

The plausible mechanisms linking elevated FLI to the estimated 10-year CVD risk are suggested above, the causal relationship between them is still unclear. In a meta-analysis to examine the causal relationship between NAFLD and ischemic heart disease (IHD) [24], there was a positive association between fat deposition in the liver and IHD. However, the causal relationship of hepatic steatosis with IHD was not clear. Another study showed that NAFLD was significantly associated with an incident risk of type 2 diabetes, but not associated with incident CVD [25]. These discrepancies are largely due to the individual's lifestyle and genetic factors that can affect the development of CVD [26].

Our study had several limitations. First, it had a cross-sectional design, which suggests that caution should be used when making causal and temporal interpretations; it is impossible to determine whether FLI is a risk factor actively involved in the development of CVD or a bystander epiphenomenon. Further large prospective studies are required to explain possible associations between FLI and CVD risks. Second, because the study participants were volunteers undergoing health promotion screenings in a single hospital and appeared to be slightly healthier than most of their community-based cohorts, the study population may not be representative of the general population. Third, because this study used secondary data from the health promotion center, we could not accurately quantify the amount of alcohol consumed and dietetic profile. Finally, we did not consider the effects of medicines such as tamoxifen, glucocorticoids, and amiodarone in relation to steatohepatitis [27]. Due to the nature of a secondary dataset from a health promotion center, these variables were not fully adjusted for the statistical models.

Despite these potential limitations, positive associations between FLI and Framingham risk score in our study imply that FLI may be an independent marker of a 10-year CVD risk in the general Korean population. The current findings may be a useful additional measure in assessing CVD risk in clinical and research settings.

Finally, FLD appears to be an independent factor associated with the development of future CVD. In this way, FLD should be taken into account when considering CVD prevention. FLI is a noninvasive, inexpensive and easy test to calculate, which should be accessible for both patients and clinicians in the clinical practice. Patients with high FLI values should be counseled on the increased risk of developing CVD in the future. These patients should also be targeted for an additional cardiovascular preventive strategy, with the management of comorbidities associated with CVD onset and development.

## CONCLUSIONS

The FLI was positively and independently associated with the Framingham 10-year CVD risk in the general Korean population. Our findings suggest that the FLI, a simple, useful, and economical index, may be a useful indicator of CVD events. More comprehensive care for improving fatty liver might be helpful in preventing the incident CVD risk in clinical settings.

**Conflicts of interest:** None to declare.

**Authors' contributions:** T.H.C. collected data and wrote the manuscript. J.K.K. and J.H.K. contributed to the discussion and review. Y.J.L analyzed data and reviewed/edited the manuscript. All the authors approved the final version of the manuscript.

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