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Association of fatty liver index with all-cause and disease-specific mortality: A nationwide cohort study

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ABSTRACT

Background: Population-based data regarding the prognostic implications of hepatic steatosis have been inconsistent. We examined the association between the fatty liver index (FLI) with all-cause and disease-specific mortality in the general population.

Methods: We included subjects who underwent a health examination in 2009 using the Korean nationwide health screening database. Death and cause of death data were provided by Statistics Korea. The causes of death were classified using 10th Revision of the International Classification of Diseases codes.

Results: Among the included 10,585,844 participants, there were 418,296 deaths during a median follow-up period of 8.3 years. When adjusting for possible confounding factors, the risk of all-cause mortality linearly increased with a higher FLI score (hazard ratio [HR], 95% confidence interval [CI]: FLI 30–59, 1.19, 1.18–1.20; FLI $\geq$ 60, 1.67, 1.65–1.69, *P* for trend <0.001). The risk of disease-specific mortality including cardiovascular disease (CVD), cancer, respiratory disease and liver disease, linearly increased as the FLI score became higher (HR, 95% CI: FLI 30–59, 1.18, 1.16–1.20, FLI $\geq$ 60: 1.61, 1.56–1.65 for CVD; FLI 30–59, 1.13, 1.11–1.14, FLI $\geq$ 60, 1.41, 1.38–1.44 for cancer; FLI 30–59, 1.26, 1.22–1.29, FLI $\geq$ 60, 1.96, 1.88–2.05 for respiratory disease, FLI 30–59, 2.29, 2.21–2.38, FLI $\geq$ 60, 5.57, 5.31–5.85 for liver disease). The risk of all-cause mortality increased as the FLI score became higher across all the body mass index groups, and the greatest risk was observed in those who were underweight (HR, 95% CI = 2.43, 2.09–2.82 in FLI $\geq$ 60).

Conclusion: FLI may serve as a prognostic indicator of death and a high FLI is associated with a poor prognosis particularly in the underweight group.

1. Background

Nonalcoholic fatty liver disease (NAFLD) is a substantial public health burden, affecting about 25% of the global population [1]. About two-thirds of patients with NAFLD have simple steatosis, whereas up to 30% of patients develop progressive steatohepatitis, fibrosis, and

Abbreviations: NAFLD, nonalcoholic fatty liver disease; FLI, fatty liver index; CVD, cardiovascular disease; NHIS, National Health Insurance Service; NHSP, National Health Screening Program; ICD, International Classification of Disease; WC, waist circumference; BMI, body mass index; CCI, Charlson comorbidity index; GGT, gamma-glutamyl transferase; ALT, alanine transaminase; AST, asparate aminotransferase.

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cirrhosis [1,2]. NAFLD was found to be associated with an elevated risk of all-cause mortality compared with those without it, whereas there were no significant associations found between NAFLD and cardiovascular disease (CVD) and cancer mortality in a previous meta-analysis [3]. However, most of the included studies were from Western countries, and the sample size in each study was limited, as the diagnostic methods only consider imaging modalities or liver biopsy, which may affect the results. Until now, the prognostic impact of hepatic steatosis in terms of the distribution of cause of death had not been fully established in Asia, because of the small effect size of steatosis, requiring a large sample size and long follow-up duration to detect events of interest [4].

Although ultrasound is the first-line tool for the diagnosis of hepatic steatosis in clinical practice, serum-based noninvasive tests can be an acceptable alternative for large population-based epidemiologic studies, when ultrasound is not available or feasible [5]. The fatty liver index (FLI) is one of the best-validated measures, showing reasonable accuracy for identifying steatosis in the general population [6–8]. Several studies have investigated the relationship between FLI and mortality; however, the study populations were small, and they were conducted in men or in a specific disease setting, and were mainly carried out in Western countries [9,10]. Thus, we evaluated whether hepatic steatosis assessed using FLI could have prognostic implications for overall and disease-specific mortality, using a nationwide population-based cohort in Asia.

2. Methods

2.1. Data source

In Korea, the National Health Insurance Service (NHIS), a single government insurer, provides a mandatory universal insurance system covering about 97% of the Korean population, while the remaining 3%, who are in the low-income bracket, are covered by the Medical Aid program. The NHIS database includes claims submitted by health providers for reimbursement, and includes information on demographics, medical treatments and procedures, and disease diagnoses according to the International Classification of Disease, 10th revision (ICD-10). In addition, a biennial National Health Screening Program (NHSP) is offered for all insured members. The NHSP includes a self-reported questionnaire on lifestyle information, anthropometric measurements, and laboratory testing [11].

2.2. Study population

From the NHIS database, we included 10,585,844 Korean adults aged 20 years or older who had participated in NHSP in 2009. Among them, participants previously diagnosed with viral hepatitis or liver cirrhosis (ICD-10 code, B15–B19 or K74) were excluded. In addition, we excluded participants who reported alcohol consumption ≥30 g/day for men and ≥20 g /day for women. The participants who died or were censored within the first year of the follow-up period were also excluded. The final study population was 8,858,421 after excluding those with missing information (Supplementary Fig. 1).

The Institutional Review Board of Soongsil University approved this study (SSU-202007-HR-236-01), and we performed the study in accordance with relevant guidelines and regulations. The requirement for written informed consent was waived.

2.3. Calculation of FLI

The FLI was calculated based on the following equation, using body mass index (BMI), waist circumference (WC), triglyceride (TG), and gamma-glutamyl transferase (GGT) information [6].

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

According to the original study, an FLI score < 30 rules out fatty liver and ≥ 60 suggests fatty liver with good diagnostic accuracy.[6] It was also validated in the Korean population with area under the receiver operating characteristic curve, ranging from 0.79 to 0.87 [7,12]. The participants were categorized into three groups by FLI: <30 [reference], 30–59, and ≥60.

2.4. Outcome

Death data and cause of death from death certificates were provided by Statistics Korea, which is linked to the NHIS database. Cause of death was identified according to the Korean Standard Classification of Diseases and Causes of Death, based on ICD-10 codes. Specific causes of death were classified into CVD (I00-I99), malignant neoplasm (including hepatocellular carcinoma, C00-C97), respiratory disease (J00-J99), and liver disease (excluding hepatocellular carcinoma, K70-76). The deaths due to malignant neoplasm were further categorized by cancer sites: esophagus (C15), stomach (C16), colorectum (C18–C20), lung (C33, C34), liver and bile duct (C22–C24), breast (C50, for women), and prostate (C61, for men). They were followed up from one year after the day of NHSP until December 31, 2019, or date of death; whichever came first.

2.5. Covariates

Through health exams, the height, weight, WC, and blood pressure were measured, and BMI was calculated as weight (kg) divided by height (m^2). Laboratory tests included serum levels of glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine transaminase (ALT), aspartate aminotransferase (AST), and GGT. The Charlson comorbidity index (CCI) was assessed by ICD-10 codes [13].

Self-report questionnaires were obtained for smoking status, alcohol use, and physical activity. Comorbidities were defined based on clinical information from NHSP, ICD-10 code, and prescription history of relevant medication. Smoking status was categorized as non, former, and current smoker. Alcohol consumption was estimated by multiplication of the amount of alcohol consumed per occasion by frequency of alcohol intake per week. The participants were classified into nondrinkers and mild to moderate drinkers. When participants exercised at a high intensity at least three times per week or at a moderate intensity at least five times per week, they were defined as undertaking regular physical activity.

For diabetes mellitus, use of hypoglycemic agents and insulin, ICD-10 codes (E11–14), or a fasting glucose level of at least 126 mg/dL were indicators. Hypertension was defined by a participant taking antihypertensive medications, ICD-10 codes (I10–13 and I15), or elevated blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg) at a health exam. Use of antihypertensive medications includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics. Dyslipidemia was defined by ICD-10 code (E78), lipid-lowering medications, or a total cholesterol level of greater than 240 mg/dL.

2.6. Statistical analysis

Differences among three groups by FLI were tested by one-way analysis of variance for continuous variables and Chi-square tests for categorical variables. Mean ± standard deviation (SD) values for normally distributed continuous variables, geometric mean with 95% confidence interval (CI) values for skewed distributed continuous variables, and numbers with proportions for categorical variables are presented.

The incidence rates for all deaths and disease-specific deaths (numbers of deaths per 1000 person-years) were estimated. To evaluate the association between FLI and risk of death, Cox proportional hazards analyses were conducted. Multivariable adjusted models were used as follows: model 1 was adjusted by age and sex, model 2 was additionally adjusted for lifestyle habits (smoking status, alcohol consumption, and physical activity), and income level, model 3 was additionally adjusted for comorbidities (diabetes mellitus, hypertension, and dyslipidemia), ALT, and CCI score, and model 4 was additionally adjusted for WC and BMI. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-tailed *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 presents the baseline characteristics of the study population. The mean age in FLI < 30 was younger than in other groups. FLI < 30 mostly consisted of women (59.7%) compared that the group FLI ≥ 60, which consisted mainly of men (80.6%). Those with FLI ≥ 60 were more likely to be former or current smokers and alcohol consumers than the other groups. Comorbidities such as diabetes mellitus, hypertension, and dyslipidemia were more prevalent in the group with FLI ≥ 60. Those with FLI ≥ 60 more frequently use anti-hypertensive, lipid lowering or anti-diabetic agents. A greater BMI and WC values, higher fasting glucose and triglyceride levels, and higher ALT/AST/GGT levels were observed in those with FLI ≥ 60.

3.2. Association between FLI and all-cause/disease-specific mortality

During the median follow-up period of 8.3 years, there were 418,296 deaths with a 5.7 incidence rate (per 1000 person years [PY]) among the total population. The main causes of death were as follows: cancer (35.0%), CVD (20.2%), respiratory disease (9.7%), and liver disease (5.2%).

Those with FLI ≥ 60 had a higher risk of all-cause mortality (hazard ratio [HR], 95% CI = 1.05, 1.04–1.06), while those with a 30–59 FLI had a lower risk of all-cause mortality (HR, 95% CI = 0.91, 0.90–0.91) compared to the reference group. Regarding CVD-specific mortality, a similar association was observed based on FLI scores. The risk of cancer-specific mortality increased as the FLI score became higher (HR, 95% CI: FLI 30–59, 1.00, 0.99–1.02; FLI ≥ 60, 1.15, 1.13–1.17, *P* for trend <0.001). Meanwhile, respiratory disease-specific mortality decreased as the FLI score became higher (HR, 95% CI: FLI 30–59, 0.74, 0.72–0.76; FLI ≥ 60, 0.82, 0.79–0.85, *P* for trend <0.001). Risk of liver-related mortality linearly increased with a higher FLI score (HR, 95% CI: FLI 30–59, 1.52, 1.48–1.57; FLI ≥ 60, 2.82, 2.72–2.92, *P* for trend < 0.001) (Model 3, Table 2).

When we further adjusted for WC and BMI (Model 4), the risk of all-cause mortality linearly increased with a higher FLI score (HR, 95% CI: FLI 30–59, 1.19, 1.18–1.20; FLI ≥ 60, 1.67, 1.65–1.69, P for trend <0.001). The risk of disease-specific mortality including CVD, cancer, respiratory disease and liver disease, linearly increased as the FLI score became higher (HR, 95% CI: FLI 30–59, 1.18, 1.16–1.20, FLI ≥ 60: 1.61, 1.56–1.65 for CVD; FLI 30–59, 1.13, 1.11–1.14, FLI ≥ 60, 1.41, 1.38–1.44 for cancer; FLI 30–59, 1.26, 1.22–1.29, FLI ≥ 60, 1.96,

Table 1
Baseline characteristics according to fatty liver index.

	Fatty liver index			
	< 30 (*n* = 5,812,188) 65.6%	30–59 (*n* = 2,020,351) 22.8%	≥ 60 (*n* = 1,025,882) 11.6%	*p*-Value
Age	46.2 ± 14.4	50.7 ± 13.5	48.0 ± 12.9	< 0.001
<40	1,948,880 (33.5)	462,746 (22.9)	299,546 (29.2)	< 0.001
40–64	3,041,655 (52.3)	1,154,032 (57.1)	582,336 (56.8)	
≥65	821,653 (14.1)	403,573 (20.0)	144,000 (14.0)	
Sex				< 0.001
Male	2,344,638 (40.3)	1,382,708 (68.4)	827,022 (80.6)	
Female	3,467,550 (59.7)	637,643 (31.6)	198,860 (19.4)	
Smoking				< 0.001
Non	4,142,541 (71.3)	1,041,714 (51.6)	410,511 (40.0)	
Former	609,699 (10.5)	379,670 (18.8)	206,852 (20.2)	
Current	1,059,948 (18.2)	598,967 (29.7)	408,519 (39.8)	
Alcohol drinking				< 0.001
Non	3,550,783 (61.1)	1,030,384 (51.0)	409,846 (40.0)	
Mild to moderate	2,261,405 (38.9)	989,967 (49.0)	616,036 (60.0)	
Regular physical activity	1,014,831 (17.5)	378,969 (18.8)	174,883 (17.1)	< 0.001
Low income level[a]	970,496 (16.7)	283,522 (14.0)	140,455 (13.7)	< 0.001
Comorbidity				
Diabetes mellitus	301,302 (5.2)	259,309 (12.8)	193,274 (18.8)	< 0.001
Anti-diabetic medication number				< 0.001
0	5,607,653 (96.5)	1,844,882 (91.3)	911,188 (88.8)	
1	60,701(1.0)	51,519 (2.6)	32,558 (3.2)	
≥ 2	143,834 (2.5)	123,950 (6.1)	82,136 (8.0)	
Metformin	155,701 (2.7)	133,349 (6.6)	88,118 (8.6)	< 0.001
Sulfonylurea	156,293(2.7)	139,166 (6.9)	92,094 (9.0)	< 0.001
Insulin	33,049 (0.6)	22,928 (1.1)	13,659 (1.3)	< 0.001
Hypertension	1,059,982 (18.2)	735,775 (36.4)	458,344 (44.7)	< 0.001
Anti-hypertension medication	709, 575 (12.2)	511,653 (25.3)	293,108 (28.6)	< 0.001
Anti-hypertension medication type				
ACEi / ARB	423,332 (7.3)	323,252 (16.0)	198,318 (19.3)	< 0.001
Beta blocker	173,273 (3.0)	145,551 (7.2)	93,557(9.1)	< 0.001
CCB	358,800 (6.2)	261,978 (13.0)	150,326(14.7)	< 0.001
Diuretics	16,011 (0.3)	13,023 (0.6)	7810 (0.8)	< 0.001
Dyslipidemia	737,159 (12.7)	523,639 (25.9)	351,631 (34.3)	< 0.001
Statin use	372,007 (6.4)	269,278 (13.3)	158,102 (15.4)	< 0.001
CCI score	0.6 ± 1.1	0.8 ± 1.3	0.8 ± 1.3	< 0.001
Body mass index	22.2 ± 2.4	25.5 ± 2.2	28.0 ± 4.9	

(*continued on next page*)

Table 1 (*continued*)

	Fatty liver index			
	< 30	30–59	≥ 60	*p*-Value
	(*n* = 5,812,188) 65.6%	(*n* = 2,020,351) 22.8%	(*n* = 1,025,882) 11.6%	
				< 0.001
Waist circumference	75.6 ± 7.0	86.0 ± 5.4	92.4 ± 9.9	< 0.001
Systolic BP	119.2 ± 14.4	126.6 ± 14.4	129.9 ± 14.7	< 0.001
Diastolic BP	74.2 ± 9.6	78.8 ± 9.6	81.4 ± 10.0	< 0.001
Fasting glucose	93.6 ± 19.0	101.2 ± 26.4	107.4 ± 33.2	< 0.001
Total cholesterol	189.4 ± 39.1	203.8 ± 41.9	212.4 ± 44.9	< 0.001
HDL-C	58.7 ± 29.9	52.7 ± 36.5	50.3 ± 38.0	< 0.001
LDL-C	122.2 ± 249.6	124.1 ± 129.7	118.5 ± 141.2	< 0.001
TG[b]	86.8 (86.7–86.8)	154.2 (154.1–154.3)	227.7 (227.5–227.9)	< 0.001
AST[b]	21.2 (21.2–21.2)	25.0 (25.0–25.0)	30.4 (30.4–30.5)	< 0.001
ALT[b]	17.3 (17.3–17.3)	26.2 (26.1–26.2)	37.3 (37.3–37.4)	< 0.001
GGT[b]	18.4 (18.4–18.4)	35.2 (35.1–35.2)	62.8 (62.7–62.9)	< 0.001

Values are presented as mean ± standard deviation or median (range) for continuous variables and number (%) for categorical variables.
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; CCI, Charlson comorbidity index; BP, blood pressure; HDL—C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein -cholesterol; TG, triglyceride; AST, aspartate transaminase; ALT, alanine transferase; GGT, gamma-glutamyl transferase.
[a] Lower 20% of income.
[b] Geometric mean with 95% confidence interval.

1.88–2.05 for respiratory disease, FLI 30–59, 2.29, 2.21–2.38, FLI ≥ 60, 5.57, 5.31–5.85 for liver disease, Fig. 1).

3.3. Stratified analysis

To exclude the confounding effect of BMI, we stratified participants by BMI (<18.5, 18.5–23, 23–25, and ≥ 25), and the risk of all-cause mortality increased as the FLI score increased across all BMI group (Fig. 2). The greatest risk was observed in those who were underweight (BMI < 18.5) compared to the other BMI groups (HR, 95% CI = 2.43, 2.09–2.82 in the FLI ≥ 60 group, Table 3). When we applied different reference (BMI <18.5 and FLI < 30) enabling comparison across the all BMI groups, the underweight NAFLD group had the highest risk of mortality (Supplementary Table 1).

Next, we stratified the study population by the presence of abdominal obesity (WC ≥ 90 cm for men and ≥80 cm for women). The increased risk of all-cause mortality in the FLI ≥ 60 group was more prominent in subjects without abdominal obesity (HR 1.69) compared to those with abdominal obesity (HR 1.54, *P* for interaction <0.001, Supplementary Table 2). When we performed subgroup analyses stratified the study population by use of statin or presence of diabetes, the association between FLI and mortality was generally consistent with main findings. The increased risk of all-cause mortality in the FLI ≥ 60 group was slightly prominent in subjects without statin use (HR 1.67) compared to those with statin use (HR 1.61, *P* for interaction <0.001) and in subjects without diabetes (HR, 1.70) *vs* those with diabetes (HR, 1.59, *P* for interaction <0.001, Supplementary Table 2).

Stratified analyses by age, the increased risk for all-cause mortality in subjects with FLI ≥ 60 was more prominent in the 40–64 and < 40 year group (HR, 1.91) compared to the older (≥65 years) group (HR, 1.53, Supplementary Table 3). The associations for all-cause and disease-specific mortality were consistently observed in both men and women (Supplementary Table 4).

3.4. Association between the FLI and site-specific cancer mortality

Compared to the reference group, esophageal, stomach, colorectal, lung hepatobiliary, breast, and prostate cancer mortality increased as the FLI score increased (all *P* for trends <0.001). The group FLI ≥ 60 showed a higher risk of esophageal (HR, 95% CI = 2.49, 2.14–2.90), stomach (HR, 95% CI = 1.46, 1.36–1.56), colorectal (HR, 95% CI = 1.47, 1.38–1.57), lung (HR, 95% CI = 1.41, 1.35–1.47), hepatobiliary (HR, 95% CI = 2.35, 2.24–2.46), breast (HR, 95% CI = 1.38, 1.20–1.59), and prostate (HR, 95% CI = 1.23, 1.08–1.40) cancer mortality (Supplementary Fig. 2).

4. Discussion

To our knowledge, this study is the first to present a comprehensive analysis of the association between hepatic steatosis, defined using FLI scores, with all-cause and disease-specific mortality, based on a nationwide, population-based cohort study. The risk of all-cause and disease-specific mortality including CVD, cancer, respiratory disease and liver disease, linearly increased with a higher FLI score. Those who were underweight showed the greatest risk of all-cause mortality with high FLI scores compared to other BMI groups.

Although the relationship between hepatic steatosis and all-cause mortality in the general population has not been clearly established [14], increased NAFLD-related mortality has been observed in several studies. NAFLD was associated with a 93% higher relative risk of overall mortality, compared to a matched general population [15]. In terms of NAFLD assessed using FLI, there was a significant association between FLI with hepatic mortality in a large population-based survey in Italy [16]. However, previous studies were performed with Western populations, and the number of death events was relatively small, preventing the researchers from being able to fully evaluate the association between FLI and mortality [4,16].

In NAFLD patients, CVD has been recognized as the primary cause of mortality, however, the relationship between NAFLD and the risk of CVD mortality is contradictory in Asia [17–19]. Asian patients with NAFLD showed metabolic differences compared to Western patients. Lean Asian people are more prone to metabolic obesity and insulin resistance than Europeans, because they accumulate more adipose fat at an equivalent body mass. Dietary habits, genetic predisposition, and lifestyles greatly differ between Asia and Western countries. Repeatedly elevated FLI from consecutive exams was associated with a higher risk of all-cause mortality and incidence of myocardial infarction and stroke [20], and an increased BMI were associated with CVD mortality among lean Asians [21]. Consistently, all-cause and CVD-specific mortality increased in those with FLI ≥ 60 in our study. BMI, as one of the components of the FLI [6], may make a significant contribution to the relationship between the FLI categories and overall and CVD mortality.

When we performed a stratified analysis by BMI, the risk of all-cause mortality increased as the FLI score increased across all BMI groups, and the association between FLI scores and all-cause mortality was the greatest in the underweight group. These findings suggest an independent association between NAFLD and all-cause mortality regardless of BMI, and indicate that lean NAFLD might be worse, which might be caused by another metabolic abnormality or genetic predisposition not related solely to weight gain [22]. In a study from the US, lean people with NAFLD were more likely to have comorbidities and CVD, and had an increased risk of all-cause and CVD mortality compared to lean individuals without NAFLD [23]. In this context, the greater mortality in lean NAFLD in our study could be related to some degree of metabolic abnormality. However, we found a strong association even after

Table 2
All-cause and disease-specific mortality by fatty liver index.

Fatty liver index	Number	Death	PYs	IR (1000 PY)	Hazard ratio (95% confidence interval)			
					Model 1	Model 2	Model 3	Model 4
All-cause of mortality								
<30	5,812,188	245,132	47,859,198.4	5.1	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
30–59	2,020,351	116,036	16,567,735.18	7.0	0.96 (0.96–0.97)	0.97 (0.96–0.98)	0.91 (0.90–0.91)	1.19 (1.18–1.20)
≥60	1,025,882	57,128	8,393,848.24	6.8	1.19 (1.18–1.20)	1.19 (1.18–1.20)	1.05 (1.04–1.06)	1.67 (1.65–1.69)
p for trend					< 0.001	< 0.001	< 0.001	< 0.001
CVD-specific mortality								
<30	5,812,188	48,559	47,859,198.4	1.0	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
30–59	2,020,351	24,255	16,567,735.18	1.5	1.06 (1.04–1.08)	1.07 (1.05–1.09)	0.94 (0.92–0.95)	1.18 (1.16–1.20)
≥60	1,025,882	11,481	8,393,848.24	1.4	1.34 (1.31–1.36)	1.35 (1.32–1.38)	1.08 (1.06–1.11)	1.61 (1.56–1.65)
p for trend					< 0.001	< 0.001	0.024	< 0.001
Cancer-specific mortality								
<30	5,812,188	83,132	47,859,198.4	1.7	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
30–59	2,020,351	42,337	16,567,735.18	2.6	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.00 (0.99–1.02)	1.13 (1.11–1.14)
≥60	1,025,882	20,836	8,393,848.24	2.5	1.20 (1.18–1.22)	1.19 (1.17–1.21)	1.15 (1.13–1.17)	1.41 (1.38–1.44)
p for trend					<0.001	<0.001	<0.001	<0.001
Respiratory disease-specific mortality								
< 30	5,812,188	27,289	47,859,198.4	0.6	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
30–59	2,020,351	9544	16,567,735.18	0.6	0.74 (0.73–0.76)	0.76 (0.74–0.77)	0.74 (0.72–0.76)	1.26 (1.22–1.29)
≥ 60	1,025,882	3804	8,393,848.24	0.5	0.82 (0.79–0.85)	0.84 (0.81–0.87)	0.82 (0.79–0.85)	1.96 (1.88–2.05)
p for trend					<0.001	<0.001	<0.001	<0.001
Liver disease-specific mortality								
<30	5,812,188	8745	47,859,198.4	0.2	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
30–59	2,020,351	6972	16,567,735.18	0.4	1.53 (1.48–1.58)	1.52 (1.47–1.57)	1.52 (1.48–1.57)	2.29 (2.21–2.38)
≥60	1,025,882	5935	8,393,848.24	0.7	2.92 (2.83–3.02)	2.85 (2.75–2.95)	2.82 (2.72–2.92)	5.57 (5.31–5.85)
p for trend					< 0.001	< 0.001	< 0.001	< 0.001

IR, incidence rate; PY, person year; CVD, cardiovascular diseases.
Model 1 was adjusted for age and sex; Model 2 was adjusted for smoking status, alcohol consumption, physical activity, and low income in addition to covariates in model 1; Model 3 was adjusted for alanine aminotransferase, diabetes mellitus, hypertension, dyslipidemia, and Charlson comorbidity index score in addition to covariates in model 2. Model 4 was adjusted for body mass index and waist circumference in addition to covariate in model 3.

adjustment for common metabolic factors. Taken together, the increase in all-cause mortality with high FLI in the underweight group likely far exceeds that which can be explained by obesity or metabolic abnormality alone. Although it is difficult to assess whether the results of this study reflect sarcopenia, a previous study reported that non-obese NAFLD showed a significant association with sarcopenic obesity, suggesting that the poor outcome in non-obese NAFLD might be mediated by sarcopenia or sarcopenic obesity [24].

Since the effect of central obesity is not merely reflected by BMI, we performed stratified analysis by abdominal obesity. As a result, the increased risk of all-cause mortality in the FLI ≥ 60 group was more pronounced in subjects without abdominal obesity compared to those with abdominal obesity, indicating a greater association between all-cause mortality and high FLI scores in the group without abdominal obesity. When we performed stratified analysis by sex, and the associations for all-cause and disease-specific mortality were consistently observed in both men and women. In contrast to our study, NAFLD was associated with increased overall mortality and death from cancer, CVD, and liver disease in women, but this association was not observed in men in a previous study [19]. These different results may be associated with heterogeneity of the study population and the diagnostic modality of measures of hepatic steatosis.

When applying Model 3, there was an inverse association with high FLI and respiratory disease-mortality in this study. Although there are few studies regarding NAFLD and respiratory mortality, Lin et al. reported an inverse relationship between NAFLD and respiratory disease-related mortality [25]. These findings may be related obesity paradox, since obesity have differential association with respiratory mortality depending on the severity [26]. When we further adjusted WC and BMI as covariates, the direction of association has changed suggesting the association may be mediated by WC or BMI. Although we could not evaluate the fibrosis stage in NAFLD, the risk of liver-related mortality linearly increased with higher FLI scores in this study, confirming previous results [27].

Patients with NAFLD have a high prevalence of obesity, and obesity *per se* is an established risk factor for various malignancies [28]. BMI is also related to obesity-related cancers [29]. Moreover, the association with higher risk of cancer has been reported to be stronger in NAFLD than in obesity without NAFLD [30]. Broadly in line with previous results, the risk of esophageal, stomach, lung, hepatobiliary, colorectal, breast, and prostate cancer-related mortality increased linearly with an increase in FLI scores. The underlying pathogenesis of metabolic cancers in NAFLD is suggested to be related to ectopic fat storage [31], low-grade chronic inflammation, and insulin resistance, which may create a micro-environment suitable for cancer development [32].

We used a population-based cohort with a larger number of participants and more disease-specific causes of mortality were considered, including CVD, cancer, respiratory disease, and liver disease. This in turn permitted a more comprehensive analysis of the distribution of death causes and mortality risk on a nationwide scale. The sufficient case numbers enabled us to assess population-level risk across the FLI groups. Furthermore, our findings support expanded the use of FLI for extrahepatic manifestations.

However, there are several limitations in this study. First, FLI as a marker for hepatic steatosis cannot differentiate simple steatosis from steatohepatitis and fibrosis. For diagnosis of NAFLD, evidence of hepatic steatosis on imaging or pathology is mandatory. However, these methods involve high costs, and are not usually feasible for the

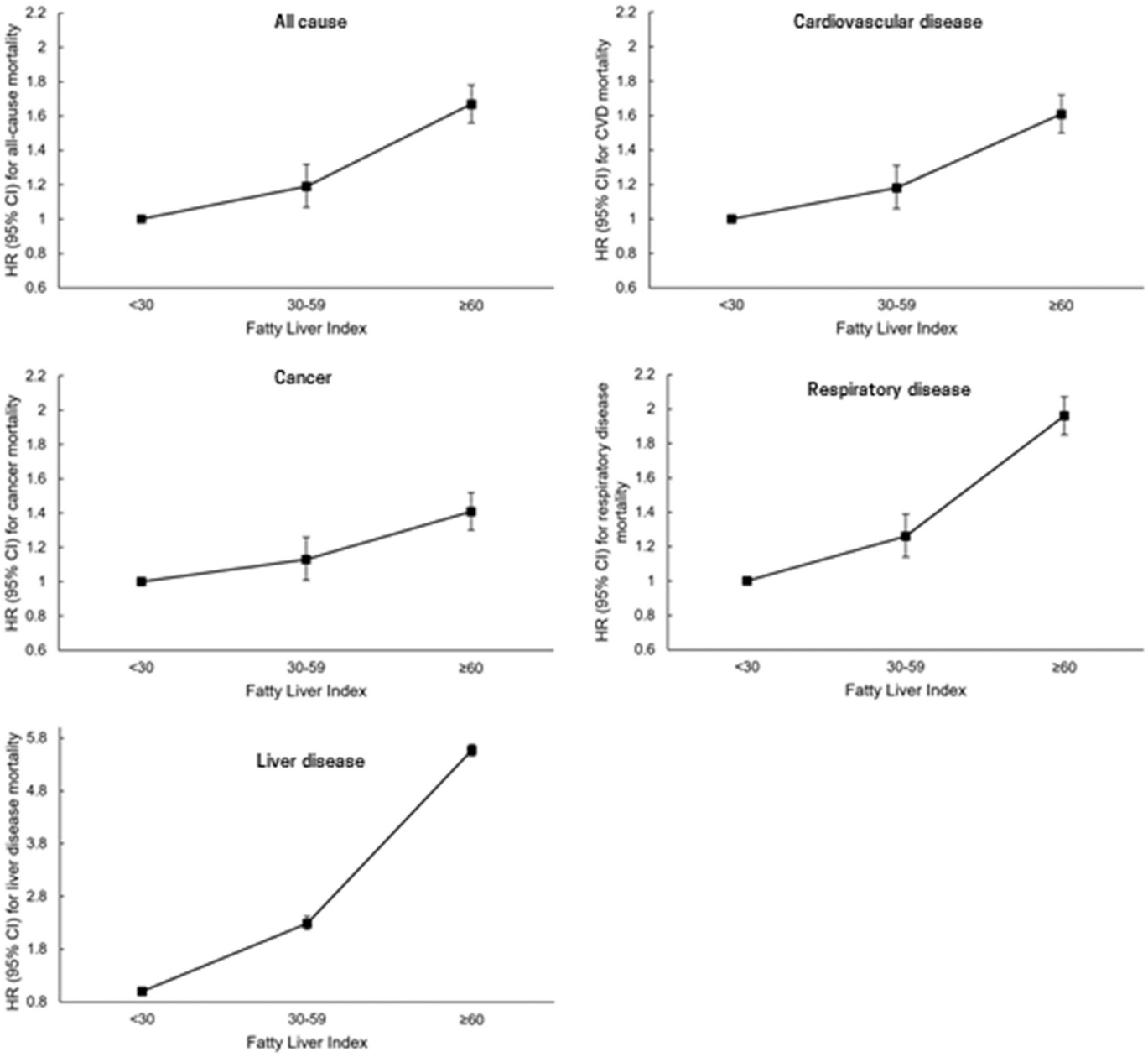

Fig. 1. Impacts of fatty liver index on all-cause and disease-specific mortality
Adjusted for age, sex, smoking status, alcohol consumption, physical activity, low income, alanine aminotransferase, diabetes mellitus, hypertension, dyslipidemia, Charlson comorbidity index, waist circumference and body mass index.
HR, hazard ratio; CI, confidence interval.

screening of fatty liver in a large population-based cohort. FLI can be used as a tool for risk stratification, and several previous large-population studies using claim data used FLI to define NAFLD [33,34]. In addition, external validation of FLI in other populations showed comparable diagnostic accuracy for NAFLD [8]. Second, there is the possibility of unmeasured confounding, such as insulin resistance. However, we tried to adjust for possible confounding variables thoroughly, including CCl score. Third, the cross-sectional analysis could not identify the impact of the change of NAFLD status on all-cause and disease-specific mortality. Finally, the study population comprised subjects from a single Asian country. Although CVD is the most common cause of death in US [35], 35% died from cancer while only 20,2% died from CVD in this cohort consistent with the report from Statistics Korea [36]. These racial/ethnic disparities in disease-specific death may be partly explained by socio-demographic, socio-economic status, health-related and dietary factors [37]. According to present ranks and recent trends, cancer may surpass CVD as the leading cause of premature death in most countries over the course of this century [38]. Further studies are warranted to validate and elucidate the underlying mechanisms for our findings.

In conclusion, here we presented a comprehensive analysis regarding overall, disease-specific, and site-specific cancer-related mortality according to FLI scores. The FLI may serve as a prognostic indicator of death, and a high FLI is associated with a poor prognosis particularly in the underweight group.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2022.155222.

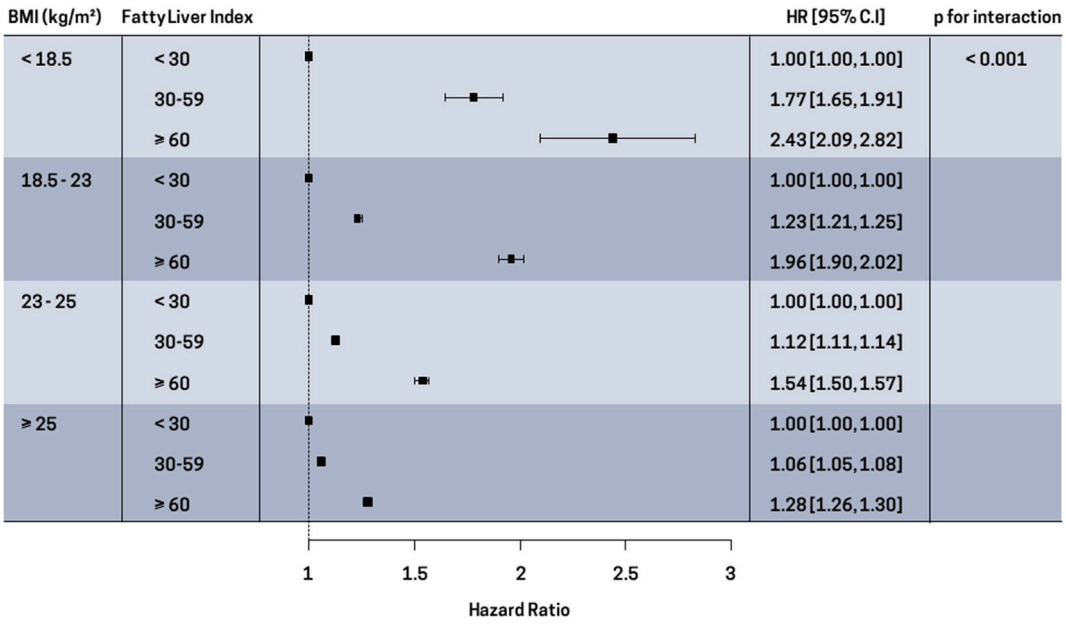

Fig. 2. The risk of all-cause mortality by fatty liver index stratified by body mass index.
Adjusted for age, sex, smoking status, alcohol consumption, physical activity, low income, alanine aminotransferase, diabetes mellitus, hypertension, dyslipidemia, and Charlson comorbidity index, waist circumference and body mass index.
BMI, body mass index; HR, hazard ratio; CI, confidence interval.

Table 3
Stratified analysis by body mass index: for all-cause mortality by fatty liver index.

BMI (kg/m^2)	Fatty liver index	N	Death	Incidence rate (per 1000 PY)	Hazard ratio (95% confidence interval)			
					Model 1	Model 2	Model 3	Model 4
<18.5	<30	338,842	25,614	9.4	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	30–59	2137	702	46.3	2.09 (1.94–2.25)	2.02 (1.88–2.18)	1.78 (1.65–1.92)	1.77 (1.65–1.91)
	≥60	448	173	55.5	2.89 (2.49–3.36)	2.86 (2.47–3.33)	2.44 (2.10–2.83)	2.43 (2.09–2.82)
	p for trend				< 0.001	< 0.001	< 0.001	< 0.001
18.5–23	<30	3,265,945	140,406	5.2	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	30–59	227,163	21,556	11.8	1.36 (1.34–1.38)	1.34 (1.32–1.36)	1.23 (1.22–1.25)	1.23 (1.21–1.25)
	≥60	28,849	4394	19.5	2.28 (2.21–2.35)	2.23 (2.16–2.29)	1.96 (1.90–2.02)	1.96 (1.90–2.02)
	p for trend				< 0.001	< 0.001	< 0.001	< 0.001
23–25	<30	1,461,115	54,321	4.5	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	30–59	599,757	35,612	7.3	1.21 (1.20–1.23)	1.19 (1.17–1.21)	1.13 (1.11–1.14)	1.12 (1.11–1.14)
	≥60	112,680	8434	9.2	1.75 (1.71–1.79)	1.70 (1.66–1.74)	1.54 (1.50–1.57)	1.54 (1.50–1.57)
	p for trend				< 0.001	< 0.001	< 0.001	< 0.001
≥25	<30	746,286	24,791	4.0	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)
	30–59	1,191,294	58,166	5.9	1.13 (1.11–1.15)	1.12 (1.10–1.14)	1.06 (1.05–1.08)	1.06 (1.05–1.08)
	≥60	883,905	44,127	6.1	1.47 (1.45–1.49)	1.44 (1.42–1.46)	1.28 (1.26–1.30)	1.28 (1.26–1.30)
	p for trend				<0.001	<0.001	<0.001	< 0.001
p for interaction					<0.001	<0.001	<0.001	<0.001

PY, person year.
Model 1 was adjusted for age and sex; Model 2 was adjusted for smoking status, alcohol consumption, physical activity, and low income in addition to covariates in model 1; Model 3 was adjusted for alanine aminotransferase, diabetes mellitus, hypertension, dyslipidemia, and Charlson comorbidity index score in addition to covariates in model 2. Model 4 was adjusted for waist circumference in addition to covariate in model 3.

CRediT authorship contribution statement

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Manuscript writing: Goh Eun Chung, Su-Min Jeong

Final approval of manuscript: All authors.

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Ethics declarations

Ethics approval and consent to participate: The Institutional Review Board of Soongsil University approved this study (SSU-202007-HR-236-01), and we performed the study in accordance with relevant guidelines and regulations. The requirement for written informed consent was waived.

Consent to publish

Not applicable.

Availability of data and materials

We used the claim data provided by the Korean National Health Insurance Service (NHIS) database. Data can only be accessed by visiting the NHIS datacenter, after approval from data access committee of NHIS (https://nhiss.nhis.or.kr/bd/ab/bdaba001cv.do).

Declaration of competing interest

The authors declare that they have no competing interests.

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