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Clinical Research Article

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Liver Fibrosis Indices for the Prediction of Mortality in Korean Subjects: A 16-Year Prospective Cohort Study

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Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; FIB-4, Fibrosis-4 score; HbA1c, glycated hemoglobin A1c; HR, hazard ratio; HSI, hepatic steatosis index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NGT, normal glucose tolerance; NLFS, NAFLD liver fat score; ROC, receiver operating characteristic.

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Abstract

Context: Nonalcoholic fatty liver disease (NAFLD) and its progression to liver fibrosis are related to higher mortality.

Objective: We investigated whether noninvasive indices of NAFLD and liver fibrosis could predict mortality in a Korean prospective cohort study.

Methods: We followed 4163 subjects from the Korean Genome and Epidemiology Study biannually over 16 years. Cox proportional hazards regression was used to calculate the hazard ratios (HRs) of NAFLD or liver fibrosis indices in the total group of subjects and subgroups according to body mass index (BMI) and glucose metabolism status.

Results: The mean age (± SD) of the subjects was 55.7 ± 8.7 years and 39.2% were men. During a median follow-up period of 15.6 years, 643 subjects (15.4%) died. The Fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS), and aspartate aminotransferase to platelet ratio index were consistently higher in deceased subjects regardless of baseline glucose metabolism status. The FIB-4 and NFS displayed acceptable discrimination power for mortality, with area under the receiver operating characteristic curve values of 0.686 and 0.666, respectively. The adjusted HRs for FIB-4 and NFS were 1.41 (95% CI, 1.18-1.68) and 1.43 (95% CI, 1.21-1.68), respectively. Both FIB-4 and NFS were significantly associated with liver-specific mortality but not cardiovascular mortality. The association between mortality with fibrosis indices were more prominent in subjects with a lower BMI (<25 kg/m^2).

Conclusion: Noninvasive indices of liver fibrosis might be a significant predictor of all-cause and liver-specific mortality in Korean subjects.

Key Words: nonalcoholic fatty liver disease, hepatic fibrosis, noninvasive index, diabetes, mortality

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing, consistent with the increase in obesity globally [1]. The global prevalence of NAFLD was recently estimated to be 25.2% [2] and the prevalence of NAFLD in Korea, based on data from Korean health checkups, was similar to the global prevalence [3, 4]. Among various metabolic risk factors, diabetes is the most important risk factor for NAFLD and nonalcoholic steatohepatitis (NASH), a more severe form of NAFLD [5]. The global prevalence of NAFLD and NASH in subjects with type 2 diabetes was higher than in the general population, at 55.5% and 37.3%, respectively [6]. Furthermore, diabetes is strongly associated with the risk of NASH among subjects with NAFLD [7], and the prognosis of NASH was poor in subjects with type 2 diabetes compared with those without dysglycemia [8]. In fact, subjects with NAFLD exhibited an increased risk of type 2 diabetes [5]. Therefore, NAFLD and type 2 diabetes might be interrelated conditions, and there is a need to assess health outcomes related to NAFLD or NASH, considering baseline glucose tolerance status.

The most common cause of death of subjects with NAFLD has been thought to be cardiovascular diseases [9]. However, several Asia-based studies have revealed that liver-related mortality is a more common cause of death than cardiovascular diseases [10]. The liver fibrosis stage is the most important predictor for liver-related mortality [11]. Traditionally, liver biopsy has been required to identify the fibrosis stage and diagnose NASH. However, as liver biopsy is an invasive procedure, it is critical to select subjects who have a high probability of NASH. Various noninvasive indices have been developed to predict the presence of NASH, and these have been validated against liver biopsy results [12, 13]. The National Health and Nutrition Examination Survey revealed that these noninvasive NAFLD fibrosis indices can predict mortality in subjects with NAFLD [14]. In another prospective cohort in the United States, a higher NAFLD fibrosis score (NFS) was found to be associated with higher mortality [15].

A recent study using the Korean National Health Insurance Service database revealed that the fatty liver index was associated with all-cause mortality, and this finding was more prominent in nonobese women with diabetes [16]. However, whether liver fibrosis indices can predict mortality in Korean subjects has not been investigated. Therefore, in this study, we evaluated the ability of noninvasive NAFLD and liver fibrosis indices to predict mortality in Korean subjects from a prospective community cohort by considering their glucose metabolism status and level of obesity.

Methods

Participants

In the present study, we analyzed the Ansung data from the Korean Genome and Epidemiology Study (KoGES), which enrolled Korean adults aged 40 to 69 years. The baseline evaluation was conducted during 2001 and 2002. In total, 5018 subjects were enrolled, and follow-up examinations were conducted biannually. Glucose tolerance status was assessed using a 75-g oral glucose tolerance test and measurement of glycated hemoglobin A1c (HbA1c). We excluded subjects who consumed excessive alcohol (>30 g/day for men and >20 g/day for women). We also excluded subjects diagnosed with hepatitis and cancer in a baseline examination. The study protocol was approved by the Ethics Committee of the Korean Center for Disease Control and the Institutional Review Board of Ajou University School of Medicine (IRB No. AJIRB-CRO-07-012). All participants provided written informed consent before enrollment.

Parameters and Outcomes

All subjects were instructed to visit a community clinic after overnight fasting. The methods used for the anthropometric measurements and laboratory analysis were as previously published [17]. Fasting plasma levels of insulin were measured by radioimmunoassay (Insulin-IRMA; BioSource, Nivelles, Belgium). We calculated the hepatic steatosis index (HSI) [[18], and NAFLD liver fat score (NLFS) [19] as an index of NAFLD. Liver fibrosis scores were calculated using the Fibrosis-4 (FIB-4) index [age (years) × aspartate aminotransferase (AST) (U/L) / platelets (10^9/L) × √ alanine aminotransferase (ALT) (U/L)] [20]; NFS [−1.675 + 0.037 × age (years) + 0.094 × body mass index (BMI) (kg/m^2) + 1.13 × impaired fasting glucose or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (10^9/L) − 0.66 × serum albumin (g/dL)] [12]; BARD score [BMI ≥ 28 kg/m^2 = 1 point; AST/

ALT ratio ≥ 0.8 = 2 points; and diabetes mellitus = 1 point] [21]; and AST to platelet ratio index (APRI) [(100 × AST (U/L)/upper limit of normal)/ platelet count (10^9/L)] [22]. FIB-4 index is correlated with the stage of fibrosis, and a score < 1.3 and > 2.67 could predict the absence of advanced fibrosis and a high positive prediction of advanced fibrosis, respectively [20]. NFS also predicts the presence of advanced fibrosis according to its cutoff values of < −1.455 and > 0.676 [12]. Mortality data were obtained from the death statistics of the Korean National Statistical Office. The last update of mortality was in December 2018. We analyzed the clinical and biochemical data between living and deceased subjects at baseline.

Statistical Analysis

Data are presented as mean ± SD, or as numbers and percentages. An independent *t* test was used to compare the mean values of living and deceased subjects. Categorical variables were compared using the chi-square test. An analysis of covariance was used when covariates were adjusted. A receiver operating characteristic (ROC) curve was used to determine which indices could predict mortality, and the area under the ROC curve (AUROC) was calculated to assess the predictive power. Cutoff values for each index to predict mortality were determined with maximum sum of sensitivity and specificity using Youden's Index [23]. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of mortality associated with each index. Statistical analysis was performed using IBM SPSS Statistics (Window version 22.0). Two-sided *P* values <0.05 were considered significant.

Results

Among the 5018 subjects, 146 were not followed up, 55 lacked information about the presence of diabetes at baseline, and 749 were excluded because of alcohol history or underlying malignancy. A total of 4163 subjects (2893 with normal glucose tolerance [NGT], and 1270 with abnormal glucose metabolism) were followed up for a median of 15.6 years. The total number of deaths was 643 (15.4%), of which, 113 were from cardiovascular diseases and 34 were from liver-specific causes. Table 1 shows the clinical and biochemical characteristics of the participants at baseline for the total number of subjects and for subjects with NGT or abnormal glucose metabolism. Men and current or ex-smokers died more frequently than did women and subjects who never smoked. Deceased subjects were older and had a lower BMI than did living subjects. Glucose levels during the oral glucose tolerance test and HbA1c levels were higher in deceased than in living subjects. With regard to NAFLD indices, the HSI was lower only in deceased subjects with NGT, and the NLFS was higher in deceased subjects. Among the liver fibrosis indices, FIB-4, NFS, and APRI scores were consistently higher in subjects that subsequently died than in the surviving subjects, regardless of their baseline glucose tolerance status. Among these indices, FIB-4 displayed the highest AUROC to predict mortality (0.686; 95% CI, 0.663-0.708; $P < 0.001$) (Table 2). Using a cutoff value of 1.22, FIB-4 can predict mortality with 64.4% sensitivity and 64.6% specificity. The second highest AUROC was derived for NFS (0.666; 95% CI, 0.643-0.690; $P < 0.001$), with sensitivity and specificity of 70.0% and 55.3%, respectively, by adopting a cutoff value of −2.08 for NFS.

We categorized subjects according to liver fibrosis indices with each cutoff value for FIB-4 and NFS. When the HRs for mortality were analyzed using a Cox proportional hazards model, FIB-4 ≥ 1.22, or NFS ≥ −2.08 showed HRs of 2.98 (95% CI, 2.54-3.50), and 2.52 (95% CI, 2.16-2.93), respectively (Tables 3 and 4). After adjusting for confounding factors such as age, sex, smoking history, BMI, and HbA1c, the FIB-4 and NFS indices showed a positive association with mortality in total subjects and in subjects with NGT. This association was consistent in the subgroup with a BMI < 25 kg/m^2 but was diminished in the subgroup with a BMI ≥ 25 kg/m^2. Liver-specific mortality yielded a significant association with FIB-4, and with NFS after adjusting for confounding factors. FIB-4, but not NFS, showed a consistent association with liver-specific mortality, regardless of baseline glucose metabolism status. By contrast, the significant association between cardiovascular mortality and liver fibrosis indices was diminished after adjusting for confounding factors.

Discussion

In this prospective cohort study, we firstly demonstrated that liver fibrosis indices can predict all-cause and liver-specific mortality in Korean subjects. In this population, male sex, old age, low BMI, higher glucose levels, and smoking history were related to higher mortality. After adjusting for these confounding factors, FIB-4 and NFS were still associated with all-cause and liver-specific mortality, and this association was more prominent in subjects with a lower BMI (<25 kg/m^2). This result suggests that liver fibrosis indices, which has been used clinically to identify advanced fibrosis in subjects with NAFLD, might be useful for identifying a higher mortality group among the Korean population.

Noninvasive indices of liver fibrosis were originally developed to identify subjects who required a liver biopsy [13]. In fact, many guidelines have adopted these

Table 1. Baseline clinical and biochemical characteristics and noninvasive markers of NAFLD and liver fibrosis in subjects with normal glucose tolerance or abnormal glucose metabolism (prediabetes and diabetes)

	Total subjects		Normal glucose tolerance		Abnormal glucose metabolism	
	Subjects alive (n = 3520)	Subjects deceased (n = 643)	Subjects alive (n = 2549)	Subjects deceased (n = 344)	Subjects alive (n = 971)	Subjects deceased (n = 299)
Men, n (%)	1253 (35.6)	377 (58.6)***	969 (38.0)	210 (61.0) ***	284 (29.2)	167 (55.9)***
Age (yr)	54.6 ± 8.6	61.9 ± 6.9***	53.8 ± 8.6	61.5 ± 7.4***	56.6 ± 8.1	62.4 ± 6.2***
BMI (kg/m^2)	24.7 ± 3.3	23.7 ± 3.3***	24.4 ± 3.2	23.3 ± 3.1 ***	25.5 ± 3.3	24.2 ± 3.4***
WC (cm)	84.7 ± 8.9	84.4 ± 8.9	83.7 ± 8.7	83.0 ± 8.6	87.2 ± 8.7	86.0 ± 9.0*
SBP (mmHg)	121 ± 18	127 ± 20***	119 ± 17	126 ± 19 ***	127 ± 19	129 ± 20
DBP (mmHg)	77 ± 10	79 ± 10**	76 ± 10	78 ± 10 ***	79 ± 11	79 ± 10
Glucose (mg/dL)	86.8 ± 15.4	89.9 ± 20.9**	83.4 ± 8.3	83.0 ± 9.5	97.2 ± 24.8	101.1 ± 28.3
PG at 1h (mg/dL)	153.4 ± 53.4	173.4 ± 62.3***	135.9 ± 39.4	144.5 ± 42.3***	206.5 ± 55.6	220.0 ± 61.2**
PG at 2h (mg/dL)	123.4 ± 46.9	141.1 ± 65.9***	103.7 ± 21.1	103.0 ± 22.1	183.2 ± 52.7	203.1 ± 66.3***
HbA1c (%)	5.8 ± 0.8	6.2 ± 1.4***	5.5 ± 0.4	5.6 ± 0.4*	6.4 ± 1.3	6.9 ± 1.7***
Cholesterol (mg/dL)	190 ± 35	186 ± 39*	187 ± 34	183 ± 36	199 ± 37	189 ± 42***
Triglyceride (mg/dL)	157 ± 100	163 ± 119	145 ± 90	146 ± 88	188 ± 117	182 ± 144
HDL-C (mg/dL)	46 ± 11	46 ± 13	47 ± 11	47 ± 13	45 ± 10	45 ± 13
LDL-C (mg/dL)	116 ± 34	112 ± 39*	113 ± 32	109 ± 34*	122 ± 39	114 ± 44**
AST (IU/L)	26.4 ± 16.5	32.6 ± 28.9***	25.9 ± 17.0	30.5 ± 17.4***	27.7 ± 15.0	35.1 ± 37.9***
ALT (IU/L)	24.7 ± 21.7	26.9 ± 20.9*	23.2 ± 18.9	24.4 ± 13.8	28.5 ± 27.5	29.8 ± 26.6
Albumin (g/dL)	4.3 ± 0.3	4.2 ± 0.4***	4.3 ± 0.3	4.2 ± 0.3***	4.3 ± 0.3	4.2 ± 0.4***
GGT (IU/L)	28.1 ± 39.7	55.6 ± 131.5***	25.3 ± 36.2	42.6 ± 115.1***	35.3 ± 47.0	70.7 ± 146.9***
BUN (mg/dL)	14.1 ± 3.7	14.9 ± 4.5***	14.1 ± 3.7	14.8 ± 4.3***	14.2 ± 3.8	15.0 ± 4.8**
Creatinine (mg/dL)	0.78 ± 0.19	0.85 ± 0.27***	0.79 ± 0.19	0.84 ± 0.19***	0.77 ± 0.18	0.86 ± 0.34***
Smoking, n (%)						
Never	2369 (68.3)	300 (47.2)***	1670 (66.5)	155 (45.9)***	699 (72.9)	145 (48.7)***
Ex-smoker	369 (10.6)	122 (19.2)	266 (10.6)	65 (19.2)	103 (10.7)	57 (19.1)
Current	733 (21.1)	214 (33.6)	576 (22.9)	118 (34.9)	157 (16.4)	96 (32.2)
HSI	35.8 ± 4.2	35.5 ± 4.3	35.5 ± 4.1	34.8 ± 4.1**	36.6 ± 4.3	36.3 ± 4.5
NLFS	0.90 ± 1.29	1.16 ± 1.56***	0.77 ± 1.26	0.89 ± 1.10	1.32 ± 1.28	1.61 ± 2.02
FIB-4	1.18 ± 0.75	1.88 ± 2.03***	1.18 ± 0.78	1.76 ± 1.66***	1.19 ± 0.67	2.02 ± 2.39***
NFS	–2.20 ± 1.12	–1.44 ± 1.38***	–2.50 ± 0.99	–1.97 ± 1.11***	–1.41 ± 1.06	–0.84 ± 1.41***
BARD	2.04 ± 0.74	2.22 ± 0.75***	1.96 ± 0.63	1.99 ± 0.46	2.24 ± 0.95	2.49 ± 0.91***
APRI	0.27 ± 0.34	0.42 ± 0.66***	0.26 ± 0.38	0.37 ± 0.46***	0.27 ± 0.22	0.49 ± 0.82***

Data are unadjusted means (SD), or n (%). *P* values were determined using a Student *t* test and chi-square test.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, Fibrosis-4 score; HbA1c, glycated hemoglobin A1c; HSI, hepatic steatosis index; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NLFS, NAFLD liver fat score; PG, plasma glucose; SBP, systolic blood pressure; WC, waist circumference;

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 2. Areas under the ROC curve for markers of NAFLD and liver fibrosis for prediction of mortality

	Total	Normal glucose tolerance	Abnormal glucose metabolism
	AUROC (95% CI)	AUROC (95% CI)	AUROC (95% CI)
HSI	0.476 (0.451–0.501)	0.451 (0.418–0.484)**	0.475 (0.437–0.513)
NLFS	0.557 (0.530–0.583)***	0.551 (0.518–0.584)**	0.528 (0.481–0.574)
FIB-4	0.686 (0.663–0.708)***	0.713 (0.686–0.741)***	0.655 (0.619–0.691)***
NFS	0.666 (0.643–0.690)***	0.635 (0.603–0.667)***	0.631 (0.594–0.668)***
BARD	0.559 (0.534–0.583)***	0.496 (0.466–0.527)	0.579 (0.542–0.616)***
APRI	0.599 (0.573–0.624)*	0.631 (0.599–0.663)***	0.560 (0.520–0.601)**

Abbreviations: APRI, AST to platelet ratio index; AUROC, area under the receiver operating characteristic curve; HSI, hepatic steatosis index; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NGT, normal glucose tolerance; NLFS, NAFLD liver fat score.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3. FIB-4 and all-cause, liver-specific, and cardiovascular mortality

	Total		Normal glucose tolerance		Abnormal glucose metabolism	
	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality						
FIB-4 < 1.22	Reference	Reference	Reference	Reference	Reference	Reference
FIB-4 ≥ 1.22	2.98 (2.54–3.50)***	1.41 (1.18–1.68)***	3.53 (2.81–4.43)***	1.56 (1.21–2.01)**	2.44 (1.94–3.08)***	1.27 (0.99–1.63)
BMI < 25.0	2.98 (2.43–3.65)***	1.48 (1.18–1.84)*	3.30 (2.52–4.32)***	1.48 (1.10–1.99)*	2.38 (1.75–3.26)***	1.40 (1.00–1.97)*
BMI ≥ 25.0	2.69 (2.04–3.24)***	1.32 (0.98–1.77)	3.72 (2.41–5.72)***	1.79 (1.10–2.91)*	2.10 (1.56–3.03)***	1.15 (0.78–1.70)
Liver-specific mortality						
FIB-4 < 1.22	Reference	Reference	Reference	Reference	Reference	Reference
FIB-4 ≥ 1.22	7.58 (3.14–18.30)***	6.40 (2.42–16.94)***	5.59 (2.06–15.15)**	4.09 (1.33–12.58)*	17.44 (2.25–135.27)**	15.58 (1.79–135.68)*
BMI < 25.0	14.25 (3.35–60.60)***	13.96 (3.03–64.24)**	8.93 (2.02–39.58)**	7.50 (1.51–37.26)*	70.41 (0.33–15095.08)	232649.61 (0.0–1.896E+133)
BMI ≥ 25.0	3.32 (0.94–11.77)	2.74 (0.64–11.71)	2.95 (0.66–13.18)	1.56 (0.28–8.66)	4.82 (0.44–53.41)	7.98 (0.55–116.02)
Cardiovascular mortality						
FIB-4 < 1.22	Reference	Reference	Reference	Reference	Reference	Reference
FIB-4 ≥ 1.22	2.52 (1.72–3.68)***	1.23 (0.82–1.86)	2.98 (1.75–5.07)***	1.29 (0.71–2.34)	2.07 (1.20–3.57)**	1.20 (0.67–2.14)
BMI < 25.0	1.87 (1.13–3.09)*	0.87 (0.51–1.50)	2.44 (1.27–4.70)**	1.04 (0.51–2.12)	1.14 (0.51–2.53)	0.67 (0.29–1.58)
BMI ≥ 25.0	4.00 (2.21–7.23)***	1.86 (0.99–3.53)	4.77 (1.81–12.55)**	2.01 (0.68–5.90)	3.55 (1.68–7.53)**	1.95 (0.88–4.36)

Adjusted HR[a] was adjusted by age, sex, smoking history, body mass index, and HbA1c.

Abbreviations: BMI, body mass index; FIB-4, Fibrosis-4 score; HR, hazard ratio.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 4. NAFLD fibrosis score (NFS) and all-cause, liver-specific, and cardiovascular mortality

	Total		Normal glucose tolerance		Abnormal glucose metabolism	
	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality						
NFS < −2.08	Reference	Reference	Reference	Reference	Reference	Reference
NFS ≥ −2.08	2.52 (2.16–2.93)***	1.43 (1.21–1.68)***	2.30 (1.86–2.85)***	1.29 (1.03–1.62)*	2.08 (1.48–2.91)***	1.25 (0.88–1.77)
BMI < 25.0	2.76 (2.26–3.37)***	1.50 (1.21–1.86)***	2.29 (1.79–2.92)***	1.25 (0.96–1.62)	2.45 (1.57–3.82)***	1.46 (0.91–2.33)
BMI ≥ 25.0	2.75 (2.01–3.77)***	1.32 (0.94–1.86)	2.59 (1.69–3.97)***	1.41 (0.89–2.24)	1.70 (1.01–2.84)*	0.91 (0.54–1.56)
Liver-specific mortality						
NFS < −2.08	Reference	Reference	Reference	Reference	Reference	Reference
NFS ≥ −2.08	5.03 (2.34–10.82)***	5.20 (2.29–11.82)***	4.04 (1.65–9.90)**	3.39 (1.27–9.03)*	3.40 (0.44–26.33)	3.19 (0.39–26.03)
BMI < 25.0	3.91 (1.55–9.85)**	3.50 (1.29–9.67)*	4.04 (1.38–11.83)*	3.28 (1.01–10.59)*	2.52 (3.14–20.12)	1.89 (0.22–16.33)
BMI ≥ 25.0	3.76 (0.80–17.71)	3.70 (0.69–19.76)	4.26 (0.83–21.94)	2.87 (0.48–17.28)	30.12 (0.0–3063966.277)	426404.072 (0.0∞)
Cardiovascular mortality						
NFS < −2.08	Reference	Reference	Reference	Reference	Reference	Reference
NFS ≥ −2.08	2.69 (1.84–3.92)***	1.27 (0.84–1.91)	2.622 (1.55–4.42)***	1.37 (0.78–2.39)	1.51 (0.74–3.10)	0.77 (0.36–1.61)
BMI < 25.0	3.91 (1.55–9.85)**	1.21 (0.70–2.10)	2.32 (1.24–4.35)**	1.31 (0.67–2.53)	1.67 (0.57–4.88)	0.91 (0.30–2.76)
BMI ≥ 25.0	3.14 (1.60–6.16)**	1.42 (0.69–2.92)	3.66 (1.39–9.64)**	1.79 (0.63–5.09)	1.40 (0.53–3.66)	0.72 (0.27–1.96)

Adjusted HR was adjusted by age, sex, smoking history, body mass index, and HbA1c.

Abbreviations: BMI, body mass index; HR, hazard ratio; NFS, nonalcoholic fatty liver disease liver fibrosis score.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

noninvasive indices for assessing subjects with NAFLD [24], including the Fatty Liver Research Group of the Korean Diabetes Association [25]. Our study and others have demonstrated that liver fibrosis indices have clinical implications beyond predicting liver fibrosis. In health checkup data from Taiwan, these fibrosis indices were associated with a risk of chronic kidney disease [26]. In addition, an advancing fibrosis score was shown to be related to a progressive increase in mortality based on the data from the National Health and Nutrition Examination Survey [14] and the Rochester Epidemiology Project [15]. In the present study, we confirmed that liver fibrosis indices can predict mortality in the Korean population. Interestingly, liver fibrosis indices could predict all-cause and liver-specific mortality but not cardiovascular mortality after adjusting for cardiometabolic risk factors. In addition, associations between fibrosis indices and all-cause and liver-specific mortality were observed more consistently in subjects with NGT than in those with abnormal glucose metabolism, and in subjects with a lower BMI than in those with a higher BMI. Previous observational studies compared the prognosis of nonobese NAFLD patients with obese NAFLD patients [27]. In general, metabolic abnormalities were more prevalent in obese subjects with NAFLD than in nonobese subjects with NAFLD. However, the mortality and development of severe liver disease were reported higher in subjects with nonobese NAFLD than obese counterparts in some studies [28, 29]. Genetic predisposition or unhealthy lifestyle might involve the health outcome of NAFLD. Our study added the new insight that liver fibrosis indices might represent poor health outcome in lean population regardless of NAFLD.

In contrast to hepatic steatosis, NASH is driven by a "second hit," such as inflammation or oxidative stress [30], and it has a graver clinical course than does simple hepatic steatosis. Therefore, the ability to detect and predict NASH is the most crucial process in subjects with NAFLD. The gold standard to diagnose NASH is liver biopsy, which is invasive, but alternative noninvasive tools, such as magnetic resonance elastography, are expensive [25]. In this regard, these definitive diagnostic methods cannot be applied in all subjects with NAFLD. Therefore, noninvasive indices such as FIB-4 and NFS are more feasible in general practice. In this study, we were able to identify the risk of mortality successfully using these parameters.

However, this study did have several limitations. First, we did not perform a liver ultrasound examination of the subjects, which is a detection method for fatty liver disease. In the same context, no information was available about any histological abnormalities in subjects with a high liver fibrosis index. Second, this study was conducted in a single region in Korea; therefore, the findings cannot reliably be generalized and compared directly with data from Western countries. Third, antidiabetic medications might have some impact on NAFLD and NASH indices, but no medication data were collected.

In conclusion, the results of this study demonstrated that high FIB-4 and NFS scores, which are indirect indices for NASH, independently predicted all-cause and liver-specific mortality, which emphasizes the clinical importance of these liver fibrosis indices.

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