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Diagnostic performance of the fibrosis-4 index and the NAFLD fibrosis score for screening at-risk individuals in a health check-up setting

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Abstract

Background: The fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) have been used as noninvasive screening methods for advanced fibrosis in patients with NAFLD. However, their diagnostic performance has not been evaluated in at-risk individuals regardless of hepatic steatosis. This study evaluated the performance of the FIB-4 and NFS in at-risk groups of health check-up examinees at mass screening centers.

Methods: This retrospective, cross-sectional study included 8545 participants who underwent voluntary magnetic resonance elastography at a discounted fee during their regular health check-ups at 13 mass screening centers nationwide. The at-risk group was defined as those with any of the following conditions: NAFLD, 2 or more metabolic abnormalities, diabetes mellitus, or abnormal aminotransferase levels. A magnetic resonance elastography cutoff of $\geq$3.6 kPa was used to define conventional advanced fibrosis.

Results: According to the proposed criteria, the proportion of at-risk individuals was 67.4%–80.2% in the health check-up cohort without viral or alcohol-associated liver disease. The prevalence of individuals with advanced hepatic fibrosis in each at-risk group was ~2.3%–2.8% according to various criteria. It was higher in patients without NAFLD than in those with NAFLD. A total of 28.2%–39.6% of those in each at-risk group did not show hepatic steatosis on ultrasonography. The performance of FIB-4 for

Abbreviations: AACE, American Association of Clinical Endocrinology; Abn., transminase. abnormal aminotransferases; AGA, American Gastroenterological Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; FIB-4, fibrosis-4 index; MA, metabolic abnormality; MA2, metabolic abnormality ≥2; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; NIT, Noninvasive Test; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SBP, systolic blood pressure.

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advanced fibrosis in the at-risk group was comparable with that in the NAFLD group. FIB-4 showed a better area under the receiver operating characteristic curve and sensitivity than NFS in the at-risk group.

Conclusions: FIB-4 demonstrated superior performance compared with the NFS, and its performance in at-risk individuals was similar to that observed for patients with NAFLD.

INTRODUCTION

NAFLD is the most prevalent chronic liver disease in developed countries. The stage of hepatic fibrosis is the most important prognostic factor for liver-related and overall mortality in patients with NAFLD.[1,2] However, routine screening for fibrosis is not recommended in the general population, in which there is a low prevalence of fibrosis; this is because of the lack of evidence for cost-effectiveness. Significant fibrosis is reported to have a prevalence of up to 5.1%–9.5% based on magnetic resonance elastography (MRE) findings.[3,4] Regardless of hepatic steatosis, for the early recognition of patients with fibrosis and adequate referral from primary care, current clinical practice guidelines recommend the application of noninvasive tests (NITs) not only in patients with hepatic steatosis, as identified by imaging, but also in those with obesity, elevated liver enzymes, diabetes, and risk factors for metabolic or cardiovascular diseases.[5–8] These patients are termed the at-risk group for NAFLD-related fibrosis. In this recently proposed at-risk group, routine screening for hepatic fibrosis is recommended regardless of hepatic steatosis. In fact, a previous study showed that ~40% of individuals with significant fibrosis among the general population showed no evidences of hepatic steatosis and would likely be missed if a screening strategy, which focuses only on those with fatty liver, were applied.[9] However, the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) have not been evaluated for their diagnostic performances as screening methods in the at-risk group within the general population.

The diagnostic performance of NFS is suggested to be lower than that of FIB-4 in individuals with obesity and/or diabetes.[10–13] Similarly, the performance of NIT is affected by both the characteristics of the population and the prevalence of advanced fibrosis. Therefore, it is necessary to determine whether previous NITs show reasonable diagnostic performances in the recently proposed at-risk group. In addition, various definitions of at-risk groups have been proposed by different guidelines and expert opinions, without any consensus being reached. In this study, we evaluated the diagnostic performances of FIB-4 and NFS for advanced hepatic fibrosis in an at-risk group from a health check-up cohort.

METHODS

Study design

This was a retrospective, cross-sectional study. The participants underwent voluntary MRE for a discounted fee during their regular health check-ups at 13 mass screening centers nationwide. This study was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul and was approved by the institutional review board of Hanyang University Hospital (IRB No. HY-2021-04-001-001). A waiver for informed consent was obtained.

Protocol and rationale for abdominal sonography and MRE during health check-ups

The universal health check-up program is performed regardless of the center, with the same protocol being implemented. It includes body measurements (height, weight, waist circumference, body mass index, and vital signs), blood and urine samples (complete blood cell counts, electrolytes, liver and renal function tests, lipid profiles, and routine urinalysis), and abdominal sonography. FIB-4 and NFS were calculated using these data. In Korea, abdominal sonography is one of the most basic screening tests performed as part of an annual or biennial obligatory health check-up under the Act of Employment. In addition, it can be conducted at the examinees' request for a small fee. Intriguingly, optional MRE is widely performed in these 13 nationwide mass screening health promotion centers, with ~2500 tests performed per year. This large-scale testing has been shown to be feasible; it is provided at a greatly discounted fee (less than USD100 per person) on the same day as the health check-up of the patient, without knowing their abdominal sonography results. The results of this universal health check-up are sent to the individual a month after the check-up. Patients with known chronic liver diseases are managed under a separate health check-up program. They are offered (and biannually required to undergo) upper abdominal sonography at 10% of the standard fee; this program is

run by the National Health Insurance Service in Korea. Therefore, these patients were less likely to have been included in the present study.

Inclusion and exclusion criteria

Participants who underwent MRE as part of their regular health check-ups between January 1, 2017, and May 30, 2020, were included. Individuals with missing data on the history of alcohol intake, laboratory variables used in the calculation of FIB-4 or NFS, abdominal ultrasonography, or MRE were excluded. Individuals with a history of significant alcohol intake (>210 g/wk for men and >140 g/wk for women) or evidences of viral hepatitis [positive results for HBsAg or antibody against the HCV (anti-HCV)] were also excluded.

Cutoff values of FIB-4 and NFS

For participants aged below 65 years, the cutoff values for FIB-4 and NFS were 1.3 and −1.455, respectively.[14] Meanwhile, for those aged 65 years or older, the cutoff values used for FIB-4 and NFS were 2.0 and 0.12, respectively.

Definition of metabolic risk factors

We defined metabolic risk factors as follows:[15] (1) waist circumference ≥ 85 cm for women and ≥ 90 cm for men, (2) blood pressure $\geq 130/85$ mm Hg and/or history of antihypertensive medications, (3) serum triglycerides ≥ 150 mg/dL, (4) HDL cholesterol <50 mg/dL for women and <40 mg/dL for men, and (5) fasting glucose level ≥ 100 mg/dL with hemoglobin $A_{1c} \geq 5.7\%$ and/or history of antidiabetes medications.

Definition of the at-risk group for advanced hepatic fibrosis and NAFLD

Definitions of the at-risk group differed slightly from those of previous reviews and guidelines. In the clinical care pathway proposed by the American Gastroenterological Association (AGA), patients with 2 or more metabolic risk factors, type 2 diabetes mellitus (DM), steatosis on any imaging modality, or elevated aminotransferase levels are defined as at-risk.[5] Individuals with obesity and/or features of metabolic syndrome, prediabetes, or type 2 DM, and those with hepatic steatosis or persistently elevated aminotransferases are considered at high risk for fibrosis according to the American Association of Clinical Endocrinology (AACE) Clinical Practice Guidelines.[7] Individuals who are overweight/obese and have metabolic syndrome, type 2 DM, hepatic steatosis, or persistently elevated aminotransferase levels are considered to be at high risk for fibrosis according to the European Association for the Study of the Liver (EASL) patient guidelines.[8] In this study, the at-risk group was defined as having hepatic steatosis on ultrasonographic findings with nonalcoholic etiology (nonalcoholic steatotic liver disease and NAFLD), 2 or more metabolic abnormalities, DM, and/or abnormal transaminase levels [serum aspartate aminotransferase >40 IU/L or serum alanine aminotransferase >40 IU/L]. Individuals with NAFLD were defined as those health check-up examinees who had hepatic steatosis on abdominal ultrasonography without a history of significant alcohol intake or positive results for HBsAg or anti-HCV.

Assessment of severity of steatosis and fibrosis

The presence of hepatic steatosis was evaluated by ultrasonography. Severity was graded as normal, mild, moderate, or severe according to the degree of fat infiltration.[16] The examination parameters were liver echotexture, attenuation, and visualization of the intrahepatic vessel borders and/or diaphragm. Liver stiffness was measured by MRE, which was performed using MRE hardware (GE Healthcare, Waukesha, WI) with a 1.5-T imaging system and a 2-dimensional MRE protocol.[17] The acquired MRE images were processed automatically. Liver stiffness was assessed by a radiologist using regions of interest, excluding the vessels. The MRE cutoff values for conventional significant and advanced hepatic fibrosis were ≥ 3.0 kPa and ≥ 3.6 kPa, respectively.[18] We used multiple cutoff values for conventional advanced hepatic fibrosis in the sensitivity analysis.

Statistical analyses

Continuous and categorical variables are presented as mean $\pm$ SD and number (percentage), respectively. Continuous variables were analyzed using the Student independent *t* test, and categorical variables were analyzed using the chi-squared test. Statistical analyses were performed using SPSS software (version 26.0 for Windows; IBM Corp., Armonk, NY). The area under the receiver operating characteristic curve (AUROC) curves of FIB-4 and NFS for screening MRE values of $\geq$ 3.6 kPa were compared using the DeLong test in MedCalc (version 20; MedCalc Software Ltd., Ostend, Belgium) in both at-risk individuals and those with NAFLD. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were compared with various FIB-4 and NFS cutoff values (FIB-4: 1.0–1.3, NFS: 2.25–1.455) in at-risk individuals and in those with NAFLD, respectively. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

A total of 8545 participants who underwent MRE during their regular health check-ups were included in this study. Of these, 1805 were excluded because of a lack of abdominal ultrasonography data (n = 1118), history of alcohol intake or laboratory variables (n = 260), or technical failure of MRE (n = 427). Individuals with a history of significant alcohol consumption or positive results for serological viral markers (HBsAg or anti-HCV) were also excluded (n = 1634) (Figure 1). A total of 5106 health check-up examinees without chronic viral hepatitis or significant alcohol intake were analyzed. The prevalence of NAFLD, 2 or more metabolic abnormalities, DM, and abnormal aminotransferase levels was 48.4%, 48.8%, 8.2%, and 23.5%, respectively.

In the predefined at-risk group, a considerable number of subjects did not show hepatic steatosis on abdominal sonography (28.2%, 35.9%, and 39.6% according to the AGA, AACE, and EASL guidelines, respectively). Among at-risk individuals, those without hepatic steatosis showed a higher prevalence of advanced fibrosis than those without hepatic steatosis (3.8% vs. 2.3%, respectively; $p = 0.018$). Those without hepatic steatosis showed more favorable metabolic profiles, such as lower waist circumference and body mass index or lower levels of serum triglyceride and glucose, which could underestimate the risk of fibrosis (Table 1).

Comparison of hepatic fibrosis among the various groups at-risk based on the predefined definitions

The proportion of individuals in the at-risk group varied widely among the different criteria in this large cohort of health check-up examinees [67.4% (3443/5106), 75.6% (3859/5106), and 80.2% (4093/5106) according to the AGA, AACE, and EASL guidelines, respectively] (Table 2). However, the prevalence of conventional advanced hepatic fibrosis (MRE ≥ 3.6 kPa) was 2.8%, 2.5%, and 2.3% in at-risk groups as defined by the

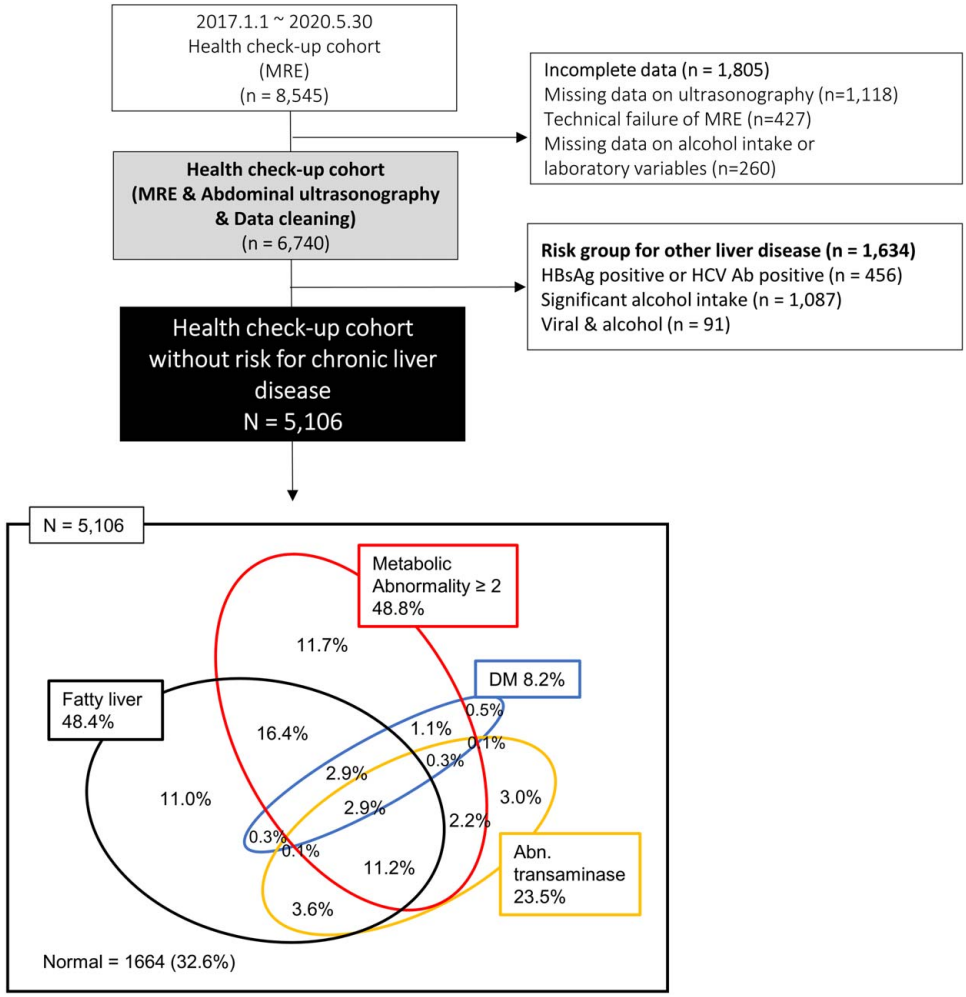

FIGURE 1 Study flow. Abbreviations: Abn., transminase, abnormal aminotransferases; DM, diabetes mellitus; MRE, magnetic resonance elastography.

TABLE 1 Baseline characteristics

	Total subjects (N = 5106)	At-risk group n = 3442 (67.4%)	At-risk group		p
			NAFLD (−) n = 970 (19.0%)	NAFLD (+) n = 2472 (48.4%)	
Age (y)[a]	46.9 ± 10.4	48.2 ± 10.2	50.1 ± 10.8	47.4 ± 9.8	<0.001
Male	4165 (81.6)	2996 (87.0)	777 (80.1)	2219 (89.8)	<0.001
Hypertension	1470 (28.8)	1320 (38.3)	411 (42.4)	909 (36.8)	0.002
Diabetes	421 (8.2)	421 (12.2)	104 (10.7)	317 (12.8)	0.09
No. metabolic risks[a]	1.64 ± 1.35	2.22 ± 1.25	2.18 ± 1.0	2.23 ± 1.3	0.242
Metabolic syndrome	1343 (26.3)	1343 (39.0)	300 (30.9)	1043 (42.2)	<0.001
BMI (kg/m^2)[a]	24.8 ± 3.2	25.8 ± 3.0	24.5 ± 2.8	26.4 ± 3.0	<0.001
Waist circumference (cm)[a]	85.5 ± 9.0	88.6 ± 8.1	85.2 ± 8.1	90.0 ± 7.6	<0.001
SBP (mm Hg)[a]	116 ± 13	119 ± 13	119 ± 14	119 ± 13	0.347
DBP (mm Hg)[a]	75 ± 9	76 ± 9	76 ± 9	76 ± 9	0.562
AST (IU/L)[a]	30 ± 18	33 ± 21	32 ± 19	34 ± 22	0.046
ALT (IU/L)[a]	32 ± 30	39 ± 35	32 ± 33	41 ± 35	<0.001
GGT (U/L)[a]	58 ± 91	70 ± 107	66 ± 92	72 ± 112	0.14
Albumin (mg/dL)[a]	4.5 ± 0.2	4.5 ± 0.2	4.4 ± 0.2	4.5 ± 0.2	<0.001
Triglyceride (mg/dL)[a]	145 ± 110	103 ± 23	149 ± 95	181 ± 121	<0.001
HDL (mg/dL)[a]	52 ± 12	49 ± 11	52 ± 13	48 ± 10	<0.001
Glucose (mg/dL)[a]	99 ± 20	103 ± 23	101 ± 21	103 ± 24	0.04
FIB-4[a]	1.12 ± 0.65	1.16 ± 0.71	1.30 ± 0.83	1.10 ± 0.65	<0.001
NFS[a]	−2.33 ± 1.18	−2.19 ± 1.22	−2.02 ± 1.28	−2.25 ± 1.19	<0.001
Liver stiffness (kPa)[a]	2.32 ± 0.54	2.37 ± 0.58	2.35 ± 0.69	2.38 ± 0.54	0.307
Significant hepatic fibrosis (≥3.0 kPa)	379 (7.4)	317 (9.2)	98 (10.1)	219 (8.9)	0.256
Advanced hepatic fibrosis (≥3.6 kPa)	101 (2.0)	95 (2.8)	37 (3.8)	58 (2.3)	0.018

Note: Data are expressed as number (percent).
The at-risk group was defined as patients sharing any of the following risk factors: fatty liver, 2 or more metabolic abnormalities, diabetes, or abnormal aminotransferases.
[a]Data are shown as mean ± SD.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, fibrosis-4 index; GGT, γ-glutamyl transferase; NFS, NAFLD fibrosis score; SBP, systolic blood pressure.

AGA, AACE, and EASL guidelines, respectively. These values were not significantly different from those in patients with NAFLD (2.3%).

Among the various criteria of the at-risk group, patients with DM had the highest incidence of advanced hepatic fibrosis (8.8%). In contrast, elevated aminotransferases (6.0%), 2 or more metabolic risk factors (3.1%), and hepatic steatosis on sonography (2.3%) were associated with the highest prevalence of hepatic fibrosis (Figure 2A). The proportions of each grade of fibrosis according to the

TABLE 2 Proportion of patients in the at-risk group and prevalence of advanced hepatic fibrosis according to the guidelines

	Prevalence	≥3.0 kPa of MRE value	≥3.6 kPa of MRE value	Fatty liver	Diabetes	Abnormal aminotransferase	Metabolic risk factors	Obesity
AGA	67.4 (3443/5106)	9.2	2.8	O	O	O	≥2	X
AACE	75.6 (3859/5106)	8.7	2.5	O	O prediabetes	O	≥2	O
EASL	80.2 (4093/5106)	8.4	2.3	O	O	O	≥3 CVD	O overweight

O indicates that subjects were included in the at-risk group.
X indicates that subjects were not included in the at-risk group.
Abbreviations: AACE, American Association of Clinical Endocrinology; AGA, American Gastroenterological Association; CVD, cerebrovascular disease; EASL, European Association for the Study of the Liver; MRE, magnetic resonance elastography.

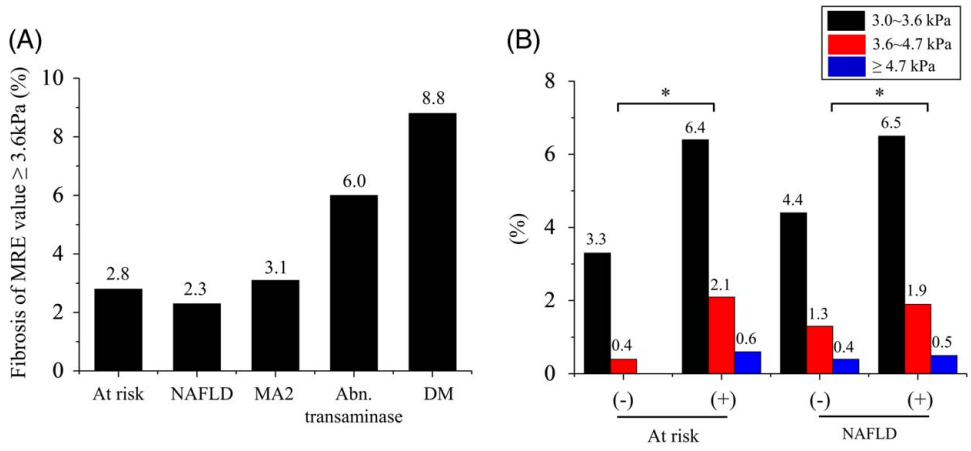

FIGURE 2 Prevalence of advanced hepatic fibrosis in health check-up examinees according to various risk factors (A). The distribution of MRE-confirmed hepatic fibrosis in health check-up examinees according to at-risk and/or NAFLD (B). *a p-value < 0.001 between the risk factor (−) and risk factor (+) groups. Abbreviations: Abn., transminase, abnormal aminotransferases; DM, diabetes mellitus; MA2, metabolic abnormality ≥2; MRE, magnetic resonance elastography.

MRE cutoffs for each risk factor are summarized in Figure 2B and Table 3. The burden of hepatic fibrosis both in the at-risk group and among individuals with NAFLD was higher than that in participants who were not in these groups. Among individuals with advanced hepatic fibrosis, 94.1% belonged to the at-risk group. Meanwhile, three-quarters belonged to the group with 2 or more metabolic risk abnormalities or elevated aminotransferase levels. Approximately half of the individuals with advanced fibrosis had hepatic steatosis on abdominal sonography, and only 36.6% had DM (Supplemental Figure S1, http://links.lww.com/HC9/A492).

Performance of FIB-4 and NFS for screening advanced hepatic fibrosis in various at-risk groups

The AUROC of FIB-4 was higher than that of NFS (AGA: 0.832 vs. 0.772, $p < 0.001$; AACE: 0.834 vs. 0.773, $p = 0.004$; EASL: 0.837 vs. 0.783, $p < 0.001$) on screening for fibrosis in various at-risk groups (Figure 3). In contrast, the performance of FIB-4 and NFS for screening conventional advanced fibrosis (MRE values ≥3.6 kPa) did not differ in patients with NAFLD (0.826 vs. 0.803, $p = 0.317$). The results did not differ with a higher MRE cutoff value (3.8 kPa) being used to define conventional advanced hepatic fibrosis (0.863 vs. 0.817, $p = 0.024$) as per the AGA guidelines.

Diagnostic performance of FIB-4 and NFS in at-risk groups using various cutoff values

FIB-4 and NFS showed better diagnostic accuracy and positive predictive value for the screening of advanced fibrosis (MRE value: ≥3.6 kPa) as the cutoff values increased (Table 4). In contrast, in selected patients who tested positive in FIB-4 or NFS, the sensitivity decreased as the cutoff values increased. The sensitivity, specificity, positive predictive value, and negative predictive value of FIB-4 and NFS did not differ between at-risk and NAFLD groups. In the at-risk group, the sensitivity of NFS (61.7%) was lower than that of FIB-4 (71.6%) at the current low cutoff.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the performance of FIB-4 and NFS in screening for advanced fibrosis in at-risk individuals with a lower prevalence of fibrosis. The proportion of at-risk individuals ranged from 67.4 to 80.2% of health check-up examinees, underlining the importance of selecting adequate and available noninvasive tools to screen for high-risk groups of patients at primary care centers. Furthermore, 28%–39.6% of individuals in the at-risk group did not show hepatic steatosis on abdominal sonography. Therefore, it is crucial not to solely focus on hepatic steatosis or aminotransferase levels when defining at-risk groups. More than 90% of individuals with advanced fibrosis can be included when at-risk individuals are screened by primary care physicians. This was also discussed in our previous study.[9]

Various factors influence the diagnostic performance of NITs, such as age distribution, prevalence of DM, and obesity within the population of interest. These factors may affect the accuracy and reliability of NITs in assessing hepatic fibrosis.[11,14] Therefore, the performances of FIB-4 and NFS in the at-risk group should be validated, considering the possible spectrum bias. In this study, the diagnostic performance of the FIB-4

TABLE 3 The distribution of MRE-confirmed hepatic fibrosis in the health check-up cohort according to various risk factors

	Total	At-risk group (AGA)		At-risk group (AACE)		At-risk group (EASL)		NAFLD		MA ≥ 2		Abn. transaminase		Diabetes	
		(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)
Number (%)	5106 (100.0)	1664 (32.6)	3442 (67.4)	1247 (24.4)	3859 (75.6)	1013 (19.8)	4093 (80.2)	2634 (51.6)	2472 (48.4)	2616 (51.2)	2490 (48.8)	3906 (76.5)	1200 (23.5)	4685 (91.8)	421 (8.2)
< 2.6 (kPa)	76.9	82.0	74.4	83.8	74.7	84.7	75.0	79.5	74.1	81.0	72.7	80.0	66.7	78.4	60.1
2.6–3.0 (kPa)	15.7	14.3	16.4	12.8	16.6	11.6	16.7	14.4	17.0	14.5	16.8	14.7	18.9	15.3	19.7
3.0–3.6 (kPa)	5.4	3.3	6.4	3.0	6.2	3.1	6.0	4.4	6.5	3.5	7.5	4.5	8.4	4.9	11.4
3.6–4.7 (kPa)	1.6	0.4	2.1	0.4	1.9	0.6	1.8	1.3	1.9	0.9	2.2	0.7	4.3	1.2	6.2
≥ 4.7 (kPa)	0.4	0.0	0.6	0.0	0.6	0.0	0.5	0.4	0.5	0.1	0.8	0.1	1.7	0.2	2.6

Abbreviations: AACE, American Association of Clinical Endocrinology; Abn., transminase, abnormal aminotransferases; AGA, American Gastroenterological Association; EASL, European Association for the Study of Liver; MA, metabolic abnormality; MRE, magnetic resonance elastography.

index in the at-risk group was comparable with that in the group with NAFLD. However, the NFS was less sensitive than FIB-4 in the at-risk group using the current cutoff values. Notably, FIB-4 demonstrated better performance in screening for conventional advanced hepatic fibrosis, especially in the at-risk group, regardless of the criteria used. This is consistent with the results of a previous study that showed FIB-4 performing well not only in those with hepatic steatosis or metabolic risk but also in those without, in contrast to NFS.[13] Furthermore, FIB-4 outperformed NFS in screening for advanced fibrosis in patients with diabetes.[10] Recent guidelines also indicate that the FIB-4 score should be used as the primary step in screening for fibrosis, as it is considered to have higher diagnostic accuracy than other NITs and a good correlation with clinical outcomes among patients with NAFLD.[5] Considering these points, the use of FIB-4 to screen for hepatic fibrosis in at-risk individuals is a reasonable approach.

The results of this study should be interpreted cautiously because there is no consensus on the definition of at-risk groups for fibrosis of a nonalcoholic etiology. Nevertheless, the presence of DM, metabolic syndrome, or hepatic steatosis on imaging, or persistently abnormal aminotransferase levels are important risk factors in the general population. The lack of effective treatments and cost-effective screening tools cause physicians to hesitate in implementing the screening system in the general population. Therefore, a lot of cost-effectiveness work on adequate at-risk groups and available noninvasive tools from primary care centers would be needed.

Another important area is identifying reasonable cutoff values in the at-risk group with a low prevalence of advanced hepatic fibrosis. Approximately, a quarter of those in the at-risk group (25.6% and 23.1% according to the FIB-4 and NFS, respectively) were diagnosed as positive by current low cutoff values, and with sensitivities of 71.6% and 61.7% according to the FIB-4 and NFS, respectively (Table 4). In other words, ~30%–40% of patients with advanced hepatic fibrosis may have been missed during the first screening step. Moreover, when the current high cutoff values were used, few patients (3.0% and 1.1% according to the FIB-4 and NFS, respectively) were diagnosed as positive at the first screening step. However, if the cutoff values were lowered to 1.0 for FIB-4 or −2.25 for NFS, approximately half of the at-risk group could be classified as positive, and the sensitivity could be increased up to 89.5% for FIB-4 and 83.0% for NFS. The screening strategy at the primary care level should aim to not miss any patients with a high hepatic fibrosis burden, and to identify subjects who can be managed through intensive lifestyle modification at an early stage. Moreover, second-step tests, such as FibroScan and MRE, wait for patients to be diagnosed by FIB-4 or NFS before performing further evaluation. Therefore, we believe that

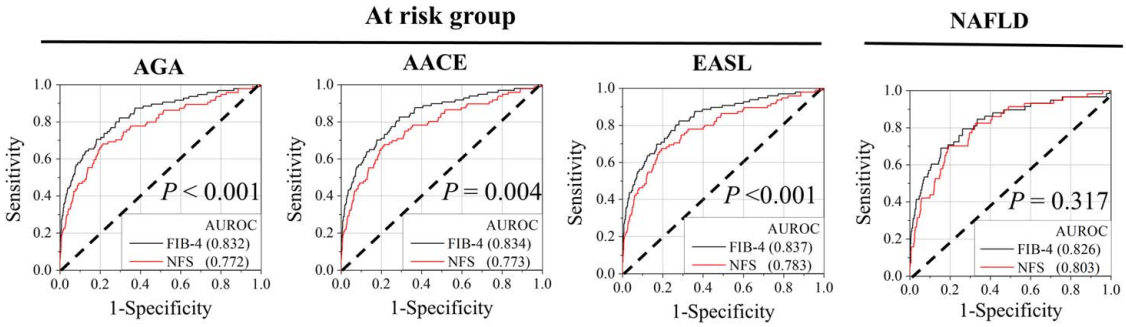

FIGURE 3 ROC curves for the diagnosis of conventional advanced fibrosis (MRE value ≥3.6 kPa) by FIB-4 or NFS in the at-risk group as per various guidelines and NAFLD. *p*-value when the ROC curve for diagnosing advanced hepatic fibrosis using FIB-4 was compared with the ROC curve using NFS in the at-risk population and NAFLD, respectively. Abbreviations: AACE, American Association of Clinical Endocrinology; AGA, American Gastroenterological Association; AUROC, area under receiver operating characteristic curve; EASL, European Association for the Study of Liver; NFS, NAFLD fibrosis score; FIB-4, fibrosis-4 index; MRE, magnetic resonance elastography; ROC, receiver operating characteristic.

TABLE 4 Diagnostic performance for advanced hepatic fibrosis in at-risk and NAFLD groups according to various cutoff values of FIB-4 and NFS

	Diagnosed patients (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
(A) FIB-4 at-risk group						
Cutoff: 2.67[a]	3.0	35.8	97.9	33.0	98.2	96.2
Cutoff: 1.3 (2.0)[b]	25.6	71.6	75.7	7.7	98.9	75.6
Cutoff: 1.3	28.2	76.8	73.2	7.5	99.1	73.3
Cutoff: 1.2	34.6	82.1	66.7	6.5	99.2	67.2
Cutoff: 1.1	42.1	87.4	59.2	5.7	99.4	60.0
Cutoff: 1.0	50.8	89.5	50.3	4.9	99.4	51.4
(B) FIB-4 at NAFLD						
Cutoff: 2.67[a]	2.4	31.0	98.3	30.0	98.3	96.7
Cutoff: 1.3 (2.0)[b]	22.9	70.7	78.3	7.3	99.1	78.9
Cutoff: 1.3	24.9	72.4	76.3	6.8	99.1	77.0
Cutoff: 1.2	31.1	79.3	70.1	6.0	99.3	71.1
Cutoff: 1.1	38.1	84.5	63.0	5.2	99.4	64.2
Cutoff: 1.0	46.4	87.9	54.6	4.5	99.5	56.0
(C) NFS at-risk group						
Cutoff: 0.676[a]	1.1	16.0	99.3	38.5	97.6	97.0
Cutoff: −1.455 (0.12)[b]	23.1	61.7	78.0	7.4	98.6	77.5
Cutoff: −1.455	26.4	69.1	74.8	7.3	98.8	74.7
Cutoff: −1.75	34.7	75.5	66.5	6.0	99.0	66.7
Cutoff: −2	42.6	77.7	58.4	5.0	98.9	58.9
Cutoff: −2.25	50.2	83.0	50.7	4.6	99.1	51.6
(D) NFS at NAFLD						
Cutoff: 0.676[a]	1.0	12.3	99.3	29.2	97.9	97.3
Cutoff: −1.455 (0.12)[b]	21.3	64.9	79.7	7.1	99.0	79.4
Cutoff: −1.455	24.1	70.2	77.0	6.8	99.1	76.8
Cutoff: −1.75	32.3	78.9	68.8	5.7	99.3	69.1
Cutoff: −2	40.4	82.5	60.7	4.8	99.3	61.2
Cutoff: −2.25	52.1	87.7	53.0	4.3	99.5	53.8

[a]The current high cutoff.
[b]The current low cutoff.
Abbreviations: FIB-4, fibrosis-4 index; NFS, NAFLD fibrosis score; NPV, negative predictive value; PPV, positive predictive value.

lower cutoff values with more relaxed standards are more appropriate for primary care settings. In line with this, Shah et al[19] suggested that an FIB-4 cutoff of 1.0 would be appropriate to use for a primary care referral pathway. However, the optimal cutoff value can vary according to socioeconomic status and medical environment.

This study had some limitations. First, MRE data were used as a reference standard for fibrosis. Although MRE is a valuable method for diagnosing hepatic fibrosis, it cannot fully replace liver biopsy. Ultrasonography was used to diagnose steatosis. Ultrasonography has the drawback of potentially missing mild steatosis. However, it remains the most commonly used method to diagnose steatosis in real-world practice. This study evaluated the diagnostic performance of FIB-4 in at-risk individuals in primary care settings. In a recent study, the performance of B-mode ultrasonography showed significant improvement, with an AUC of 0.822, sensitivity of 83.4%, and specificity of 81.0%, using magnetic resonance-proton density fat fraction (MR-PDFF) as the reference standard.[20] Second, there is no consensus on the best MRE cutoff value for diagnosing advanced hepatic fibrosis. However, the results did not differ when different cutoff values of 3.6 or 3.8 kPa were used. Third, the use of this large-scale MRE cohort of health check-up examinees could have led to selection bias. Immigrants, those without social security, and those with psychiatric diseases were more likely to be excluded from this study, although they would not be included in the general population with a low prevalence of liver fibrosis. However, the prevalence of DM among these health check-up examinees was 8.2%, which is significantly lower than the 16.7% reported in the general population in Korea.[21] Therefore, it would be appropriate to consider this cohort as having no higher risk of fibrosis than that of the general population. Overall, our data certainly reflect real-world data more closely than hospital cohort data.

In conclusion, the importance of appropriate risk stratification for hepatic fibrosis at the primary care level has increased with the increasing global fibrosis burden. Accordingly, recent guidelines have expanded the range of target populations for hepatic fibrosis screening to include at-risk groups with risk factors for hepatic fibrosis, besides fatty liver. In our study, the at-risk group without hepatic steatosis had a higher prevalence of advanced hepatic fibrosis than that with steatosis. FIB-4 performed well, not only in patients with NAFLD but also in the at-risk group. Moreover, the AUROCs and sensitivity of FIB-4 in diagnosing advanced fibrosis in the at-risk group were higher than those of NFS. Thus, risk stratification for hepatic fibrosis in the at-risk group using FIB-4 may be a reasonable approach.

DATA AVAILABILITY STATEMENT

Data are available on request only due to privacy/ethical restrictions.

AUTHOR CONTRIBUTIONS

Concept and design: Dae Won Jun; data collection and management: Jonghyun Lee, Mimi Kim, Seon Cho, Eun-Hee Nah, and Hye-Lin Kim; interpretation of data: Eileen L. Yoon and Dae Won Jun; manuscript writing: Huiyul Park; supervision: Dae Won Jun and Eun-Hee Nah. All authors have approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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