Validation of a Novel Cutoff Point for the Fibrosis-4 Index Modified by Age in Patients with Fatty Liver Diseases

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Research article

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Abstract

Background/purpose: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new concept that better expresses the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Although the Fibrosis-4 Index (FIB-4) can easily predict the degree of liver fibrosis, its diagnostic ability, especially in the elderly, requires validation. This study aimed to validate the diagnostic ability of revised cutoff points for FIB-4 in patients with MAFLD and NAFLD.

Methods: This cross-sectional study included participants who underwent a health check-up from 2014 to 2019. The proportion and number of low, indeterminate, and high cutoff group between the conventional and revised cutoff points for FIB-4 were compared. The diagnostic ability of these points was compared using the aspartate aminotransferase (AST) to platelet ratio index (APRI) as a standard.

Results: Of 21,801 participants, 5,559 (25.5%) had MAFLD and 4,463 (20.5%) had NAFLD. Using revised cutoff points, the proportion of the indeterminate group dropped from 46% to 15% in the MAFLD and 43% to 14% in the NAFLD group. Approximately 60% of patients with MAFLD and NAFLD from the indeterminate group with conventional FIB-4 moved to the low group with a revised FIB-4. Even after age adjustment, the APRI significantly increased for each FIB-4 category and the area under the receiver operating characteristic curve with a diagnosis of APRI $\geq$ 1.0 increased in both the MAFLD and NAFLD groups.

Conclusions: Using cutoff points for the FIB-4 modified by age, the proportion of the indeterminate group dropped and the diagnostic ability increased for both MAFLD and NAFLD.

Introduction

Fatty liver disease (FLD) is a major form of chronic liver disease, with an estimated global prevalence of 25% [1]. FLD was classified into two forms by the presence or absence of excess alcohol intake: alcoholic and nonalcoholic fatty liver disease (NAFLD). NAFLD is a clinical consequence of obesity and can progress to nonalcoholic steatohepatitis (NASH). Recent studies have clearly shown that the fibrosis stage, without other histological features of steatohepatitis, is a major cause of liver-related mortality in patients with NAFLD [2, 3]. Thus, key issues in patients with NAFLD are the differentiation of NASH from simple steatosis and identification of advanced hepatic fibrosis.

In 2020, an international panel proposed a new definition for the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD) [4]. MAFLD was defined as an independent metabolic disease that warranted a positive diagnosis, rather than a “none”-disease rubric. The criteria for identifying MAFLD are based on the evidence of hepatic steatosis, in addition to the presence of one of the following three criteria, namely, being overweight/obesity, presence of diabetes mellitus (DM), or evidence of metabolic dysregulation [4]. Currently many hepatologists rely on the pathophysiological, genetic, and clinical background differences between MAFLD and NAFLD [5].

Percutaneous liver biopsy is the gold standard for the diagnosis of NAFLD. However, disadvantages include the risk of complications due to the invasiveness of the procedure, sampling errors, and high cost [6]. The non-invasive fibrosis test overcomes many limitations of a liver biopsy and is now routinely incorporated into specialist clinical practice [7–9]. A recent meta-analysis (based on 64 studies and 13,046 patients with NAFLD) compared the Fibrosis-4 Index (FIB-4) and NAFLD fibrosis score (NFS) for diagnosing advanced fibrosis and found that the area under the receiver operating characteristic (AUROC) was 0.84 and 0.84, respectively [10]. FIB-4 may be more attractive to general practitioners, as it is based on widely available and simple parameters (age, transaminases, and platelets) and is easier to calculate than NFS. Shah et al. proposed that FIB-4 of ≥ 2.67 had an 80% positive predictive value and that ≤ 1.30 had a 90% negative predictive value for diagnosing advanced fibrosis in patients with NAFLD (Fig. 1A) [11]. However, as FIB-4 includes age in the formula, the specificity for advanced fibrosis declines with age, becoming unacceptably low for the elderly (≥ 65 years) [12]. In addition, when using FIB-4, a significant proportion of patients (around 30%) fall in the intermediate-risk category [9, 13] and cannot be correctly classified. Recently, Ishiba et al. analyzed 1,050 biopsy-proven Japanese patients with NAFLD and reported that FIB-4 was not effective for the diagnosis of advanced fibrosis in patients with NAFLD using the conventional cutoff points by Shah et al [14]. In addition, the newly defined cutoff points, which have been adapted for each age group, improved its diagnostic performance (Fig. 1B) [14]. However, no studies have applied these revised cutoff points for FIB-4 to the general population.

Therefore, this cross-sectional study was conducted to validate the new FIB-4 cutoff points, modified by age, and clarify the accuracy of determining cases of advanced liver fibrosis in patients with MAFLD and NAFLD in the general population.

Materials And Methods

Study population

We retrospectively enrolled participants for this cross-sectional study derived from the ongoing MedCity21 health examination registry between April 1, 2014, and December 31, 2019. The MedCity21 health examination registry protocol was a comprehensive agreement and approved by the Ethics Committee of Graduate School of Medicine, Osaka City University (approval No. 2927). In addition, this cross-sectional study on liver disease was a part of the MedCity21 health examination registry and was conducted in full accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, Osaka City University (approval No. 2019-076, February 21, 2020). Written/verbal approved consent was not obtained from the enrolled participants because this study was a retrospective observational study using only existing information. Instead, we provided with an opt-out option, as explained in the instructions posted on the website of the hospital.

This study included participants (n = 23,122) who underwent a medical examination including abdominal ultrasonography for the first time within the above-mentioned period. Exclusion criteria were alcohol

intake ≥ 60 g/day (n = 729); positive serology for HBsAg (n = 311); positive serology for HCV antibodies (n = 171); and lack of data on platelet count (n = 111). One participant had an HBV/HCV co-infection. In total, 21.801 participants were initially analyzed (Fig. 2).

Clinical assessment

All study participants underwent a comprehensive health assessment, including medical history, physical examination, laboratory testing, and abdominal ultrasound at baseline. The body mass index (BMI) was calculated as weight in kilograms, divided by height, in meters, squared. After an overnight fast, blood samples were collected and analyzed following standard laboratory procedures for total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, gamma-glutamyl transferase, total cholesterol (TC), low density lipoprotein -cholesterol, high-density lipoprotein -cholesterol (HDL-C), triglycerides (TG), creatinine, fasting plasma glucose, and glycated hemoglobin (HbA1c). The Lumipulse HBsAg and HCV assay (Fujirebio Inc., Tokyo, Japan) were used to measure the serum markers, including HBsAg and anti-HCV antibodies. Presence/absence of DM, hypertension and dyslipidemia; these were diagnosed according to standard criteria [4, 15, 16].

The severity of liver fibrosis was assessed by two non-invasive markers. First, the FIB-4 index was calculated as follows: age (years) × AST (U/L)/ (platelet count [× 10^9/L] × ALT [U/L]$^{1/2}$) [17]. The conventional cutoff points for the patients with NAFLD were described as follows: the low (LCO) and high (HCO) cutoff points were 1.3 and 2.67, respectively [11]. A score < 1.3 (low FIB-4) was considered as the absence of advanced fibrosis and a score > 2.67 (high FIB-4) was considered as the presence of advanced fibrosis. A score of 1.3–2.67 (indeterminate FIB-4) was considered indeterminate (Fig. 1A) [11]. The new LCO and HCO proposed by Ishiba et al. were described as follows: 1.05 and 1.21 in ≤ 49 years, 1.24 and 1.96 in 50–59 years, 1.88 and 2.67 in 60–69 years, and 1.95 and 2.67 in ≥ 70 years (Fig. 1B) [14].

Second, the AST to platelet ratio index (APRI) was calculated according to the following formula: APRI = [(AST (U/L) / upper limit of normal [30 U/L]) / platelet count (10^9/L)] × 100 [18]. With an APRI threshold of 1.0, the sensitivity and specificity for advanced fibrosis in patients with NAFLD were 50.0% and 84.0%, respectively [9]. We used APRI ≥ 1.0 to indicate advanced fibrosis.

Alcohol intake screening measures and definition of alcoholic liver disease

Daily alcohol consumption was calculated, in grams, using a modified template from our previous research [19]. Briefly, we classified the frequency of alcohol intake into three categories: intake 1 day/week, 3 days/week, and on a daily basis. We also classified each participant's average alcohol consumption into four categories: alcohol consumption 10 g, 30 g, 50 g, and 70 g. Daily alcohol consumption (g/day) was calculated as: (frequency of alcohol intake) × (average alcohol consumption (g)) / 7.

Diagnostic criteria and definition of groups

MAFLD and non-MAFLD

MAFLD was diagnosed based on a radiologically diagnosed hepatic steatosis and the presence of any one of the following three conditions, namely, overweight/obesity, presence of DM, or evidence of metabolic dysregulation [4]. The metabolic dysregulation was defined as the presence of two or more of the following conditions: (a) Waist circumference ≥ 90 cm in men and 80 cm in women. (b) Blood pressure ≥ 130/85 mmHg or a specific drug treatment. (c) TG ≥ 150 mg/dL or specific drug treatment. (d) HDL-C < 40 mg/dL for males and < 50 mg/L for females. (e) Prediabetes (fasting glucose levels 100–125 mmol/L or HbA1c 5.7–6.4%). The homeostasis model assessment of insulin resistance (HOMA-IR) score and high-sensitivity C-reactive protein levels were excluded because these risk factors were not routinely measured in the Japanese health check-up. The non-MAFLD population referred to patients who do not meet the above conditions. According to the consumption of alcoholic beverages, patients with MAFLD were further classified as MAFLD with alcohol intake (referred to as the non-overlapping MAFLD group, see Fig. 2) and MAFLD without alcohol intake (referred to as the overlapping group, Fig. 2) [20].

NAFLD and non-NAFLD

NAFLD was based on ultrasound evidence of FLD and the exclusion of both secondary causes such as viral hepatitis and excessive alcohol consumption (≥ 30 g per day for males and ≥ 20 g per day for females) [21, 22].

Non-metabolic dysfunction NAFLD (Non-overlapping NAFLD)

There were some cases that met the diagnostic criteria for NAFLD but did not meet the definition of MAFLD; in short, they had liver steatosis but not obesity or metabolic dysfunction or diabetes. We defined this population as the non-overlapping NAFLD group (Fig. 2) [20].

Abdominal ultrasound and assessment of disease severity

Fatty liver was diagnosed by abdominal ultrasonography using the Toshiba Aplio 500 device (Toshiba Medical Systems Corporation, Ohtawara, Japan). Abdominal ultrasonography was performed at MedCity21 by experienced medical sonographers registered with the Japan Society of Ultrasonics in Medicine. Hepatic steatosis was semi-quantified according to the criteria described by Hamaguchi, based on the presence of hepatorenal contrast, bright hepatic echoes, deep attenuation, and vessel blurring [23].

Statistical analysis

The characteristics of the study participants at baseline were compared using chi-square and t tests for categorical and continuous variables, respectively. Sensitivity and specificity, which reflect the probabilities of false-positive and false-negative assessment, respectively, and were determined for selected cutoff values and the AUROC were calculated. The Youden index was used to identify the

optimal cutoff points. The mosaic plot is a graphical representation of the two-way frequency table or contingency table. A mosaic plot is divided into rectangles; the vertical length of each rectangle is proportional to the proportions of the Y variable in each level of the X variable [24]. A p-value of < 0.05 was considered statistically significant. Statistical analyses were conducted using JMP 13.0.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of patients

A total of 21,801 subjects with completed ultrasonography and laboratory data were identified from the MedCity21 health examination registry (Fig. 2 and Supplementary Information 1). There were 9,980 (45.8%) males, with a mean age of 50.5 years, and a mean BMI of 22.7 kg/m^2. DM and hypertension were identified in 1,584 (7.3%) and 4,626 (21.2%) participants, respectively. MAFLD was diagnosed in 5,559 (25.5%) participants, while NAFLD was diagnosed in 4,463 (20.5%) of the overall population. A total of 345 (1.6%) cases met the definition of NAFLD but not the MAFLD criteria (non-overlapping NAFLD group).

Clinical characteristic of MAFLD and NAFLD

Clinical characteristics of patients with MAFLD and NAFLD are shown in Supplementary Information 1. The mean age of patients with MAFLD and NAFLD was 53.3 and 52.8 years, respectively, and 67.3% and 61.8% were male, respectively. The mean BMI of patients with MAFLD and NAFLD was 26.1 and 25.8 kg/m^2, T2DM was present in 18.6% and 17.3, and 8.2% and 7.9% were on treatment with antidiabetic medications, respectively. Current and past histories of smoking were noted in 53.8% and 46.5% of patients, respectively. Daily alcohol consumption (mean [standard deviation]) of patients with MAFLD and NAFLD was 13.4 (16.4) and 4.8 (6.6) g/day, respectively. The mean FIB-4 of patients with MAFLD and NAFLD was 1.14 and 1.09, and the mean APRI was 0.39 and 0.36, respectively.

FIB-4 categories by two different cutoffs in patients with MAFLD, NAFLD

We compared the proportion of indeterminate FIB-4 in patients with MAFLD and NAFLD based on their two different FIB-4 categories (Fig. 3). In the MAFLD group, the proportion of the indeterminate group was 46% using the cutoff points described by Shah et al. [11], but it was reduced to 15% by the cutoff point described by Ishaba [14]. Similarly, the proportion of the indeterminate group decreased from 43–14% in the NAFLD group and from 33–12% in the non-overlapping NAFLD group.

The number of Indeterminate FIB-4 by two different cutoffs in patients with MAFLD and NAFLD

We investigated, in detail, the reasons for change in the proportion of the indeterminate FIB-4 index between the two different cutoff points (Fig. 4). In the MAFLD group, 2,563 patients were in the indeterminate FIB-4 group according to the cutoff points by Shah et al. [11] and 1,539 (60%) were classified as low FIB-4 according to the cutoff points by Ishaba. In the NAFLD group, 1,927 patients were classified as indeterminate FIB-4 (according to Shah et al. [11]) and 1,197 (62%) were reclassified as low FIB-4 (according to Ishaba [14]). We also performed a sub-analysis of the MAFLD group with or without alcohol intake (Supplemental Information 2). As expected, the proportion of high FIB-4 according to Ishiba et al. [14] was significantly higher in the MAFLD with alcohol intake group (equal to the non-overlapping MAFLD group) than in the MAFLD without alcohol intake group (equal to the overlapping group) (9.4% [135/1,441] vs. 4.0% [164/4,118], $p < 0.0001$). In all groups, the number of patients classified with low and high FIB-4 was the same for both the cutoff points described by Shah et al. [11] and by Ishaba [14] (Fig. 4 and Supplementary Information 2).

Relationship between FIB-4 and age categories by revised FIB-4 cutoffs

We confirmed a change in the distribution of the FIB-4 categories due to an age group adjustment (Supplemental Information 3). Using the cutoff point described by Shah et al. [11], as age increased, the proportion of indeterminate FIB-4 also increased in all groups. Using the cutoff points by Ishiba et al. [14], the proportion of the indeterminate FIB-4 group decreased, especially for the group that were ≥ 60 years.

Relation between APRI and each of two different FIB-4 categories

We validated the utility of the revised FIB-4 cutoff points using APRI, an age-independent predictor of liver fibrosis. Table 1 illustrates the comparison between the mean value of APRI and the two different cutoff points for FIB-4. In the MAFLD group, APRI was significantly increased between the low and indeterminate groups, between the indeterminate and high groups, and between the low and high groups (all $p < 0.0001$), respectively. Finally, we compared the diagnostic ability of the two different cutoff points using APRI ≥ 1.0. With an aged-modified FIB-4, the AUROC increased in the MAFLD, NAFLD, and non-overlapping NAFLD groups (Fig. 5).

Discussion

This is the first study, to our knowledge, to validate the new FIB-4 cutoff points for patients with MAFLD and NAFLD using a general population. The proportion of the indeterminate FIB-4 group decreased to approximately one-third in both the MAFLD and NAFLD groups (Fig. 3). Reducing inappropriate referrals to secondary care hepatologists represents an opportunity to reduce unnecessary investigations, inconvenience, harm to patients, pressure on secondary care services, and costs for the healthcare system [25]. It is important to know how many subjects require further examination for predicting

advanced fibrosis in the general population. Therefore, our results have important implications for general practitioners.

McPherson et al. recently analyzed 634 European patients with biopsy-proven NAFLD and reported that the specificity of advanced fibrosis diagnosed by the FIB-4, declined with age, and was especially low in patients aged ≥ 65 years (35% for the FIB-4) [12]. They concluded that a) FIB-4 is not suitable for patients aged < 35 years, b) the existing thresholds (LCO and HCO were 1.3 and 2.67) should continue to be used in patients aged 35–65 years, and c) revised thresholds (LCO and HCO were 2.0 and 2.67) are recommended for those aged ≥ 65 years [12]. More recently, Ishiba et al. compared their FIB-4 cutoff points to those described by McPherson et al. and showed that cutoff points by Ishiba et al. had a more accurate diagnostic ability than those by McPherson et al., especially in the younger population. Ishiba et al. [14] performed this analysis using > 1,000 biopsy-proven NAFLD. In addition, as in this study, the cases used for the study by Ishiba et al. [14] were Asians. For these reasons, we examined the cutoff points described by Ishiba et al.

Recently, some authors have reported differences between MAFLD and NAFLD. Lin et al. examined 13,083 subjects from the NHANES III database and reported that patients with MAFLD were significantly older, had higher BMI levels, higher proportions of metabolic comorbidities (DM, hypertension) and higher HOMA-IR, lipid and liver enzymes than those with NAFLD [26]. More recently, Yamamura et al. analyzed 765 Japanese patients with FLD and reported that liver stiffness was higher in the MAFLD group than in the NAFLD groups (7.7 vs. 6.8 kPa, $p = 0.0010$) [21]. We also confirmed that the proportion of cases with DM and hypertension was higher in the MAFLD group than in the NAFLD group (18.6% vs. 17.3%, and 39.4% vs. 34.1%, respectively). FIB-4 and APRI were also higher in the MAFLD group than in the NAFLD group (mean: 1.14 vs. 1.09 and 0.39 vs. 0.36, respectively). This is probably because the MAFLD group included the non-overlapping MAFLD group (equal to MAFLD with alcohol intake). APRI was significantly higher in the non-overlapping MAFLD group than in the overlapping group (0.44 vs. 0.37, $p < 0.0001$).

Several limitations must be considered while interpreting the study results. First, this was a retrospective single-center study. Second, the selection bias is a major limitation. Most participants were apparently healthy enough to engage in their work and were also sufficiently conscious of their health to voluntarily undergo health check-ups [27]. Therefore, the results of this study may not be applicable to individuals who are not generally healthy. Third, details of the duration of alcohol intake were not available. Fourth, as the subjects who received health check-ups generally did not have the information about their fibrosis stage due to liver stiffness measurement and/or liver biopsy, the exact proportion of advanced fibrosis in this population is unknown.

In conclusion, using cutoff points for the FIB-4 modified by age, the proportion of the indeterminate group dropped to approximately one-third and the diagnostic ability increased for both MAFLD and NAFLD. Our data may provide primary care physicians with useful information regarding the referral of patients with MAFLD/NAFLD with advanced fibrosis to hepatology center.

Abbreviations

ALT
alanine aminotransferase
AST
aspartate aminotransferase
AUROC
area under the receiver operating characteristic curve
BMI
body mass index
DM
diabetes mellitus
FIB-4
Fibrosis-4 Index
FLD
fatty liver disease
HbA1c
glycated hemoglobin
HBV
hepatitis B virus
HCO
high cutoff point
HCV
hepatitis C virus
HDL
high-density lipoprotein
HOMA
Homeostasis model assessment
IR
insulin resistance
LCO
low cutoff point
MAFLD
metabolic dysfunction-associated fatty liver disease
NAFLD
nonalcoholic fatty liver disease
NASH
nonalcoholic steatohepatitis
NFS
NAFLD fibrosis score

TC
total cholesterol
TG
triglycerides

Declarations

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Conflict of interest/competing interests: All authors declare that they have no conflict of interest.

Ethics approval: The study protocol was approved by the Ethics Committee of Graduate School of Medicine, Osaka City University (approval No. 2019-076, February 21, 2020).

Consent to participate: Written/verbal approved consent was not obtained from the enrolled participants because this study was a retrospective observational study using only existing information.

Consent for publication: Not applicable.

Code availability: Not applicable.

Authors' contribution:

Formal analysis: HF and NN; resources: HF, SF, TK, YN, and ST. software: HF; writing, original draft preparation: HF; writing, review and editing: SU, ME, and AT; supervision and project administration: NK.

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Tables

Table 1

Comparison of APRI between the two different cutoffs for FIB-4.

A. MAFLD group (n=5,559)

	Shah			Ishiba		
	n	APRI†		n	APRI†	
High	123	1.22 (0.91)	*	299	0.97 (0.72)	*
Indeterminate	2,563	0.45 (0.22)	*	848	0.52 (0.19)	*
Low	2,873	0.30 (0.13)	*	4,412	0.32 (0.13)	*

B. NAFLD group (n=4,463)

	Shah			Ishiba		
	n	APRI†		n	APRI†	
High	67	1.12 (0.12)	*	181	0.89 (0.55)	*
Indeterminate	1,927	0.43 (0.20)	*	616	0.50 (0.18)	*
Low	2,469	0.29 (0.12)	*	3,666	0.32 (0.12)	*

C. Non-overlapping NAFLD group (n=345)

	Shah			Ishiba		
	n	APRI†		n	APRI†	
High	2	1.22 (0.88)	*	17	0.73 (0.48)	*
Indeterminate	114	0.39 (0.20)	*	41	0.39 (0.10)	*
Low	229	0.27 (0.09)	*	287	0.28 (0.09)	*

Abbreviations: APRI: aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 Index; MAFLD: Metabolic dysfunction-associated fatty liver disease; n: number; NAFLD: nonalcoholic fatty liver disease. †mean (standard deviation). *p<0.0001.

Figures

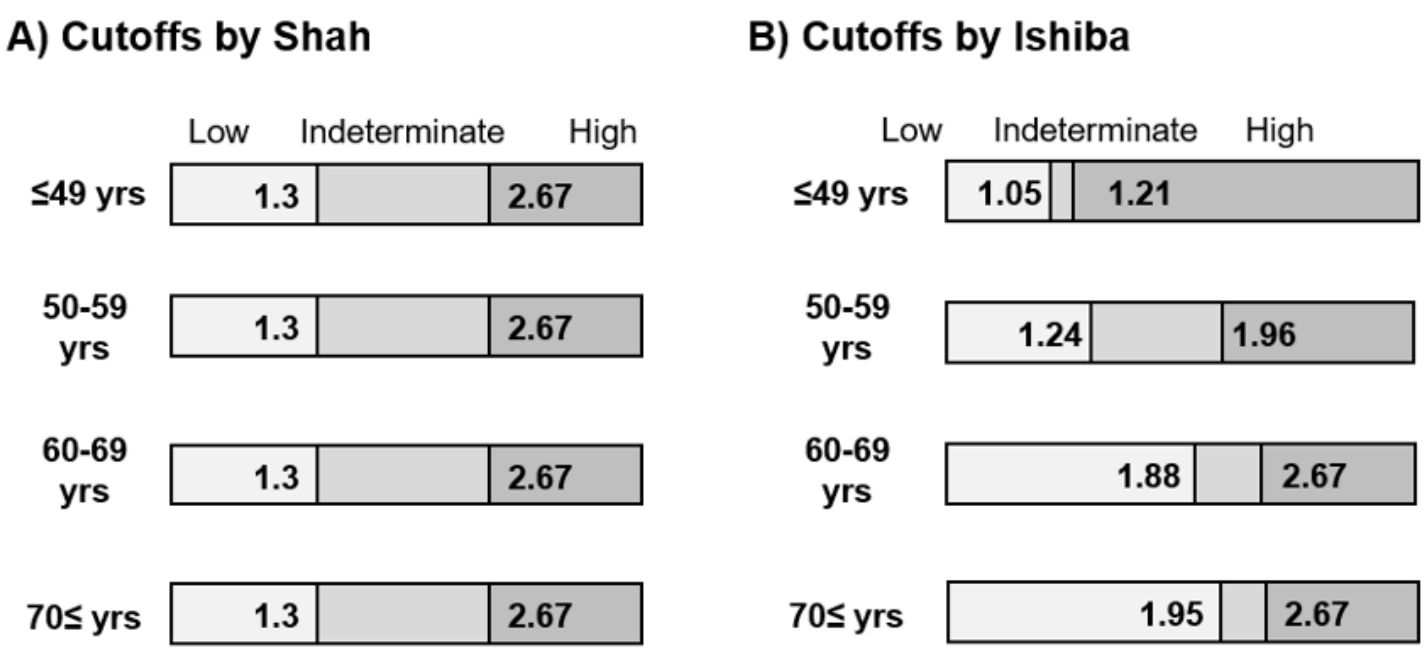


Figure 1

Two different cutoffs for FIB-4 Abbreviation: yrs, years; FIB-4, Fibrosis-4 Index.

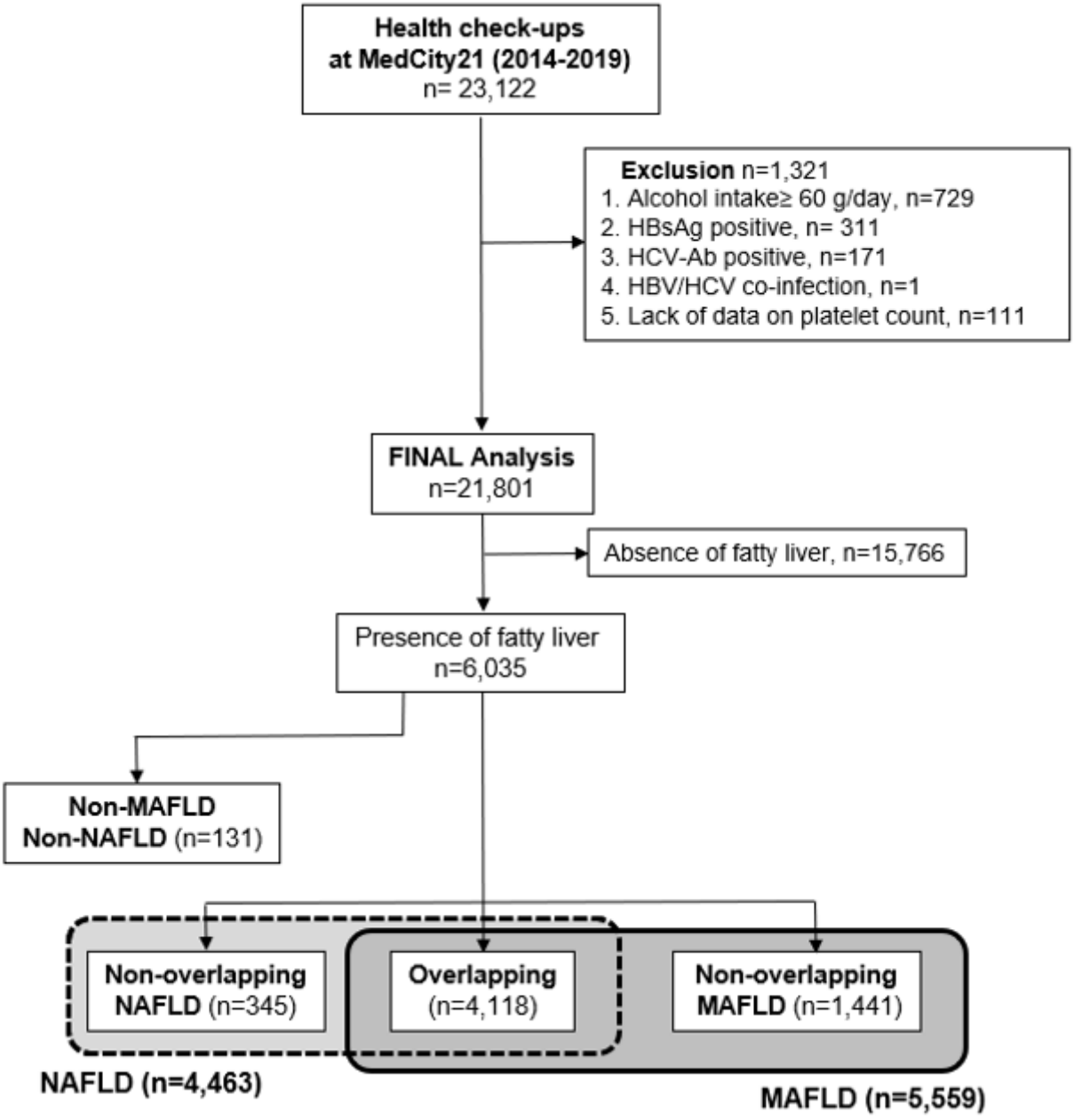


Figure 2

Flow diagram of the participants in this study Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.

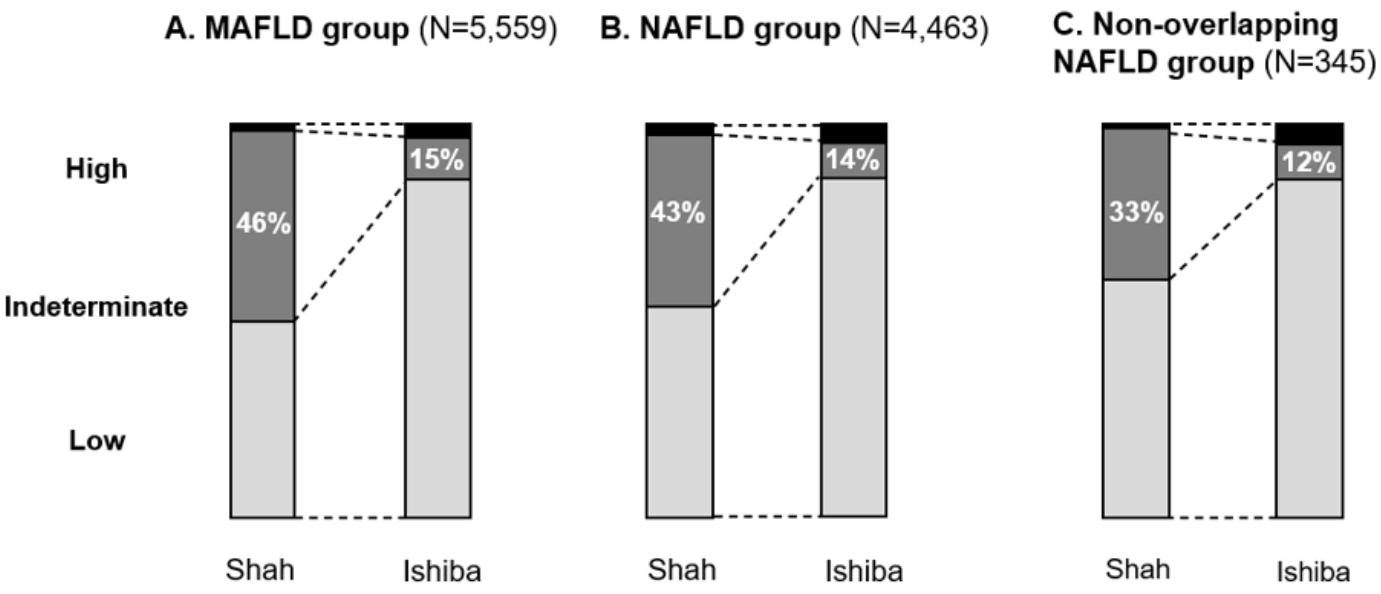
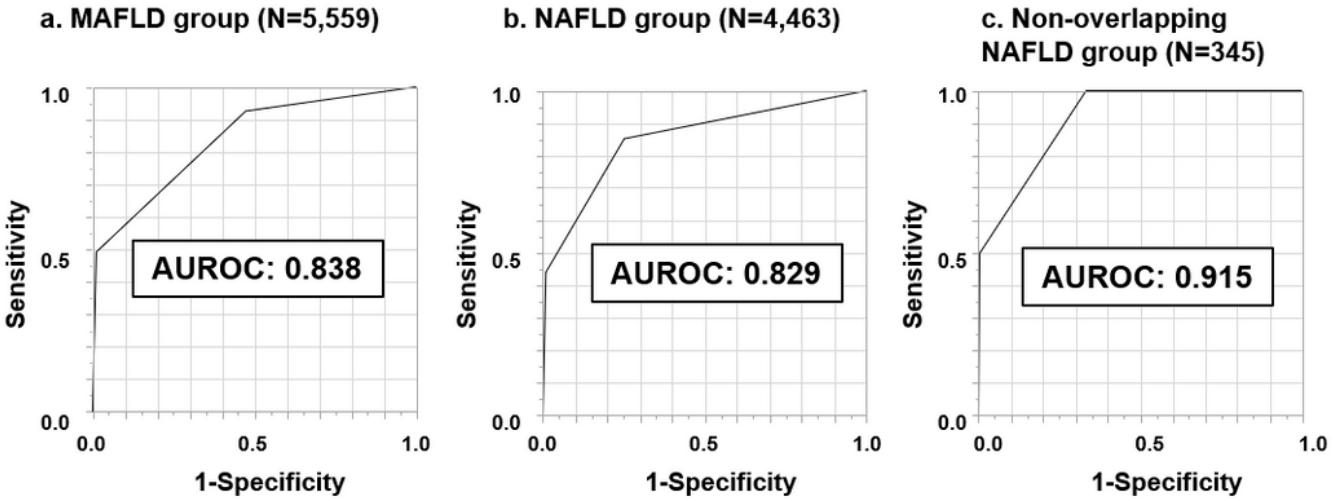


Figure 3

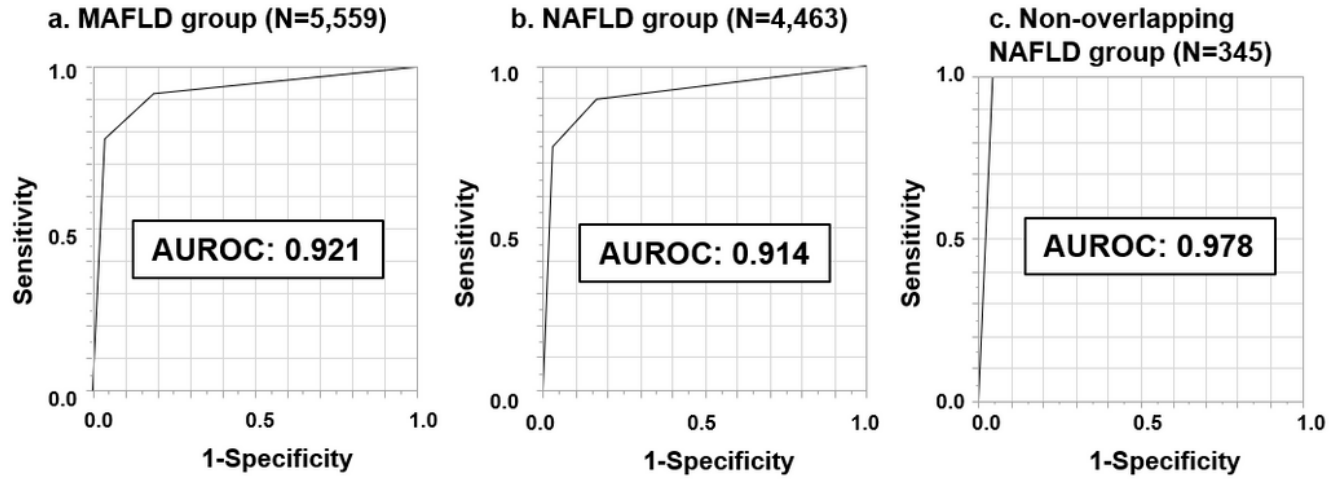
The proportion of indeterminate groups diagnosed by two different cutoffs for FIB-4 Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; FIB-4, Fibrosis-4 Index.

A. Cutoffs by Shah



	Cutoffs	Se	Sp	PPV	NPV	LR+	LR-
MAFLD	LCO	88.5%	71.9%	6.6%	99.6%	3.2	0.16
NAFLD	LCO	85.3%	74.9%	5.0%	99.7%	3.4	0.19
Non-overlapping NAFLD	LCO	100.0%	66.8%	1.7%	100.0%	3.0	0.00

B. Cutoffs by Ishiba

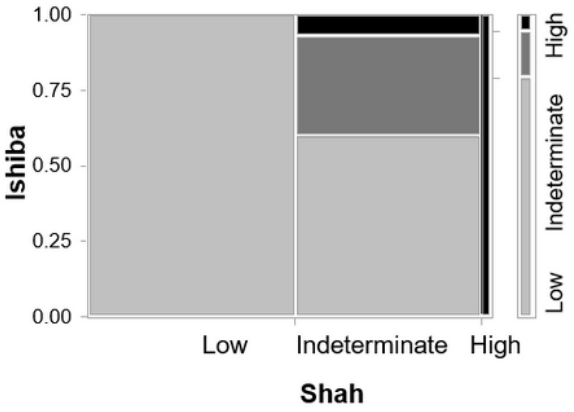


	Cutoffs	Se	Sp	PPV	NPV	LR+	LR-
MAFLD	HCO	77.9%	96.2%	31.8%	99.5%	20.8	0.23
NAFLD	LCO	89.7%	83.5%	7.7%	99.8%	5.4	0.12
Non-overlapping NAFLD	HCO	100.0%	95.6%	11.8%	100.0%	22.9	0.00

Figure 4

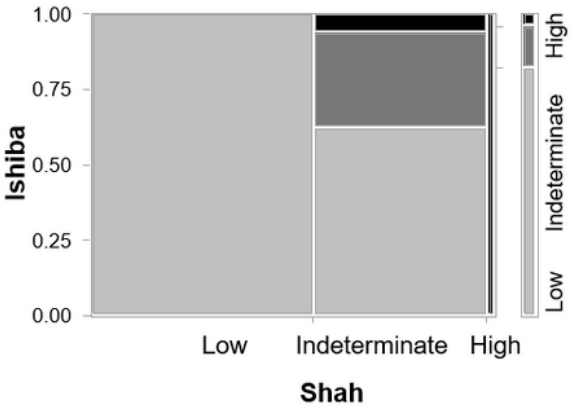
The number of low, indeterminate, and high groups diagnosed by two different cutoffs for FIB-4
Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; FIB-4, Fibrosis-4 Index.

A. MAFLD group (N=5,559)



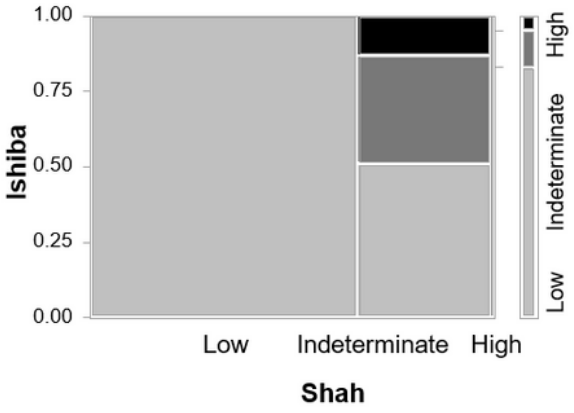
	Shah			
Ishiba	Low	Indeterminate	High	**Total**
High	0	176	123	299
Indeterminate	0	848	0	848
Low	2,873	1,539	0	4,412
Total	2,873	2,563	123	5,559

B. NAFLD group (N=4,463)



	Shah			
Ishiba	Low	Indeterminate	High	**Total**
High	0	114	67	181
Indeterminate	0	616	0	616
Low	2,469	1,197	0	3,666
Total	2,469	1,927	67	4,463

C. Non-overlapping NAFLD group (N=345)



	Shah			
Ishiba	Low	Indeterminate	High	**Total**
High	0	15	2	17
Indeterminate	0	41	0	41
Low	229	58	0	287
Total	229	114	2	345

Figure 5

The comparison between APRI ≥ 1.0 and two different criteria of FIB-4 Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4 Index; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.

Supplementary Files

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- BMCGastroenterologySupplementalInformation20201219.pptx