Gastro Hep Advances 2023;2:1093–1102

ORIGINAL RESEARCH—CLINICAL

Validation of Noninvasive Markers for HCC Risk Stratification in 1389 Patients With Biopsy-proven NAFLD

Hidenori Toyoda,[1] Hideki Fujii,[2,3] Michihiro Iwaki,[4] Hideki Hayashi,[5] Satoshi Oeda,[6,7] Hideyuki Hyogo,[8] Miwa Kawanaka,[9] Asahiro Morishita,[10] Kensuke Munekage,[11] Kazuhito Kawata,[12] Sakura Yamamura,[13] Koji Sawada,[14] Tatsuji Maeshiro,[15] Hiroshi Tobita,[16] Yuichi Yoshida,[17] Masafumi Naito,[17] Asuka Araki,[16] Shingo Arakaki,[15] Takumi Kawaguchi,[13] Hidenao Noritake,[12] Masafumi Ono,[18] Tsutomu Masaki,[10] Satoshi Yasuda,[1] Eiichi Tomita,[5] Masato Yoneda,[4] Norifumi Kawada,[2] Akihiro Tokushige,[19] Yoshihiro Kamada,[20] Hirokazu Takahashi,[6] Shinichiro Ueda,[19] Shinichi Aishima,[21] Yoshio Sumida,[22] Atsushi Nakajima,[3] and Takeshi Okanoue,[23] the Japan Study Group of Nonalcoholic Fatty Liver Disease (JSG-NAFLD)

[1]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan; [2]Departments of Premier Preventive Medicine, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; [3]Department of Hepatology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; [4]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [5]Department of Gastroenterology and Hepatology, Gifu Municipal Hospital, Gifu, Japan; [6]Liver Center, Saga University Hospital, Saga, Japan; [7]Department of Laboratory Medicine, Saga University Hospital, Saga, Japan; [8]Department of Gastroenterology, JA Hiroshima Kouseiren General Hospital, Hatsukaichi, Japan; [9]Department of General Internal Medicine2, Kawasaki Medical Center, Kawasaki Medical School, Okayama, Japan; [10]Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, Kita-gun, Japan; [11]Department of Gastroenterology and Hepatology, Kochi Medical School, Kochi, Japan; [12]Hepatology Division, Department of Internal Medicine II, Hamamatsu University School of Medicine, Hamamatsu, Japan; [13]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; [14]Division of Metabolism and Biosystemic Science, Gastroenterology, and Hematology/Oncology, Asahikawa Medical University, Asahikawa, Japan; [15]First Department of Internal Medicine, University of the Ryukyus Hospital, Okinawa, Japan; [16]Department of Hepatology, Shimane University Hospital, Izumo, Japan; [17]Department of Gastroenterology and Hepatology, Suita Municipal Hospital, Suita, Japan; [18]Division of Innovative Medicine for Hepatobiliary & Pancreatology, Faculty of Medicine, Kagawa University, Takamatsu, Japan; [19]Department of Clinical Pharmacology and Therapeutics, Graduate School of Medicine, University of the Ryukyu, Okinawa, Japan; [20]Department of Advanced Metabolic Hepatology, Osaka University Graduate School of Medicine, Suita, Japan; [21]Department of Pathology and Microbiology, Faculty of Medicine, Saga University, Saga, Japan; [22]Graduate School of Healthcare Management, International University of Healthcare and Welfare, Tokyo, Japan; and [23]Hepatology Center, Saiseikai Suita Hospital, Suita, Japan

BACKGROUND AND AIMS: Nonalcoholic fatty liver diseases (NAFLD) and nonalcoholic steatohepatitis (NASH) can cause hepatocellular carcinoma (HCC). We examined histological features and reported noninvasive markers/models for stratifying the risk of HCC development in patients with biopsy-proven NAFLD or NASH. **METHODS:** A total of 1389 patients who had a histological diagnosis of NAFLD or NASH based on liver biopsy and underwent regular surveillance for HCC were included. The ability to predict HCC development was compared between histological features including liver fibrosis and NAFLD activity score, and noninvasive markers/models including aMAP (age, male, albumin–bilirubin, and platelet) score, FIB-4 (Fibrosis-4) index, and ALBI (albumin-bilirubin) score calculated at the time of biopsy. **RESULTS:** The C index of aMAP score was 0.887, which was consistent with the original report, comparable to FIB-4 index (0.878), and higher than those of ALBI score (0.789), histological liver fibrosis (0.723), and NAFLD activity score (0.589). The hazard ratios for HCC development in the aMAP intermediate and high-risk groups were 21.0 (95% confidence interval [CI], 3.6–402.0) and 110.3 (95% CI, 16.3–2251.4), respectively, in comparison to the aMAP score low-risk group. Those in the FIB-4 index moderate- and high-fibrosis groups were 10.3 (95% CI, 1.7–199.8) and 93.1 (95% CI, 16.3–1773.8), respectively, in

Abbreviations used in this paper: **CI, confidence interval; FLIP, the fatty liver inhibition of progression; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.**

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2023.07.018

comparison to the FIB-4 index mild-fibrosis group. No patients in the aMAP score low-risk group developed HCC during the study period. **CONCLUSION:** For stratifying the risk of HCC development in patients with biopsy-proven NAFLD or NASH, both aMAP score and FIB-4 index showed high discriminative ability as noninvasive markers, which were superior histological features.

Keywords: Nonalcoholic Fatty Liver Disease; Hepatocellular Carcinoma; aMAP Score; FIB-4 Index; ALBI Score.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the most prevalent liver disease worldwide.[1] It can progress to nonalcoholic steatohepatitis (NASH) that has histological features of steatosis, inflammation, and fibrosis, and can cause cirrhosis, hepatocellular carcinoma (HCC), or end-stage liver disease.[2,3] Previous studies have shown that patients with NASH, especially those with fibrosis, have an increased risk of liver-related complications including cirrhosis and HCC, liver-related mortality,[4–8] and cardiovascular disease.[5,9] Although several previous studies have reported that the main causes of mortality in patients with NAFLD or NASH are not liver-related, our recent study on Japanese patients with biopsy-proven NAFLD revealed that the main causes of mortality are liver-related, not related to other metabolic comorbidities.[10] In the majority of these patients, the cause of this liver-related mortality was HCC.

In this context, surveillance for HCC in patients with NAFLD is important for early detection and diagnosis, which enables the use of curative treatment and can improve survival. Ultimately, this can result in the reduction of liver-related mortality in patients with NAFLD. However, it is unpractical and difficult to perform HCC surveillance for all patients with NAFLD. Therefore, stratifying by HCC risk is necessary. In particular, identifying patients with low likelihood of developing HCC for whom surveillance for HCC can be omitted is urgently required.

Liver fibrosis is the factor that closely associated with the development of HCC.[11] In this context, liver fibrosis markers such as FIB-4 (Fibrosis-4) index were reportedly associated with the risk of HCC.[12] In addition, aMAP (age, male, albumin–bilirubin, and platelet) score was recently reported as a risk model for HCC development in patients with liver disease of various etiologies.[13] The original study found that the score is especially useful for identifying patients with liver diseases at low risk of developing HCC. However, whether the score can be accurate in patients with NAFLD remains to be confirmed. In this study, we validated these noninvasive markers/models for stratifying the risk of HCC in patients with biopsy-proven NAFLD and compared its ability to assess HCC risk with other markers or histological features.

Patients and Methods

Patients and Follow-up

This study was conducted using the database of the Japan Study Group of NAFLD, which contains information on patients with biopsy-proven NAFLD. This database contains data from 15 academic liver centers in Japan. We identified all patients diagnosed with biopsy-proven NAFLD between December 1, 1994, and December 31, 2020. NALFD was diagnosed histologically for all patients. The absence of chronic liver diseases other than NAFLD among patients in the dataset was confirmed, including excessive alcohol intake (>30 g/day in men and >20 g/day in women) and liver disease of other etiologies, including viral hepatitis, autoimmune hepatitis, drug-induced liver disease, primary biliary cholangitis, or primary sclerosing cholangitis.

This registry-based, multicenter historical cohort study was approved by the Institutional Review Board of Saga University Hospital (approval no. 2020-04-R-02; June 30, 2020) and by the institutional review board of each participating institution. Written informed consent was waived because the study used preexisting data.

Baseline data on patient demographics, laboratory values, and past medical history on the date of liver biopsy were extracted. Diabetes mellitus, hypertension, and dyslipidemia were diagnosed according to standard criteria.[14–16] Patients were followed every 6–12 months, typically every 6 months with ultrasonography and laboratory testing, including alpha-fetoprotein testing performed at every visit. If a hepatic nodule was detected with ultrasonography or a tumor marker was elevated, additional cross-sectional imaging studies (computed tomography, magnetic resonance imaging, or both) were performed. The diagnosis of HCC was based on appropriate imaging characteristics (arterial enhancement and delayed washout) or compatible histology. The follow-up period started on the date of biopsy and continued until March 31, 2021.

Histological Assessment and Definition of NAFLD

Histological assessments were performed based on liver specimens obtained by ultrasonography-guided fine-needle liver biopsy, with hematoxylin and eosion stain and Azan stain. Digital images of biopsy samples were obtained using a batch slide scanner (NanoZoomer 3.2.15; Hamamatsu Photonics, Hamamatsu, Japan). The images were transmitted for central reading and scoring by an experienced pathologist (S.A.), who was blinded to the patients' clinical and laboratory data. NAFLD was defined as the presence of ≥5% hepatic steatosis, as described by Kleiner et al.[17] Grading and staging were performed as described by Brunt et al[18] and Kleiner et al.[17] NAFLD activity scores (NASs) were assigned, as previously reported.[19] NASH was diagnosed according to the FLIP (fatty liver inhibition of progression) algorithm.[20] We defined active NASH as NASH with significant liver fibrosis (stage ≥F2) and an elevated NAS (≥4).[21,22]

Calculation of aMAP Score and Other Laboratory Markers

Laboratory markers were calculated based on the laboratory values obtained on the day of liver biopsy. The aMAP score

was calculated for each patient using the original formula[13]:

$$\begin{aligned}\text{aMAP score} = \big(\{&0.06 \times \text{age[years]} + 0.89 \times \\ &\text{sex(Male}: 1, \text{Female}: 0) + 0.48 \times \\ &[(\log_{10}\text{ total bilirubin}[\mu\text{mol/L}] \times 0.66) \\ &+ (\text{albumin[g/L]} \times -0.085)] - 0.01 \times \\ &\text{platelets count}\left[10^9/\text{L}\right]\} + 7.4\big)/14.77 \times 100.\end{aligned}$$

Patients were categorized into low-risk (score 0–50), medium-risk (score 50–60), or high-risk (score 60–100) groups according to the original report.[13]

The laboratory liver fibrosis marker, FIB-4 index, was calculated with the formula[23]:

$$\begin{aligned}\text{FIB} - 4\text{ index} = &\text{AST[IU/L]} \times \text{age[years]}/ \\ &\text{platelet count}\left[10^9/\text{L}\right] \times \text{ALT[IU/L]}^{1/2}.\end{aligned}$$

Patients were categorized as having mild fibrosis (<1.30), moderate fibrosis (1.30–2.67), and severe fibrosis or cirrhosis (>2.67) according to a previous report.[24]

ALBI (albumin-bilirubin) score, a laboratory measure of liver function, was calculated with the following formula[25]:

$$\begin{aligned}\text{ALBI score} = &(\log_{10}\text{ total bilirubin}[\mu\text{mol/L}] \times 0.66) \\ &+ (\text{albumin[g/L]} \times -0.085).\end{aligned}$$

Patients were categorized into ALBI grade 1 (score ≤ -2.60), grade 2 (score > -2.60 and ≤ -1.39), and grade 3 (score > -1.39) according to the original report.[25]

Statistical Analysis

Continuous variables are expressed as medians with interquartile range (IQR). They were compared using the Mann-Whitney *U* test. Categorical variables are expressed as numbers and percentages. They were compared using the chi-square test or Fisher exact test.

The discriminative ability of each model was first assessed visually by plotting the Kaplan-Meier estimate of the incidence of HCC for each group and compared with the log-rank test. Second, we calculated the discriminative ability quantitatively using the concordance-index. We used the standard Harrell's C-index. For the C-index, higher values indicate better discrimination. A C-index of 0.50 indicates no discrimination, whereas a C-index of 1.0 indicates perfect discrimination.

Cox proportional hazards models were used in multivariate analyses to adjust for factors potentially associated with the development of HCC, including age, sex, and diabetes mellitus. Data analysis was performed using JMP statistical software, version 11.0.0 (Macintosh version; SAS Institute, Cary, NC) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

A total of 1398 patients underwent liver biopsy and were diagnosed with NAFLD during the study period. Among them, 9 patients who had a history of HCC at the

Table 1. Baseline Characteristics of the Study Patients (n = 1,389)

Demographics	
Age (y)	57 (45–65)
Sex (male/female)	594 (42.8)/795 (57.2)
Body mass index (kg/m^2)	27.4 (24.8–30.6)
Diabetes mellitus (no/yes)	887 (63.9)/502 (36.1)
Hypertension (no/yes)	807 (58.1)/581 (41.9)
Dyslipidemia (no/yes)	589 (42.4)/800 (57.6)
Laboratory values	
Platelet count (10^3/μL)	215 (175–263)
Alanine aminotransferase (IU/L)	73 (47–110)
Aspartate aminotransferase (IU/L)	51 (35–74)
Gamma-gultamyl transpeptidase (IU/L)	60 (40–99)
Albumin (g/dL)	4.4 (4.1–4.6)
Total bilirubin (mg/dL)	0.8 (0.6–1.0)
aMAP score	51.3 (44.2–56.9)
aMAP score (0–50/50–60/60–100)	620 (45.3)/545 (39.8)/203 (14.8)
FIB-4 index	1.55 (0.90–2.62)
FIB-4 index (<1.30/1.30–2.67/>2.67)	589 (42.4)/469 (33.8)/330 (23.8)
ALBI score	−2.96 (−3.18 to −2.70)
ALBI grade (≤ -2.60 / > -2.60 and ≤ -1.39 / > -1.39)	1126 (83.2)/226 (16.7)/2 (0.1)
Histology	
Steatosis (0/1/2/3)	8 (0.6)/974 (70.1)/271 (19.5)/136 (9.8)
Inflammation (0/1/2/3)	67 (4.8)/879 (63.3)/364 (26.2)/79 (5.7)
Ballooning (0/1/2)	452 (32.5)/611 (44.0)/326 (23.5)
NAS score	4 (3–5)
NAS score (1–2/3–4/5–8)	280 (20.2)/747 (53.8)/362 (26.1)
Fibrosis stage (0/1/2/3/4)	240 (17.3)/536 (38.6)/394 (28.4)/195 (14.0)/24 (1.7)
NASH (no/yes)	459 (33.0)/930 (67.0)

Data are expressed as medians (interquartile range) or n (%).

time of biopsy were excluded. The remaining 1389 patients were included. Table 1 shows patient characteristics on the day of liver biopsy. Patients consisted of 594 (42.8%) males and 795 (57.2%) females, with a median age of 57 (IQR, 45–65) years. Among the 1389 patients, 502 (36.1%) had diabetes mellitus, 581 (41.9%) had hypertension, and 600 (57.6%) had dyslipidemia. Based on histological examination of based liver biopsy specimens, the NAS score was 1–2 in 280 patients (20.2%), 3–4 in 747 patients (53.8%), and 5–8 in 362 patients (26.1%). The degree of liver fibrosis was F0–1 in 776 patients (55.9%), F2 in 394 patients (28.4%), and F3–4 in 219 patients (15.7%), including 24 patients (1.7%) with cirrhosis.

Incidence of Hepatocellular Carcinoma by aMAP Score, FIB-4 Index, ALBI Score, and Liver Histology

Patients were followed after biopsy for a median of 4.61 years (IQR, 2.52–10.20 years). During follow-up, 15.0% of patients dropped out. The rate of patients who dropped out was higher in patients with lower aMAP score or lower FIB-4 index (Table A1). HCC developed in 37 patients (2.7%). Table A2 shows the characteristics of these HCCs. Owing to rigorous surveillance after biopsy, HCCs were diagnosed at early stage (BCLC [Barcelona Clinic Liver Cancer] class 0 or A) in most patients and were BCLC class 0 (single nodular HCC with $\leq$2 cm in diameter) in more than a half of patients.

Based on laboratory values at biopsy, aMAP score, FIB-4 index, and ALBI score were calculated. Patients were categorized into groups based the aMAP score. There were 620 (45.3%) in the low-risk group, 545 (39.8%) in the intermediate-risk group, and 203 (14.8%) in the high-risk group. They were categorized into fibrosis groups based on the FIB-4 index. There were 589 (42.4%) in the mild-fibrosis group, 469 (33.8%) in the moderate-fibrosis group, and 330 (23.8%) in the advanced-fibrosis group. Patients were also categorized by ALBI score into grades 1–3. There were 1126 (83.2%) patients with ALBI grade 1, 226 (16.7%) with ALBI grade 2, and 2 (0.1%) with ALBI grade 3. Table A3 shows prevalence of aMAP, FIB-4 index, and ALBI score categories based on the histological liver fibrosis. There were trends to the higher values of the respective markers with the increase in the degree of histological liver fibrosis.

Figure 1 and Table 2 show the incidence of HCC in categories based on aMAP score, FIB-4 index, and ALBI score, and histological degree of liver fibrosis and NAS score. aMAP score and FIB-4 index had high discriminatory abilities for the incidence of HCC, followed by ALBI score, histological liver fibrosis, and NAS score in this order. It is noted that no patients in the aMAP score low-risk group developed HCC during the study period. The Harrel's C-index was 0.887 (95% confidence interval [CI], 0.848–0.926) for aMAP score, 0.878 (95% CI, 0.829–0.927) for FIB-4 index, 0.760 (95% CI, 0.680–0.840) for ABLI score, 0.709 (95% CI, 0.611–0.807) for histological liver fibrosis, and 0.589 (95% CI, 0.516–0.662) for NAS score.

When adjusted for patient age, gender, and diabetes mellitus (Table A4), the hazard ratios (HRs) for HCC development in patients of the aMAP intermediate and high-risk groups were 20.98 (95% CI, 3.64–402.02) and 110.25 (95% CI, 16.34–2251.41), respectively, when compared to patients in the aMAP low-risk group. The HRs for HCC development in patients with moderate fibrosis and severe fibrosis or cirrhosis based on the FIB-4 index were 10.31 (95% CI, 1.67–199.84) and 93.07 (95% CI, 16.33–1773.76), respectively, in comparison to those with mild fibrosis. The HR for HCC development in patients with ALBI grade 2 or 3 was 4.27 (95% CI, 2.08–8.64) in comparison to those with ALBI grade 1. Regarding histological assessment, the HRs for HCC development in patients with fibrosis stage of F2, F3, and F4 were 2.06 (95% CI, 0.84–5.19), 6.70 (95% CI, 2.88–16.44), and 13.07 (95% CI, 1.95–53.21), respectively, in comparison to those with F0 or F1 liver fibrosis. The HRs for HCC development in patients with NAS scores of 3–4 and 5–8 were 4.18 (95% CI, 1.24–26.05) and 4.14 (95% CI, 1.09–26.99), respectively, in comparison to those with NAS score of 1–2.

Incidence of Hepatocellular Carcinoma by aMAP Score, FIB-4 Index, and ALBI Score in Patients With Mild to Moderate Liver Fibrosis

The predictive ability of aMAP score, FIB-4 index, and ALBI score for HCC development were compared by dividing patients into 2 groups: patients with mild (F0 or F1, n = 776) to moderate (F2, n = 394) liver fibrosis and patients with advanced fibrosis (F3, n = 195) or cirrhosis (F4, n = 24). Figure 2 and Table 3 show the incidence of HCC based on the categories according to aMAP score, FIB-4 index, and ALBI score in patients with F0–F2 fibrosis. The aMAP score and FIB-4 index had best discriminatory ability for HCC. The Harrel's C-index was 0.908 (95% CI, 0.859–0.957) for aMAP score, 0.896 (0.841–0.951) for FIB-4 index, 0.760 (0.680–0.840) for ALBI score, 0.581 (0.459–0.703) for histological liver fibrosis, and 0.676 (0.623–0.729) for NAS score, respectively.

Incidence of Hepatocellular Carcinoma by aMAP Score, FIB-4 Index, and ALBI Score in Patients With Advanced Liver Fibrosis

In patients with advanced liver fibrosis (F3) or cirrhosis (F4), the aMAP score and FIB-4 index remained the best marker that stratified the incidence of HCC (Figure 3 and Table 4). The Harrel's C-index was 0.754 (95% CI, 0.648–0.860) for aMAP score, 0.714 (0.551–0.877) for FIB-4 index, 0.530 (0.378–0.682) for ABLI score, 0.535 (0.427–0.643) for histological liver fibrosis, and 0.505 (0.370–0.640) for NAS score.

Discussion

In Japan, an HCC surveillance program has been established since the 1990s. The cost for HCC surveillance has been covered by the national insurance system for all patients with liver disease, including those at minimal risk for HCC. Consequently, the survival rates of patients with HCC have increased more than in other regions due to the

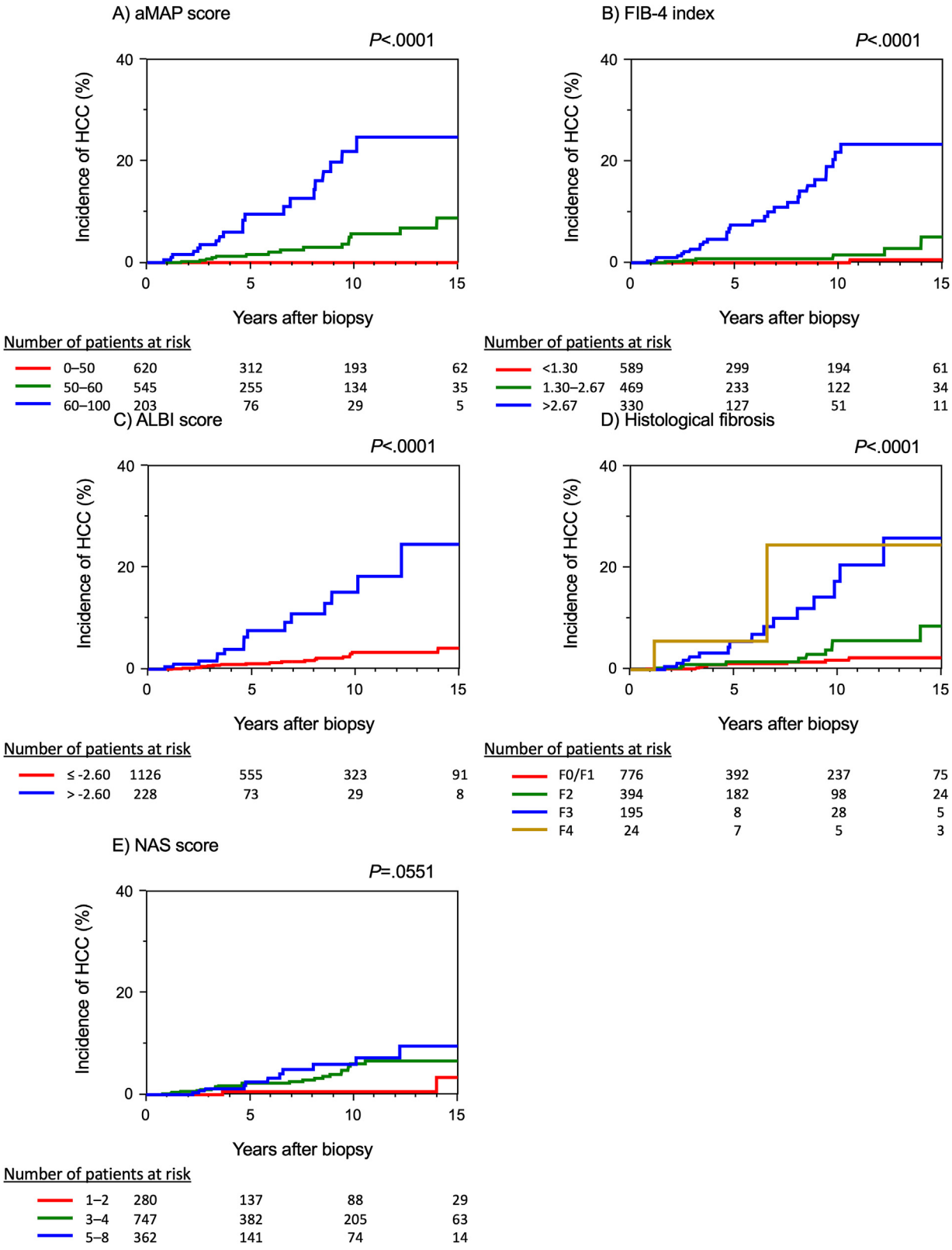

Figure 1. Incidence of hepatocellular carcinoma stratified by baseline laboratory markers or histological characteristics in the overall study population with biopsy-proven nonalcoholic fatty liver disease. (A) aMAP score, (B) Fib-4 index, (C) ALBI score, (D) histological liver fibrosis, and (E) histological NAS score.

Table 2. Incidence of Hepatocellular Carcinoma (%) After Liver Biopsy in Patients With Biopsy-proven Nonalcoholic Fatty Liver Disease (n = 1389)

Marker	Category	Number of patients (%)	1 y	3 y	5 y	10 y	15 y
aMAP score	0–50	620 (45.3)	0	0	0	0	0
	50–60	545 (39.8)	0	0.7	1.6	5.7	8.8
	60–100	203 (14.8)	0.5	3.5	9.5	21.9	24.7
FIB-4 index	<1.30	589 (42.4)	0	0	0	0	0.6
	1.30–2.67	469 (33.8)	0	0.5	0.8	1.6	5.1
	>2.67	330 (23.8)	0.3	2.6	7.5	21.8	23.4
ALBI score	≤ −2.60	1126 (83.2)	0	0.7	1.1	3.3	4.2
	> −2.60	228 (16.8)	0.5	1.7	7.6	15.2	24.7
Histological fibrosis	F0–1	776 (55.9)	0.1	0.1	1.2	1.8	2.3
	F2	394 (28.4)	0	1.0	1.5	5.7	8.5
	F3	195 (14.0)	0	2.5	5.5	17.3	25.8
	F4	24 (1.7)	0	5.6	5.6	24.4	24.4
NAS score	1–2	280 (20.2)	0	0	0.6	0.6	3.4
	3–4	747 (53.8)	0.1	1.0	2.2	6.1	6.6
	5–8	362 (26.1)	0	1.2	2.5	5.9	9.5

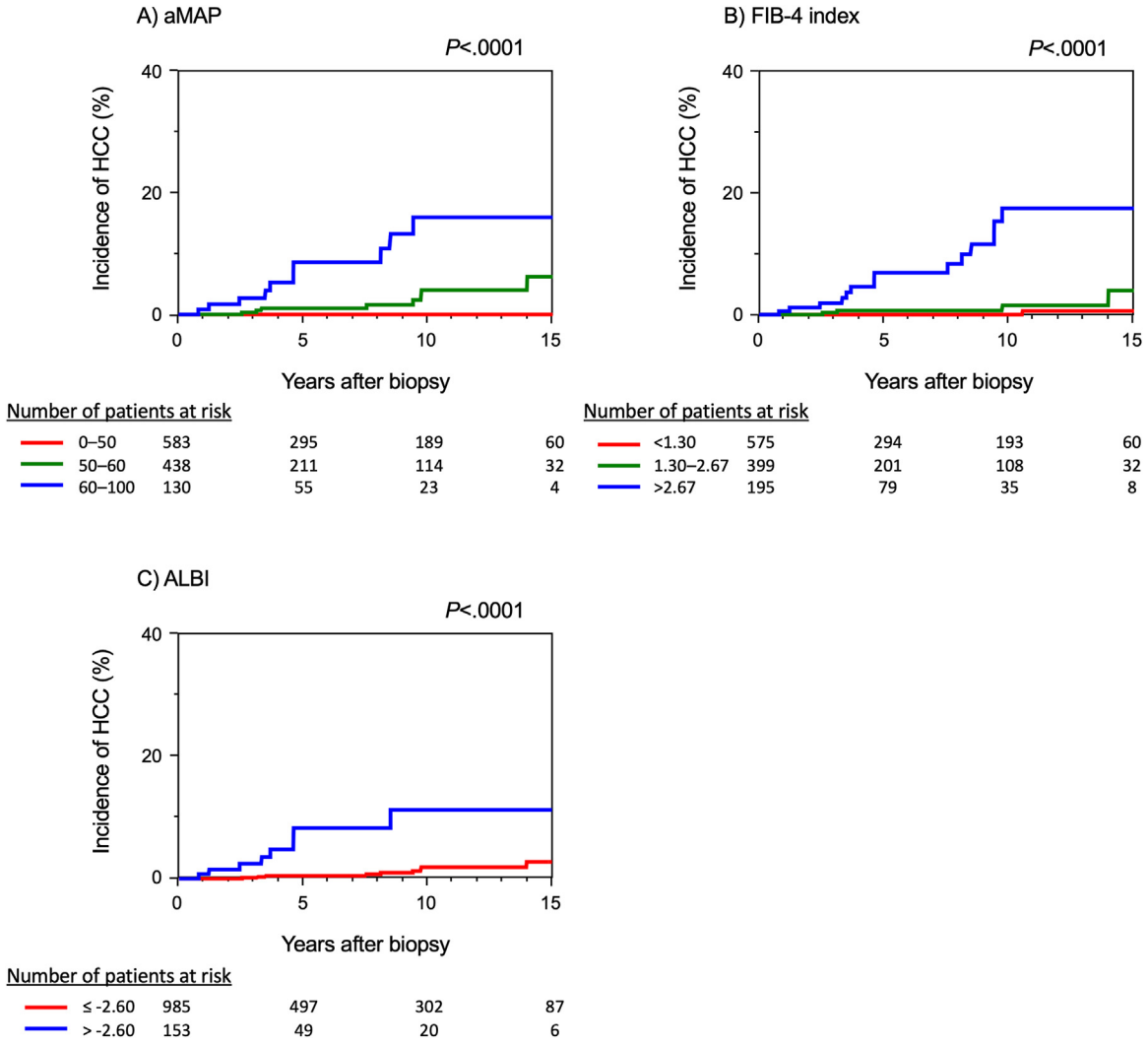

Figure 2. Incidence of hepatocellular carcinoma stratified by baseline laboratory markers in patients with F0, F1, or F2 liver fibrosis based on liver biopsy results. (A) aMAP score, (B) Fib-4 index, and (C) ALBI score.

Table 3. Incidence of Hepatocellular Carcinoma (%) After Liver Biopsy in Patients With Biopsy-proven Nonalcoholic Fatty Liver Disease

Marker	Category	Number of patients (%)	1 y	3 y	5 y	10 y	15 y
aMAP score	0–50	583 (50.7)	0	0	0	0	0
	50–60	438 (38.1)	0	0.3	1.0	4.0	6.2
	60–100	130 (11.3)	0.8	2.7	8.5	16.0	16.0
FIB-4 index	<1.30	575 (49.2)	0	0	0	0	0.6
	1.30–2.67	399 (34.1)	0	0.3	0.7	1.5	3.9
	>2.67	195 (16.7)	0.6	1.9	6.9	17.4	17.4
ALBI score	≤ −2.60	985 (86.6)	0	0.1	0.4	1.9	2.7
	> −2.60	153 (13.4)	0.7	2.5	8.3	11.3	11.3

Patients With F0–F2 Liver Fibrosis (n = 1170).

detection of early-stage HCC.[26,27] At liver centers, all patients with liver disease usually undergo regular HCC surveillance regardless of the degree of liver fibrosis, typically every 6 months. This is not an exception for patients with NAFLD. However, given in the rapid increase in the number of patients with NAFLD in recent decades globally, it is impossible to include all patients with NAFLD in HCC surveillance systems. Therefore, risk stratification for HCC development is urgently needed to classify patients with NAFLD into those at high risk of developing HCC, who should undergo surveillance, and those with a low likelihood of HCC for whom surveillance will not be necessary.

Among factors based on histological evaluation, NAS score had modest predictive ability for HCC in comparison

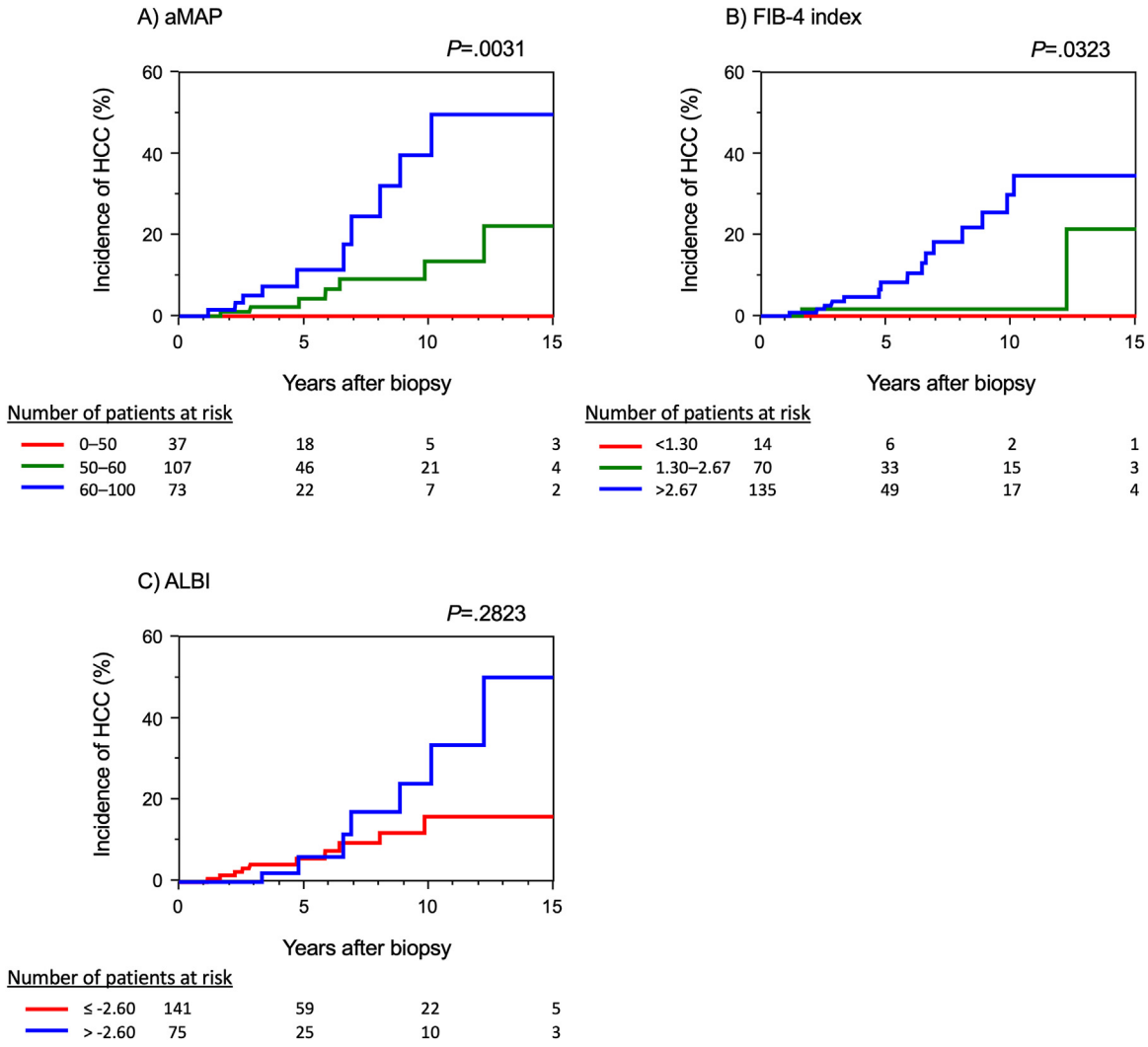

Figure 3. Incidence of hepatocellular carcinoma stratified by baseline laboratory markers in patients with F3 or F4 liver fibrosis based on liver biopsy results. (A) aMAP score, (B) Fib-4 index, and (C) ALBI score.

Table 4. Incidence of Hepatocellular Carcinoma (%) After Liver Biopsy in Patients With Biopsy-proven Nonalcoholic Fatty Liver Disease

Marker	Category	Number of patients (%)	1 y	3 y	5 y	10 y	15 y
aMAP score	0–50	37 (17.1)	0	0	0	0	0
	50–60	107 (49.3)	0	2.3	4.3	13.5	22.2
	60–100	73 (33.6)	0	5.1	11.4	39.7	49.7
FIB-4 index	<1.30	14 (6.4)	0	0	0	0	0
	1.30–2.67	70 (32.0)	0	1.7	1.7	1.7	21.4
	>2.67	135 (61.6)	0	3.6	8.3	29.9	34.6
ALBI score	≤ −2.60	141 (65.3)	0	4.2	5.8	16.1	16.1
	> −2.60	75 (34.7)	0	0	6.1	24.1	50.2

Patients With F3, F4 Liver Fibrosis (n = 219).

to histological liver fibrosis. Several previous studies have reported that liver fibrosis is the main risk factor for HCC development and steatosis is not associated with NAFLD outcomes.[11] Although histological liver fibrosis stratified the incidence of HCC, FIB-4 index, a laboratory marker of liver fibrosis, had higher predictive ability for HCC than histological liver fibrosis; the noninvasive marker showed superior ability to liver histology in assessing the risk of HCC. This might have been partly due to sampling error during needle liver biopsy for liver fibrosis due to heterogenous distribution of fibrosis within the liver.

The recently developed aMAP score appears to accurately stratify the risk of HCC development.[13] Notably, recognizing the difficulty in accurate and consistent diagnosis of cirrhosis,[28] the model was developed in patients with chronic hepatitis without specific reference to the presence or absence of cirrhosis. In addition, the aMAP score can reportedly identify patients at low risk of HCC development for whom HCC surveillance can be omitted. Although the original report included 720 of 17,374 patients (4.1%) with nonviral HCC, the etiology of underlying liver diseases in these patients was not accurately defined[13] and could have included patients with nonviral and non-NAFLD etiology. By contrast, all patients in the present study were confirmed to have NAFLD histologically. They were also confirmed to not have viral hepatitis or liver diseases of other etiologies. Therefore, the study patients were appropriate for the validation of aMAP score in patients with NAFLD. Whereas previous study validated aMAP score in patients with nonviral alcoholic liver disease,[29] this is the first study to confirm the excellent performance of aMAP score to assess the risk of HCC development in nonviral NAFLD patients. In particular, no patients in the aMAP score low-risk group (< 50), which included more than 45% of patients, developed HCC. A recent meta-analysis reported that NAFLD-related HCC is more common in patients without cirrhosis, when compared to patients with HCC by other etiologies.[30] In this context, aMAP score will be useful clinically, because this study indicated that the number of patients with NAFLD who need HCC surveillance can be substantially reduced based on their aMAP score.

Although ALBI score has been reported to be a measure of liver dysfunction,[25] recent studies have reported ALBI score as an indicator of being at high risk for HCC development.[31,32] The results of this study were consistent with results of previous studies. The present study confirmed that ALBI score can stratify the risk of HCC in patients with NAFLD. However, the discriminatory ability of ALBI score for HCC risk was inferior to that of other serum markers.

This study had several limitations. This was a hospital-based study limited to patients who underwent liver biopsy. Therefore, the predictive ability of the markers studied in patients with NAFLD for HCC development should be verified further with a community-based study. The rates of patients who dropped out during follow-up after biopsy decreased in patients with increased risk of aMAP score and fibrosis degree of FIB-4 index. This might have influenced the incidences of HCC by groups; the lower drop-out rate may have been associated with the increased incidence of HCC. The number of patients with cirrhosis, for whom surveillance for HCC is recommended in Western countries, was very small (24 patients, 1.7%). This is partly because of the risk associated with needle liver biopsy for patients with cirrhosis due to decreased platelet count. Therefore, we analyzed patients with advanced liver fibrosis and cirrhosis together. However, as noted in the American Association for Study of the Liver Diseases guidelines, the discrimination between severe fibrosis and compensated cirrhosis is often unclear, since fibrosis can be heterogenously distributed within the liver. In addition, many cases of NAFLD-related HCC reportedly develop in patients with F3 fibrosis.[30] In this context, our study confirmed the predictive ability of noninvasive markers such as aMAP score or FIB-4 index in patients with advanced liver fibrosis or cirrhosis.

Conclusion

Our study showed that aMAP score and FIB-4 index have high discriminatory ability of HCC risk in patients with biopsy-proven NAFLD. These noninvasive markers can identify patients at high risk of HCC for whom surveillance will be necessary and, in particular, those at low risk of HCC for whom surveillance can be omitted.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.07.018.

References

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.
3. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402.
4. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7:234–238.
5. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–397.
6. Simon TG, Roelstraete B, Khalili H, et al. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut 2021;70:1375–1382.
7. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017;67:1265–1273.
8. Kim GA, Lee HC, Choe J, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol 2018;68:140–146.
9. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113–121.
10. Fujii H, Iwaki M, Hayashi H, et al. Clinical outcomes in biopsy-proven nonalcoholic fatty liver disease patients: a multicenter registry-based cohort study. Clin Gastroenterol Hepatol 2023;21:370–379.
11. Younossi ZM, Henry L. Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma. JHEP Rep 2021;3:100305.
12. Loosen SH, Kostev K, Keitel V, et al. An elevated FIB-4 score predicts liver cancer development: a longitudinal analysis from 29,999 patients with NAFLD. J Hepatol 2022;76:247–248.
13. Fan R, Papatheodoridis G, Sun J, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 2020;73:1368–1378.
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Supple 1):S62–S69.
15. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH2019). Hypertens Res 2019;42:1235–1481.
16. Teramoto T, Sasaki J, Ueshima H, et al. , Japan Atherosclerosis Society (JAS) Committee for Epidemiology and Clinical Management of Atherosclerosis. Diagnostic criteria for dyslipidemia. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb 2007;14:155–158.
17. Kleiner DE, Brunt EM, Van Natta M, et al. , Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313–1321.
18. Brunt EM, Janney CG, Bisceglie AM, et al. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94:2467–2474.
19. Brunt EM, Kleiner DE, Wilson LA, et al. , NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. Hepatology 2011;53:810–820.
20. Bedossa P, FLIP Pathology Consortium. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014;60:565–575.
21. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with nonalcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020;5:362–373.
22. Ratziu V, Harrison SA, Francque S, et al. , GOLDEN-505 Investigator Study Group. Elafibrator, and agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolusiton of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147–1159.
23. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–1325.
24. Shah AG, Lydecker A, Murrey K, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fartty liver disease. Clin Gastroenterol Hepatol 2009;7:1104–1112.
25. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550–558.
26. Toyoda H, Kumada T, Kaneoka Y, et al. Impact of surveillance on survival of patients with initial hepatocellular carcinoma: a study from Japan. Clin Gastroenterol Hepatol 2006;4:1170–1176.
27. Johnson P, Berhane S, Kagebayashi C, et al. Impact of disease stage and aetiology on survival in hepatocellular carcinoma: implications for surveillance. Br J Cancer 2017;116:441–447.
28. Toyoda H, Atsukawa M, Watanabe T, et al. Marked heterogeneity in the diagnosis of compensated cirrhosis of patients with chronic HCV infection in a real-world setting: a large, multicenter study from Japan. J Gastroenterol Hepatol 2020;35:1420–1425.
29. Liu K, Yip TCF, Masson S, et al. Validation of the aMAP score to predict hepatocellular carcinoma development

in a cohort of alcohol-related cirrhosis patients. Liver Cancer Int 2022;3:99–104.
30. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol 2022;23:521–530.
31. Fujita K, Oura K, Yoneyama H, et al. Albumin-bilirubin score indicates liver fibrosis staging and prognosis in patients with chronic hepatitis C. Hepatol Res 2019; 49:731–742.
32. Tanaka Y, Ogawa E, Huang CF, et al. HCC risk post-SVR with DAAs in East Asians: findings from the REAL-C cohort. Hepatol Int 2020;14:1023–1033.

Received January 25, 2023. Accepted July 19, 2023.

Correspondence:
Address correspondence to: Yoshio Sumida, MD, PhD, Division of Hepatology and Pancreatology, Department of Internal Medicine, Aichi Medical University, Nagakute, Japan. e-mail: sumida19701106@yahoo.co.jp; Hidenori Toyoda, MD, PhD, Department of Gastroenterology, Ogaki Municipal Hospital, 4-86 Minaminokawa, Ogaki, Gifu 503-8502, Japan. e-mail: hmtoyoda@spice.ocn.ne.jp.

Authors' Contributions:
Concept and study design: Hidonori Toyoda and Yoshio Sumida. Data acquisition: All authors. Data analysis: Hidonori Toyoda, Hideki Fujii, and Akihiro Tokushige. Preparation of the manuscript: Hidonori Toyoda, Hideki Fujii, and Yoshio Sumida. Data interpretation, review and/or revision of the manuscript: All authors.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
This research was financially supported by Japan Strategic Medical Administration Research Center (J-SMARC).

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials will be available to other researchers upon request to corresponding author.

Reporting Guidelines:
Helsinki Declaration.