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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Applicability of APRI and FIB-4 as a transition indicator of liver fibrosis in patients with chronic viral hepatitis

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Abstract

Background and Aims The usefulness of APRI or FIB-4 is well established as a non-invasive liver fibrosis marker at a point of diagnosis in patients with chronic liver disease. However, their applicability for the monitoring of progression of liver fibrosis over time is yet to be determined. We aimed to clarify the feasibility of APRI and FIB-4 for the longitudinal evaluation of liver fibrosis in patients with chronic hepatitis B and C.

Methods This is a multi-center retrospective and prospective cohort study, enrolling 1029 patients with HCV and 384 patients with HBV who were histologically diagnosed by liver biopsy. The observation period of retrospective and prospective study was 14 and 12 years, respectively. The APRI and FIB-4 were traced back in cases of histologically diagnosed cirrhosis, and those were prospectively analyzed after biopsy in cases diagnosed as F3 of METAVIR score, respectively.

Results The averaged APRI and FIB-4 exhibited time-dependent increase in the retrospective study of hepatitis C patients (increase by 0.09/year in APRI and 0.29/year in FIB-4). In the prospective study of untreated hepatitis C patients, such increases were 0.14/year in APRI and 0.40/year in FIB-4, respectively. Neither the average of APRI nor FIB-4 showed a specific tendency with hepatitis B patients and treatment-experienced hepatitis C patients.

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Conclusion The APRI and FIB-4 may serve as a transition indicator of liver fibrosis in anti-viral treatment-naïve patients with chronic hepatitis C.

Keywords APRI · FIB-4 · HCV · HBV · Longitudinal change

Abbreviations

APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ROC analysis	Receiver operating characteristic analysis

Introduction

Chronic liver disease, regardless of the etiology, possesses a progressive nature of liver fibrosis over decades. Liver cirrhosis is an end-stage of liver fibrosis at high risk of decompensated liver failure or hepatocellular carcinoma (HCC). Liver biopsy has been a gold standard of the assessment of liver fibrosis. However, the repetitive performance of liver biopsy should be limited because of its invasiveness. Alternatively, some noninvasive methods have been studied for diagnosing liver fibrosis [1–3]. The World Health Organization (WHO) recommends transient elastography (TE) using ultrasound and aspartate aminotransferase to platelet ratio (APRI) and FIB-4 as the diagnostic method for liver fibrosis in chronic viral hepatitis [4, 5]. In all clinical guidelines for hepatitis B and C issued from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and the Japan Society of Hepatology (JSH), TE, APRI and FIB-4 are recommended as well for the diagnosis of liver fibrosis [6–11].

Several limitations are raised for APRI and FIB-4 in the staging fibrosis of chronic liver disease because these scores have different standards. For example, APRI score < 1.0 indicates the absence of cirrhosis (histological stage $<$ F4) and APRI > 2.0 indicates the presence of cirrhosis (F4), respectively. Although FIB-4 is useful for diagnosing advanced fibrosis (F3 or F4), the diagnostic criteria for cirrhosis are yet to be determined. Furthermore, the reliability of such a scoring system varies depending on the etiology of liver disease [12]. APRI and FIB-4 are well acknowledged as a diagnostic score at the time of evaluation, however, their feasibility as a transition indicator of fibrosis over time has yet to be determined. In chronic hepatitis C, the development to cirrhosis is observed in approximately 10–20% of patients over 20–30 years of infection [13]. Estimating the transition of the stage or the degree of liver fibrosis is valuable for the understanding of the natural course of chronic liver disease.

In this study, we investigated whether the temporal changes of APRI and FIB-4 in viral hepatitis are useful in assessing the progression of liver fibrosis. As a preliminary step, we checked whether APRI and FIB-4 of the used population reflected fibrosis, and then examined the changes in APRI and FIB-4 over time. To capture the trend more reliably of the longitudinal changes of APRI and FIB-4, we used the following two cohorts. In the "retrospective study," we examined the pre-diagnostic history of APRI and FIB-4 in patients with histologically diagnosed cirrhosis. In the "prospective study," we searched for post-diagnostic changes in APRI and FIB-4 in patients who had previously been histologically diagnosed with F3. In the latter group, we further examined the impact of the history of interferon-based or DAA therapy for patients with HCV infection on the transition of liver disease.

Methods

Patients

Patients with chronic hepatitis B and C who were histologically diagnosed until January 2018 at the following 11 institutes in Japan were enrolled: National Center for Global Health and Medicine, Kanazawa University Hospital, the Hospital of Hyogo College of Medicine, Hiroshima University Hospital, Hokkaido University Hospital, Yamagata University Hospital, University of Yamanashi Hospital, Osaka City University Hospital, Kumamoto University Hospital, Kurume University Hospital, and Musashino Red Cross Hospital. Chronic hepatitis B was defined as positive HBsAg or HBV DNA with at least 6-month intervals, whereas chronic hepatitis C was defined as positive HCV RNA. Patients with other liver diseases, such as complication of liver cancer, and insufficient data were excluded. Finally, 1014 cases of chronic hepatitis C and 364 cases of chronic hepatitis B were enrolled (Supplementary Fig. 1). Patient characteristics are presented in Table 1. In addition to the analysis of all cases, the following two cohorts were set and subanalysis was performed. "Retrospective study" cohort was a cohort with 133 cases of chronic hepatitis C and 26 cases of chronic hepatitis B with histological diagnosis as cirrhosis (F4) in whom APRI and FIB-4 were investigated retrospectively every 6 months before diagnosis as far as possible. "Prospective study" cohort was enrolled 252 cases of chronic hepatitis C and 155 cases of chronic hepatitis B diagnosed as F3 by liver biopsy whose data

Table 1 Baseline characteristics of patients

	All cases		Retrospective study		Prospective study	
	HCV	HBV	HCV	HBV	HCV	HBV
n	1014	364	133	26	252	155
Age (year)	62.6 ∓ 11.2	49.3 ∓ 13.8	66.7 ∓ 9.9	62.6 ∓ 11.2	62.7 ∓ 9.2	51.5 ∓ 13.2
Gender (Male, %)	44.1	64.3	40.0	69.2	47.2	63.9
METAVIR score 1/2/3/4	270/ 172/ 420/ 152	104/ 36/ 170/ 54	(all F4)	(all F4)	(all F3)	(all F3)
AST (U/L)	59.8 ∓ 45.6	63.1 ∓ 73.1	74.5 ∓ 50.1	39.8 ∓ 12.4	71.7 ∓ 37.6	63.4 ∓ 60.2
ALT (U/L)	65.5 ∓ 55.9	89.6 ∓ 119	73.6 ∓ 57.2	48.3 ∓ 19.9	77.7 ∓ 51.5	81.8 ∓ 85.8
Platelet count ($\times 10^{-9}$/L)	16.0 ∓ 7.3	16.9 ∓ 9.5	10.7 ∓ 3.5	13.3 ∓ 4.7	12.5 ∓ 5.2	16.7 ∓ 17.7
APRI	1.14 ∓ 1.1	1.04 ∓ 1.2	2.13 ∓ 1.5	1.20 ∓ 1.4	2.31 ∓ 1.8	1.16 ∓ 0.96
FIB-4	3.35 ∓ 2.4	1.99 ∓ 1.3	6.31 ∓ 3.7	3.56 ∓ 1.4	5.61 ∓ 3.3	2.73 ∓ 1.6
Averaged follow up period (year)	–	–	4.30 ∓ 3.9	2.90 ∓ 2.1	7.33 ∓ 4.5	8.23 ∓ 4.0

AST aspartate aminotransferase' *ALT* alanine aminotransferase'

were investigated every half a year after histological diagnosis until August 2018, when we started our research. Further analysis was done by sorting the latter cohort with treated or untreated by antiviral therapy.

This study was approved by the National Center for Global health and Medicine Clinical Research Ethics Committee (NCGM-G-002269-01) and the Musashino Red Cross Hospital Clinical Research Ethics Committee (29201). We only investigated data collected in the daily medical care with necessity; new tests were never taken to get data for this study. This study was conducted in accordance with the Declaration of Helsinki.

Collection of samples

The following data were collected and analyzed: histological degree of fibrosis (F stage of METAVIR score), sex, age, AST value, ALT value, platelet value, and APRI and FIB-4 at liver biopsy. The data from daily practice were used, and APRI and FIB-4 were calculated with the following formulas:

$$\begin{aligned}\text{APRI} = {} & (\text{AST value (IU/L)} / \\ & \text{upper limit of normal AST value (IU/L))} / \\ & \text{platelet count } \left(10^9/\text{L}\right) \times 100\end{aligned}$$

$$\begin{aligned}\text{FIB}-4 = {} & (\text{AST value (IU/L)} \times \text{age (years)}) / \\ & \left(\text{platelet count } \left(10^9/\text{L}\right) \times \sqrt{(\text{ALT value (IU/L)})}\right)\end{aligned}$$

APRI and FIB-4 were investigated retrospectively every 6 months before diagnosis in cases with histological F4 and prospectively after diagnosis in cases with histological F3.

Statistical analysis

Chi-square test, Receiver operating characteristic (ROC) analysis and Pearson correlation coefficient were used for statistical examination using the EZR software (version 1.35, Jichi Medical University Saitama Medical Center) [14].

Results

Accuracy of APRI and FIB-4 for diagnosing liver cirrhosis

Correlations between noninvasive markers and histological degree of liver fibrosis were analyzed in 1029 cases with HCV and 384 cases with HBV (Fig. 1). In hepatitis C cases, APRI increased significantly according to the degree of fibrosis (Fig. 1a, $P < 0.01$, Chi-square test), and FIB-4 also increased significantly (Fig. 1b, $P < 0.01$). However, in hepatitis B patients, APRI showed a slight increase without significance, whereas FIB-4 increased significantly according to histological fibrosis stages (Fig. 1c, d, $P = 0.41$ and $P < 0.01$, respectively).

The accuracy of APRI and FIB-4 was examined for diagnosis of advanced fibrosis (F3 or more) and cirrhosis (F4). The results in hepatitis C cases were presented in Fig. 2a, b. The area under the ROC curves (AUROC) of APRI was 0.781 (95% confidence interval [CI] 0.745–0.817) and FIB-4 was 0.796 (95% CI 0.761–0.831) for F3 diagnosis (Fig. 2a), whereas those of APRI was 0.824 (95% CI 0.777–0.87) and FIB-4 was 0.852 (95% CI 0.808–0.896) for F4 diagnosis (Fig. 2b). On the other hand, the diagnostic accuracy of advanced fibrosis and cirrhosis

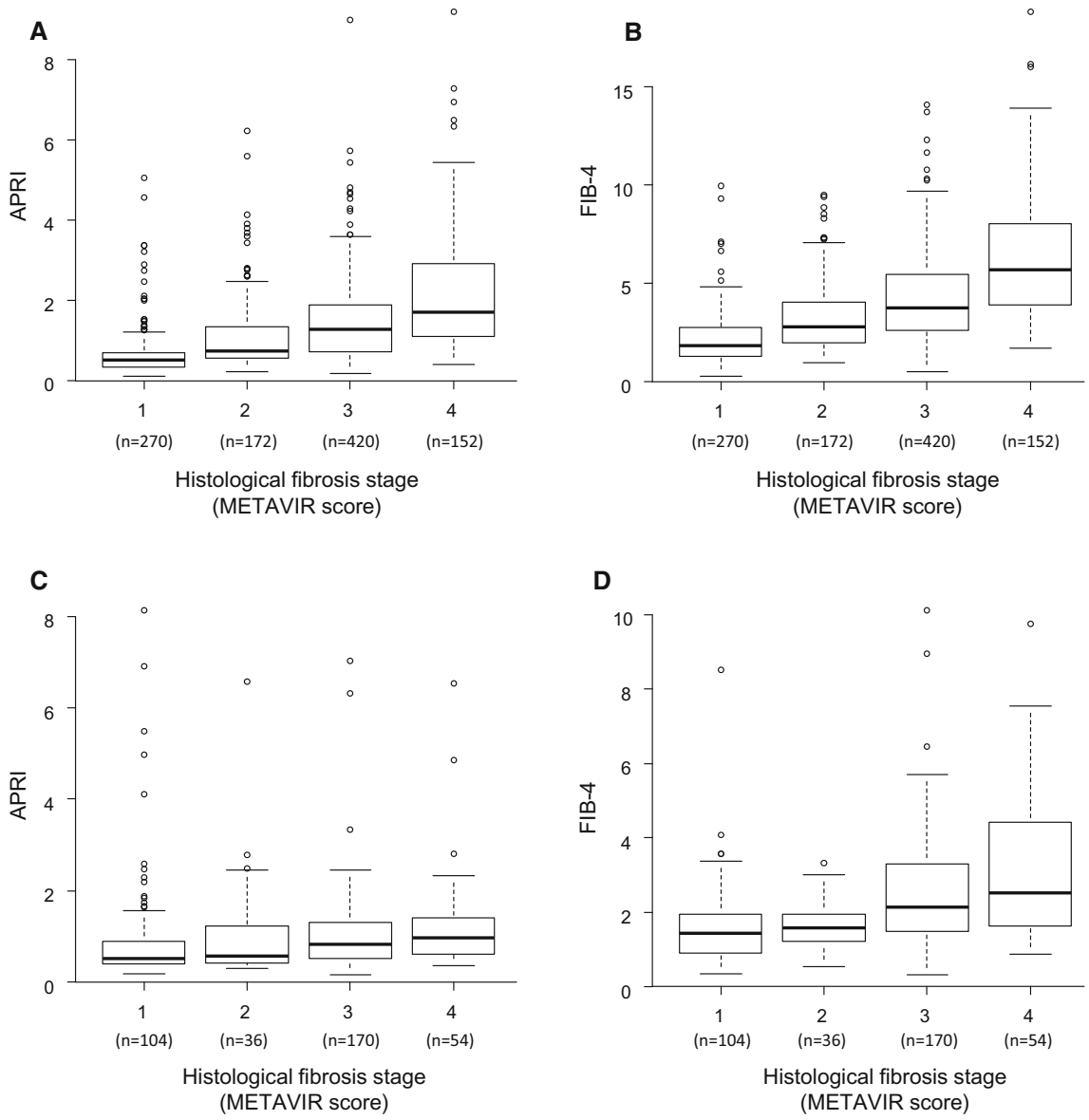

Fig. 1 APRI and FIB-4 and histological fibrosis stage. **a** APRI in hepatitis C cases significantly increased according to the METAVIR score (average value of F1 vs F2 vs F3 vs F4; 0.65 vs 1.12 vs 1.54 vs 2.24, $P < .01$, Chi-square test), and **b** FIB-4 also significantly increased (2.11 vs 3.26 vs 4.35 vs 6.28, $P < .01$). In hepatitis B patients, **c** not APRI (0.94 vs 1.09 vs 1.15 vs 1.30, $P = .41$) but **d** FIB-4 values significantly increased (1.02 vs 1.67 vs 2.59 vs 3.07, $P < .01$)

was relatively low in hepatitis B cases compared with hepatitis C patients. AUROC of APRI was 0.651 (95% CI 0.575–0.728) and FIB-4 was 0.752 (95% CI 0.679–0.826) for diagnosing advanced fibrosis (Fig. 2c), and those for diagnosing cirrhosis was 0.689 (95% CI 0.608–0.77) and 0.754 (95% CI 0.666–0.843) (Fig. 2d).

The accuracy rate was examined using cutoff values at the sensitivity of 80%, maximum Youden, and specificity of 80% (Table 2). In both hepatitis C and hepatitis B, the diagnostic accuracy for advanced fibrosis was maximized when the cutoff values with max Youden were used; cutoff values were 0.77 for APRI and 3.26 for FIB-4 in hepatitis C (accuracy rate of 73.2 and 75.0%, respectively) and 0.58 for APRI and 2.07 for FIB-4 in hepatitis B (65.2 and 71.1%). In contrast, accuracy rates became highest at the specificity of 80% for diagnosing cirrhosis; 1.53 for APRI and 4.32 for FIB-4 in hepatitis C (76.4 and 77.7%), and 1.33 for APRI and 2.49 for FIB-4 in hepatitis B (72.3 and 75.9%).

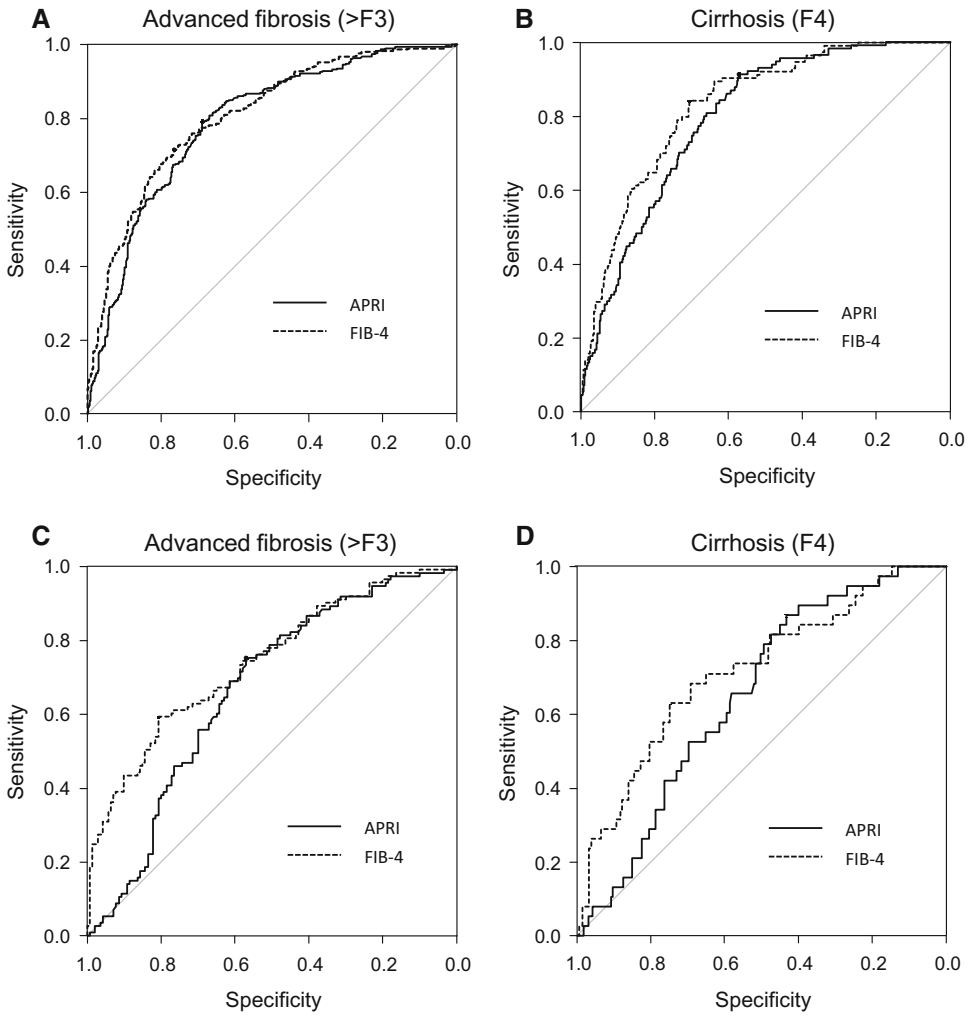

Fig. 2 ROC curves of APRI and FIB-4 for diagnosing advanced fibrosis (≥ F3) and cirrhosis (F4). In hepatitis C, **a** AUROCs of APRI and FIB-4 for ≥ F3 diagnosis were 0.792 (95% CI 0.759–0.824) and 0.807 (95% CI 0.776–0.838), and **b** those for F4 diagnosis were 0.796 (95% CI 0.757–0.834) and 0.830 (95% CI 0.793–0.867). In hepatitis B patients, **c** AUROCs of APRI and FIB-4 for > F3 diagnosis were 0.665 (95% CI 0.598–0.732) and 0.740 (95% CI 0.679–0.801), and **d** those for F4 diagnosis were 0.650 (95% CI 0.568–0.732) and 0.716 (95% CI 0.625–0.807)

Table 2 Cut off value and accuracy rate for diagnosis of Advanced fibrosis (F3 or more) and cirrhosis (F4)

	APRI score				FIB-4 index			
	Advanced fibrosis (F3 or more)		Cirrhosis (F4)		Advanced fibrosis (F3 or more)		Cirrhosis (F4)	
	Cut off	Accuracy rate	Cut off	Accuracy rate	Cut off	Accuracy rate	Cut off	Accuracy rate
HCV								
Sensitivity 80%	0.75	72.5%	1.02	68.1%	2.70	70.4%	3.65	72.3%
Best cut off (Youden index)	0.77	73.2%	0.78	62.3%	3.26	75.0%	3.61	72.6%
Specificity 80%	1.13	72.4%	1.53	76.4%	3.47	74.4%	4.32	77.7%
HBV								
Sensitivity 80%	0.52	62.5%	0.59	52.1%	1.42	61.2%	1.60	52.7%
Best cut off (Youden index)	0.58	65.2%	0.53	49.8%	2.07	71.1%	2.25	73.1%
Specificity 80%	1.09	61.3%	1.33	72.3%	2.06	70.8%	2.49	75.9%

Retrospective study of the rate of progress of APRI and FIB-4 in patients with liver cirrhosis (F4)

APRI and FIB-4 before histological diagnosis were retrospectively analyzed in cases with cirrhosis. Patients who could not be followed up for more than half a year were excluded. We were able to investigate the laboratory data of 133 cases of hepatitis C and 26 cases of hepatitis B. Patient characteristics are presented in Table 1.

Cases with hepatitis C could be traced back up to 14.5 years before diagnosis. The average APRI showed a gradual increase, with an annual increase rate of 0.09/year (Fig. 3a, $P < 0.01$, Pearson correlation coefficient). The FIB-4 also showed a gradual increase trend (Fig. 3b, annual increase rate of 0.29/year, $P < 0.01$).

In cases with hepatitis B, retrospective data could be analyzed up to 7 years before liver biopsy. There was no constant tendency observed in APRI changes along the time course (Fig. 3c). Similarly, the transition of FIB-4 did not show a certain tendency (Fig. 3d).

Prospective study of APRI and FIB-4 progression rate in histologically diagnosed F3 cases

Time course changes of APRI and FIB-4 were prospectively investigated in patients diagnosed with F3 stage by liver biopsy. Patients who could not be followed up for more than half a year were excluded; 252 cases of hepatitis C and 155 cases of hepatitis B were examined. Patient characteristics are presented in Table 1. Of the hepatitis C cases, 154 were treated after diagnosis by interferon and/or direct-acting antivirals and 98 were not treated, whereas 136 cases of hepatitis B were treated with nucleoside/nucleotide analogs and 19 cases were not treated.

APRI and FIB-4 both showed a tendency to increase according to the number of years in untreated hepatitis C cases (Fig. 4a, b); averaged annual increase rate of APRI and FIB-4 was 0.14/year and 0.40/year, respectively ($P = 0.01$ and $P < 0.01$, respectively, Pearson correlation coefficient). In contrast, any tendencies were detected in the changes of APRI and FIB-4 according to time in treated cases (Fig. 4c, d), and after eradication of hepatitis C virus by DAA regimens (supplementary Fig. 2).

The changes along time course in APRI and FIB-4 were not uniform in both treated and untreated hepatitis B groups, and there was no consistent tendency (Fig. 5).

Discussion

In this study, we sought to evaluate the feasibility of APRI and FIB-4 as an indicator of the progression of liver fibrosis in patients with viral hepatitis. Based on two different cohorts of histologically-proven patients, we found a gradual increase in APRI and FIB-4 in untreated hepatitis

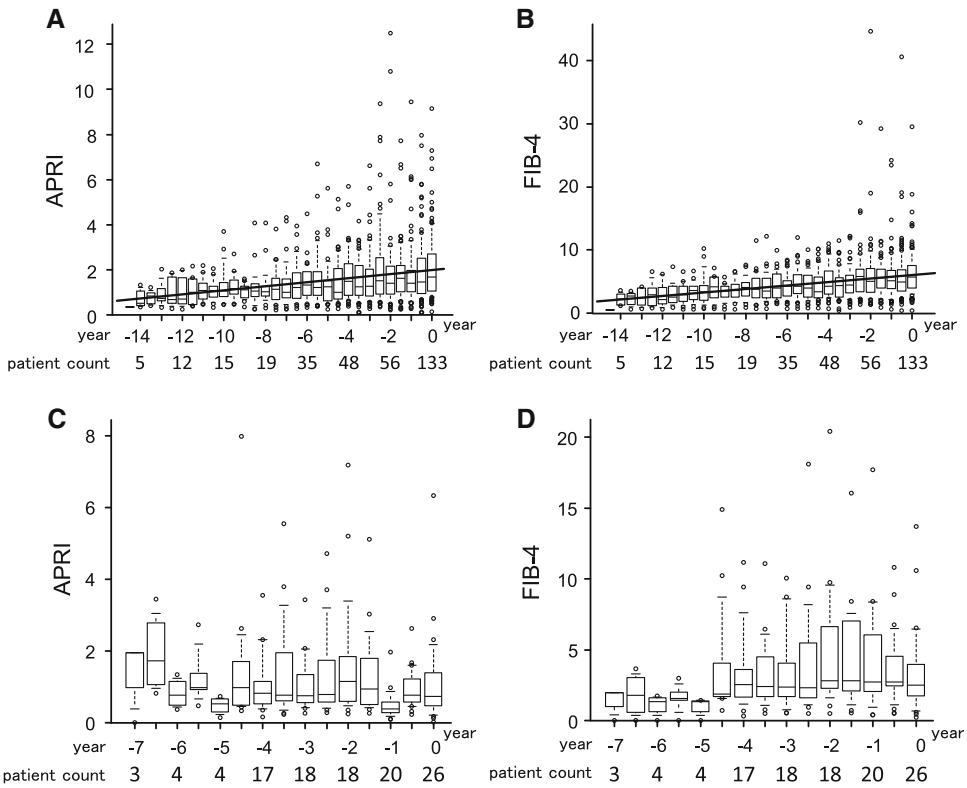

Fig. 3 Longitudinal change of APRI and FIB-4 in the retrospective surveillance of F4 patients. In hepatitis C patients, the average of **a** APRI and **b** FIB-4 was gradually increased along time course (increase rate, 0.09/ year for APRI and 0.29/ year for FIB-4, both $P < .01$, Pearson correlation coefficient). In contrast, both **c** APRI and **d** FIB-4 in hepatitis B showed no tendency over time

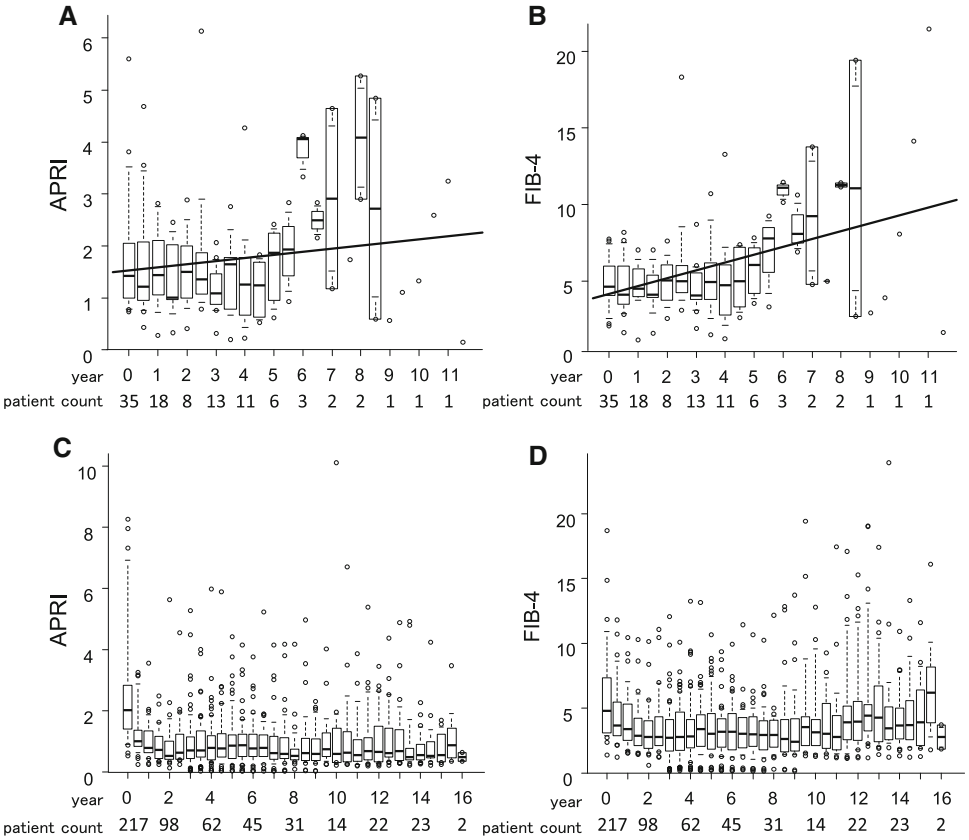

Fig. 4 Change of APRI and FIB-4 along time course in the prospective surveillance of hepatitis C patient histologically diagnosed as F3. **a** and **b** are the results of APRI and FIB-4 in untreated patients. Both biomarkers increased along the time course (increase rate of APRI and FIB-4, 0.14/year and 0.40/year, $P = 0.01$ and $P < .01$, Pearson correlation coefficient, respectively). **c** and **d** are the results in treated patients by interferon and/or direct acting antivirals, and both showed no tendencies along time course

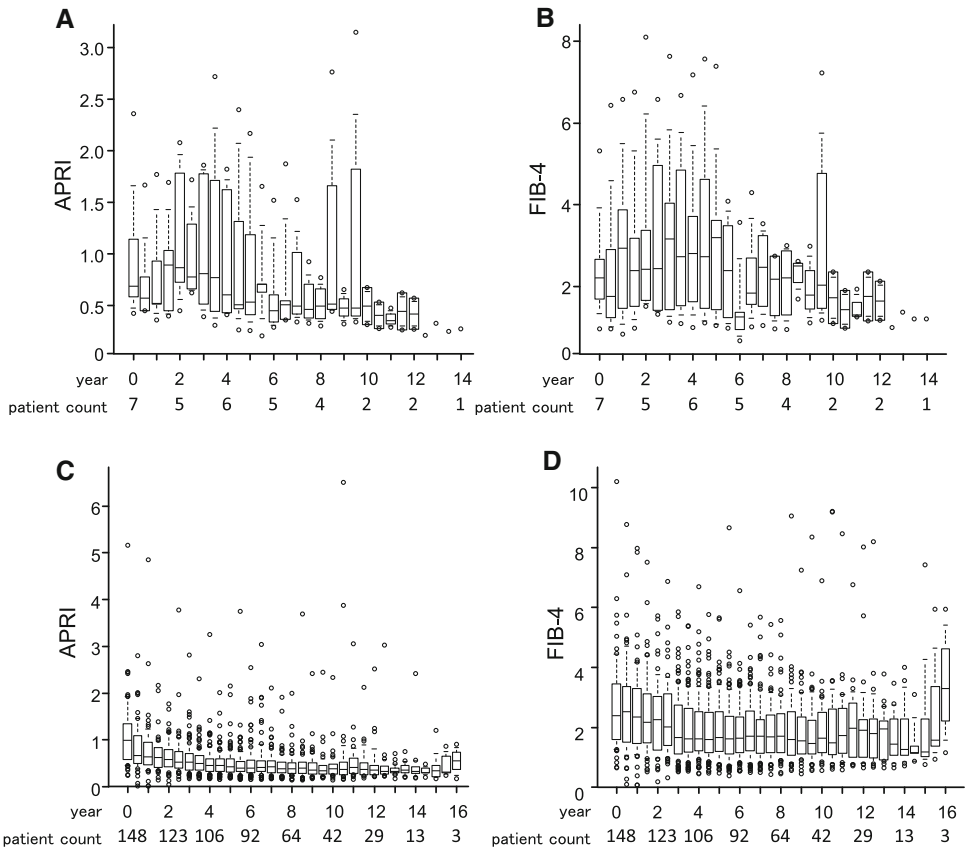

Fig. 5 Change of APRI and FIB-4 along time course in the prospective surveillance of hepatitis B patient histologically diagnosed as F3. **a** and **b** are the results in untreated patients, and **c** and **d** are the results in treated patients by nucleoside/nucleotide analogs. All series showed no tendencies along time course

C patients, while no tendencies were observed in untreated patients, especially after viral eradication. Lu et al. reported that the changes of 10-year courses of APRI and FIB-4 were marginal in 4731 chronic hepatitis C patients [15]. In their report, APRI and FIB-4 tended to increase in untreated cases, while maintained after anti-viral treatment, as same as our study. Several investigators reported the association of the changes of APRI and FIB-4 with that of histological evaluation over time. In patients with HCV and HIV co-infection who underwent repeated liver biopsy with 3-year intervals, Schmid et al. reported that APRI and FIB-4 changed slightly even in cases with histologically advanced fibrosis [16]. It is well known that liver fibrosis was improved in cases whose HCV were eradicated [17, 18]. Therefore, with further follow-up, APRI and FIB-4 may be reduced in cases who achieved viral eradication.

We found that both APRI and FIB-4 showed an accuracy rate at around 60% in the diagnosis of cirrhosis due to HBV infection, while around 70% in HCV patients. Meta-analyses reported to show that APRI and FIB-4 were moderately effective for the assessment of fibrosis stage in chronic hepatitis B [19–21]. The AUROC for diagnosing cirrhosis in HBV-infected patients was reported to be 0.6–0.7 [22, 23], which is consistent with our result.

In our study, not only in the cross-sectional but also in the longitudinal fibrosis assessment, the application of APRI and FIB-4 scores to HBV-positive patients fit harder compared to those with HCV infection. The usefulness of the longitudinal assessment of FIB-4 in hepatitis B cases was reported by Li et al. in a large cohort of 766 individuals [27]. Although the histological examination was not performed in the study, they showed an increasing tendency of FIB-4 in the long term. On the other hand, Graf et al. reported that there was no long-term change of FIB-4 in HBeAg-negative cases [28]. Sanai et al. suggested that the low viral load reduced the tutility of APRI and FIB-4 and led to lower cutoff values [24]. As for the treatment with nucleotide analogues, Kim et al. reported that 240 weeks of usage of tenofovir disoproxil fumarate (TDF) was related to the low or underestimated fibrosis stage in patients, which was confirmed by liver biopsy [25]. In contrast, Stasi et al. found that nucleoside/nucleotide analogues therapy did not influence on APRI and FIB-4 [26]. Because we were not able to stratify the groups according to viral loads or adherence of the therapies, further study is warranted. As previously showed in the last paragraph, APRI and FIB-4 are seemed to be somewhat poor at determining fibrosis in chronic hepatitis B comparing to hepatitis C. In addition, patients who did not receive treatment after biopsy may have had reasons for not receiving treatment, such as minimal inflammation in the biopsy results, or spontaneous normalization of AST and ALT levels after biopsy. In this study, the reason for untreatment was not confirmed, so it cannot be proven.

The rate of increase in both APRI and FIB-4 in the retrospective group with HCV was lower than that in the prospective group. Several plausible reasons exist for such discordance: the timing of biopsy was not controlled and histological diagnosis was not centralized. Presumably, various cases in the prospective group were enrolled as F3 stage, the state of which covers from overlapping F2 to F4. Similarly in the retrospective group, wide variation should exist from early to the late stage of F4. The APRI and FIB-4 may be relatively higher in advanced cirrhotic patients compared with those in early cases; hence the change of scores is likely to be lesser in the retrospective study group.

Various limitations exist for the present study. First, noncentralized histological diagnosis probably influenced the results. Second, the treatment response, or whether HCV was eliminated or not, was not taken into the analyses. Third, due to the small number of hepatitis B cases, we were not able to stratify the subjects based on HBeAg status or HBV DNA quantity. According to previous reports, the diagnostic power of APRI and FIB-4 for cirrhosis became weakened in cases with a low replicative state of HBV [24]. Finally, the age factor needs to be considered in the evaluation of FIB-4 as an annual transition indicator, raising the possibility of overestimation of fibrosis. As Patel et al. reviewed, noninvasive tests have limitations in the assessment of liver fibrosis even in hepatitis C [29].

The speed of fibrotic progression in the liver is a major problem for individual patients with liver disease. Hagström et al. reported that repeated FIB-4 measurement within 5 years could suggest liver disease risk in a large cohort excluding major liver diseases [30]. Tracking fibrosis markers such as FIB-4 and APRI over time may be important for predicting the future of patients even in the general public. In conclusion from our study, APRI and FIB-4 were useful for the assessment of the progression of fibrosis in untreated hepatitis C patients at an individual basis. Further study is needed for the assessment for hepatitis B patients.

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Author contributions Conceptualization: JI, MK and TK. Methodology: JI, MK and TK. Formal analysis: JI. Investigation: JI, HS, NO and MK. Resources: JI, HS, TS, NO, MK, MT, TT, NS, NE, YU, NK, SK, SN, KC, and JT. Data curation: JI, HS. Writing (original draft preparation): JI. Writing (review and editing): MK and TK.

Supervision: MK and TK. Project administration: TK. Funding acquisition: TK.

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Declarations

Conflict of interest The authors report no conflict of interest.

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