Title

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Journal

Clinical Infectious Diseases, 73(9)

ISSN

1058-4838

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Publication Date

2021-11-02

DOI

10.1093/cid/ciaa1307

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

Change in Fibrosis 4 Index as Predictor of High Risk of Incident Hepatocellular Carcinoma After Eradication of Hepatitis C Virus

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Background. It is unclear whether the fibrosis 4 index (FIB-4), a marker of liver fibrosis, at baseline and change in FIB-4 after sustained virological response (SVR) is associated with incident hepatocellular carcinoma (HCC) risk. In this study, we examined the association of incident HCC risk with baseline FIB-4 and sustained high FIB-4 (>3.25) at any time point after SVR.

Methods. A total of 3823 patients who received direct-acting antiviral treatment and achieved SVR were enrolled. The FIB-4 was measured 24 weeks after the end of direct-acting antiviral treatment and achievement of SVR (SVR24), and 1, 2, and 3 years after SVR24, after which subsequent HCC development was investigated.

Results. In patients with an FIB-4 >3.25 at SVR24 and 1, 2, and 3 years after SVR24, subsequent HCC development was significantly higher than in those with an FIB-4 ≤3.25 at each point. The rates of HCC development 1, 2, 3, and 4 years after SVR24 were significantly higher in patients with sustained FIB-4 >3.25 than in those whose FIB-4 decreased to ≤3.25 (5.4%, 9.2%, 11.7%, and 16.0%, respectively, vs 2.2%, 3.1%, 3.7%, and 4.4%; $P < .001$). The adjusted hazard ratios (95% confidence intervals) for an FIB-4 >3.25 at SVR24 and 1, 2, and 3 years later were 3.38 (2.4–4.8), 2.95 (1.9–4.7), 2.62 (1.3–5.1), and 3.37 (1.4–9.8), respectively.

Conclusions. The FIB-4 could be used to assess HCC development risk at any time after SVR, and changes in FIB-4 were associated with changes in the HCC development risk. Repeated assessments of FIB-4 could serve as a prognostic indicator of a high-risk HCC cohort that may require more intensive HCC surveillance strategy.

Keywords. FIB-4; hepatocellular carcinoma; SVR; DAA.

In chronic hepatitis C, almost all patients achieve sustained virological response (SVR) through treatment with direct-acting antiviral agents (DAAs) [1–8]. However, in some patients hepatocellular carcinoma (HCC) develops even after SVR, and strict follow-up is necessary for those with a high risk of such development [9, 10]. Liver fibrosis occurring 12–24 weeks after SVR is generally associated with HCC risk, and it is possible to identify the high-risk group by means of elastography and measurement of serum fibrosis markers [11–14]. However, long-term follow-up of all high-risk patients is difficult. In clinical practice, it is effective to narrow down high-risk groups by repeated measurement of the risk markers. Although there are reports that assess the risk of DAA treatment at the time of SVR and identify high-risk groups, few studies have examined changes in HCC risk by repeatedly measuring fibrosis markers in the long term [15, 16]. It is also unclear whether fibrosis marker levels measured at any point after the achievement of SVR are associated with the risk of carcinogenesis.

The fibrosis 4 index (FIB-4), a simple serum liver fibrosis marker calculated from age, platelet counts, and aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, has been reported to be associated with liver fibrosis and HCC risk [17–19]. Even after SVR is achieved, the FIB-4 can identify patients at high risk of carcinogenesis [15, 20]. It can be used as an index for long-term follow-up because it can be easily and repeatedly measured. Therefore, in the current study, we assessed whether it is possible to identify patient with a high risk of carcinogenesis by measuring FIB-4 at any point in time

Received 15 June 2020; editorial decision 19 August 2020; published online 5 February 2021.
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Clinical Infectious Diseases® 2021;73(9):e3349–54

DOI: 10.1093/cid/ciaa1307

after the achievement of SVR. We also determined whether changes in FIB-4 are associated with changes in HCC risk.

METHODS

Study Design

We conducted a retrospective cohort study. Fourteen institutes from the Japanese Red Cross Hospital Liver Study Group were enrolled in the study. Patients who received DAA treatment in our network of hospitals from September 2014 to July 2019 were investigated. The following categories of patients were excluded: (1) those who did not achieve SVR, (2) those who had coinfection with hepatitis B virus or human immunodeficiency virus, and (3) those with a history of HCC development. Finally, 3823 patients were enrolled in the study. The flowchart of patient selection is shown in Figure 1. The starting point for observation was set at 24 weeks after the achievement of SVR 24 weeks after the end of DAA treatment (SVR24), and any subsequent HCC development was examined. Written informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, and the study was approved by the institutional ethics review committee.

Clinical and Laboratory Data

The age and sex of each patient was recorded at SVR24. Serum samples were collected at SVR24 and 1, 2, and 3 years after SVR24. The FIB-4 was calculated according to the following formula: FIB-4 = Age [years] × AST [IU/L]/(platelets [10^9/L] × ALT [IU/L]^{½}). The cutoff value for FIB-4 was set at 3.25, according to the previously established threshold for the prediction of advanced fibrosis [17]. Patients with FIB-4 ≤3.25 or >3.25 were defined as low-risk and high-risk groups. Of all patients with FIB-4 >3.25 at SVR24, those with FIB-4 ≤3.25 at last follow-up or at the time of HCC development were classified in the improvement group, and those with FIB-4 >3.25 at last follow-up or at HCC development were classified into the nonimprovement group.

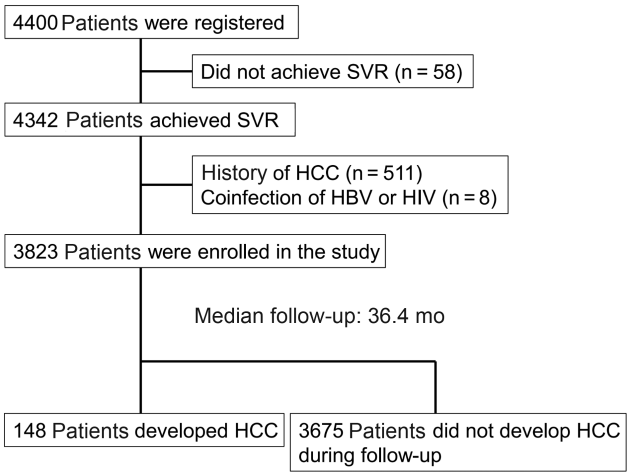

Figure 1. Flowchart of patient selection. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; SVR, sustained virological response.

HCC Surveillance and Diagnosis

Ultrasonography and blood tests, including tests for tumor markers, were performed at the start of DAA treatment and every 3–6 months for HCC surveillance. When tumor marker levels rose abnormally and/or abdominal ultrasonography revealed any lesion suggestive of HCC, computed tomography with contrast material enhancement, magnetic resonance imaging, or angiography was performed. HCC was diagnosed for tumors displaying vascular enhancement at the early phase and washout at the later phase, according to guidelines by the American Association for the Study of Liver Diseases, and the Japan Society of Hepatology. Tumor biopsy was used to diagnose tumors with nontypical imaging findings [21, 22].

Statistical Analyses

Categorical data were compared using χ^2 and Fisher exact tests, and distributions of continuous variables were analyzed with the Mann-Whitney *U* test. The change in the percentage of high-risk patients was compared using the McNemar test. The cumulative incidence of HCC was evaluated using the Kaplan-Meier method and the differences between groups were analyzed by means of log-rank tests. Adjusted hazard ratios (HRs) of HCC development were determined with the Cox proportional hazard model. Statistical significance was defined as *P* values <.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan) [23], a graphic user interface for R software, version 3.2.2 (R Foundation for Statistical Computing).

RESULTS

Patients

Patient characteristics are shown in Table 1. The median age (interquartile range) was 67 (58–75) years; 42.3% of patients were men, and 57.7% were women. The median (interquartile range) AST, ALT, and α-fetoprotein (AFP) levels were 23.0 (19–28) IU/L, 16.0 (12–22) IU/L, and 3.2 (2.2–5.0) ng/mL, all in the normal range. A total of 1000 patients (26.2%) were in the high-risk group (FIB-4 >3.25 at SVR24), and 2823 (73.8%) in the low-risk group (FIB-4 ≤3.25). Age, AST, ALT, bilirubin, γ-glutamyltransferase, and AFP levels were significantly higher in the high-risk group, while albumin levels and platelet counts were significantly lower in the high-risk than in the low-risk group. The median follow-up period was 36.4 months, and HCC developed in 148 patients during this period.

Time Course Change in FIB-4

The time-course change in the percentage of patients in the high-risk group was examined. At SVR24, 26.2% of patients

Table 1. Patient Characteristics

Characteristic	Value, Median (IQR)			
	All Patients (n = 3823)	High-risk Patients (FIB-4 >3.25) (n = 1000)	Low-risk Patients (FIB-4 ≤3.25) (n = 2823)	*P* Value
Sex, male/female, no.	1620/2203	382/618	1238/1585	.002
Age, y	67 (58–75)	74 (67–79)	65 (55–72)	< .001
AST, IU/L	23.0 (19–28)	27.0 (23–35)	21.0 (18–26)	< .001
ALT, IU/L	16.0 (12–22)	17.0 (12–24)	15.0 (12–21)	< .001
Albumin, g/dL	4.3 (4.0–4.5)	4.2 (3.9–4.4)	4.3 (4.1–4.5)	< .001
Bilirubin, mg/dL	0.7 (0.5–0.8)	0.8 (0.6–1.0)	0.7 (0.5–0.9)	< .001
GGT, IU/L	19.0 (14–28)	21.0 (16–31)	18.0 (14–26)	< .001
Platelet count, 10^9/L	169 (132–211)	112 (87–134)	188 (158–227)	< .001
AFP, ng/mL	3.2 (2.2–5.0)	4.0 (2.7–6.0)	3.0 (2.1–4.4)	< .001
FIB-4	2.31 (1.59–3.32)	4.28 (3.6–5.5)	1.89 (1.4–2.5)	< .001
Follow-up, mo	36.4 (14–42)	37.0 (15-44)	36.2 (14-42)	0.03

Abbreviations: AFP, α-fetoprotein: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis 4 index; GGT, γ-glutamyltransferase; IQR, interquartile range.

were in the high-risk group (Figure 2). This proportion changed to 25.2%, 24.7%, and 23.0% of patients, respectively, at 1, 2, and 3 years after SVR24. The percentage of high-risk patients decreased significantly over time.

Cumulative Incidence of HCC Development

We examined the cumulative incidence of HCC development at SVR24 and 1, 2, and 3 years after SVR24. The 1-, 2-, 3-, 4-, and 5-year rates of HCC development were 4.5%, 7.6%, 9.4%, 12.4%, and 16.9%, respectively, in patients at high risk (FIB-4 >3.25 at SVR24) and 0.7%, 1.4%, 2.2%, 3.3%, and 6.7% in those at low risk (FIB-4 ≤3.25 at SVR24). The incidence of HCC development was significantly higher in patients at high risk than in those at low risk ($P < .001$; Figure 3A). Similarly, the rates of HCC development 1, 2, and 3 years after SVR24 were determined using FIB-4 measured at these time points. The 1-, 2-, 3-, and 4-year rates of HCC development beginning 1 year after SVR24 in patients at high risk (FIB-4 >3.25 at 1 year after SVR24) were 3.2%, 5.5%, 9.0%, and 15.1%, respectively, significantly higher than in patients at low risk ($P < .001$; Figure 3B). The 1-, 2-, and 3-year rates of HCC development beginning 2 years after SVR24 in patients at high risk (FIB-4 >3.25 at 2 years after SVR24) were 2.0%, 6.0%, 12.2%, respectively, and the 1- and 2-year rates beginning 3 years after SVR24 in patients at high risk (FIB-4 >3.25 at 3 years after SVR24) were 4.0% and 11.2% (Figures 3C and D). The rates were significantly higher than in patients at low risk (both $P < .001$).

Patients with FIB-4 >3.25 at SVR24 were categorized into 2 groups according to the change of FIB-4. Patients with FIB-4 ≤3.25 at the last follow-up or the time of HCC development were classified in the improvement group, and those with FIB-4 >3.25 at last follow-up or the time of HCC development were classified in the nonimprovement group. Up to 28.3% of patients were in the improvement group, and 71.7% were in the nonimprovement group. HCC development rates were examined in the 2 groups. The rates of HCC development 1, 2, 3, and 4 years after SVR24 were 5.4%, 9.2%, 11.7%, and 16.0%, respectively, in the nonimprovement group and 2.2%, 3.1%, 3.7%, and 4.4% in the improvement group. The rate of HCC development was significantly higher for patients in the nonimprovement group than for those in the improvement group ($P < .001$; Figure 4).

FIB-4 at Each Time Point and Subsequent HCC Development Risk

We investigated FIB-4 at each time point and subsequent HCC development risk. Sex, albumin, bilirubin,

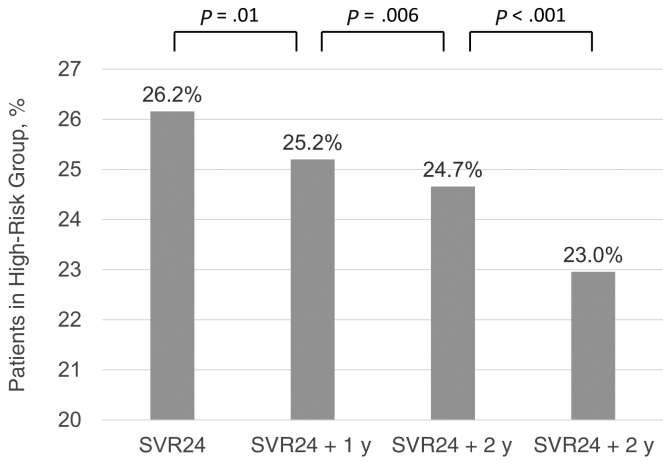

Figure 2. Change in proportion of high-risk patients (fibrosis 4 index [FIB-4] >3.25) over time. Abbreviation: SVR24, 24 weeks after achievement of sustained virological response.

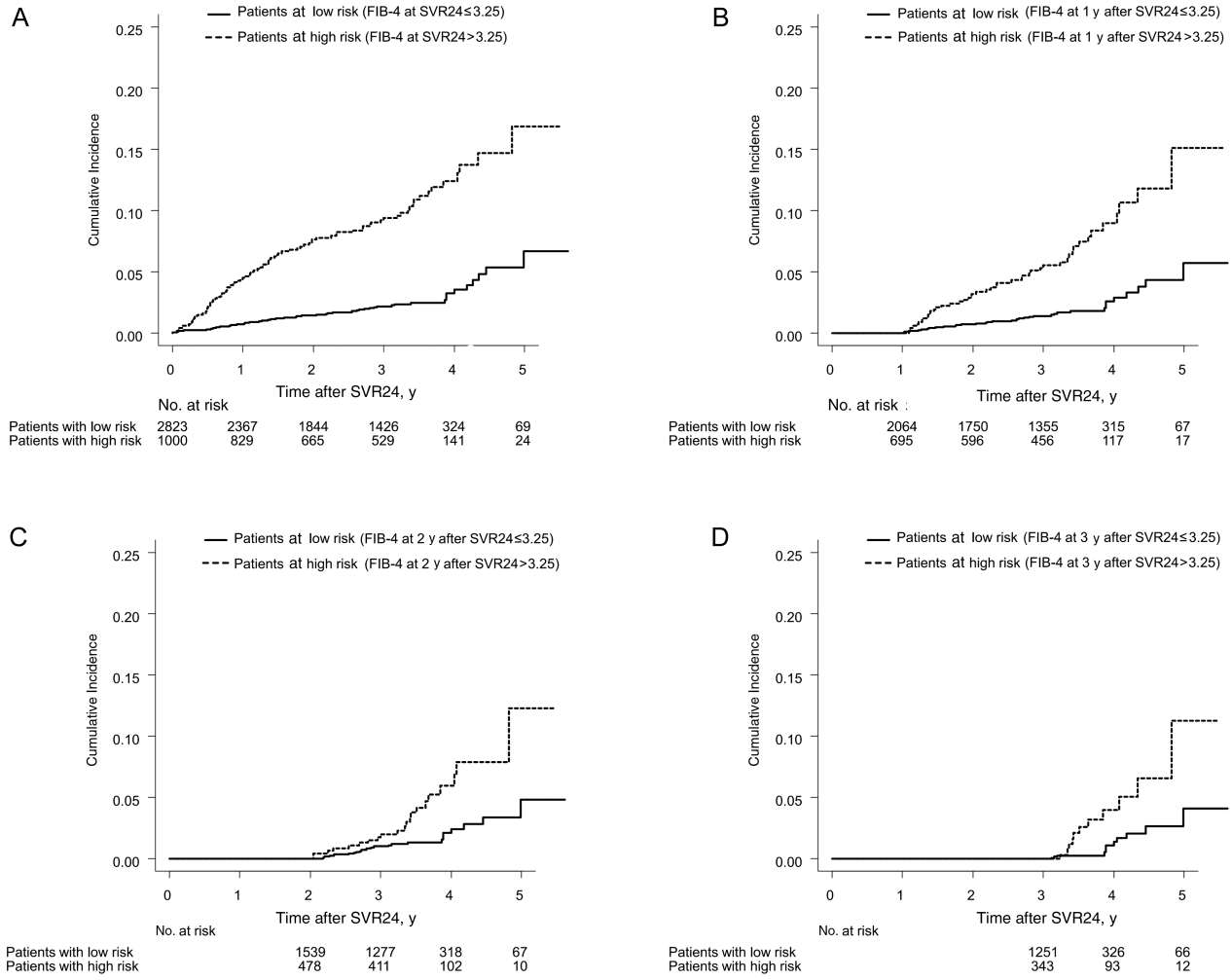

Figure 3. Cumulative rates of hepatocellular carcinoma development after sustained virological response (SVR) stratified by fibrosis 4 index (FIB-4). Patients were classified into 2 groups according to FIB-4 at 24 weeks after achievement of SVR (SVR24) (*A*) and 1 (*B*), 2 (*C*), and 3 (*D*) years after SVR24.

γ-glutamyltransferase, and AFP levels, and FIB-4 were used for the analysis. The serum markers examined at the same time with FIB-4 were each used for analysis. The adjusted HRs (95% confidence intervals) for an FIB-4 >3.25 at SVR24 and 1, 2, and 3 years after SVR24 were 3.38 (2.4–4.8; $P < .001$), 2.95 (1.9–4.7; $P < .001$), 2.62 (1.3–5.1; $P = .004$), and 3.37 (1.4–9.8; $P = .009$), respectively (Table 2).

DISCUSSION

The current study showed that the risk of HCC development can be evaluated by measuring FIB-4 at any time after SVR. The number of patients at high risk decreased over time, and if FIB-4 decreased after SVR, the risk of HCC development also decreased. By repeatedly measuring FIB-4, it is possible to continuously evaluate the cancer risk and efficiently identify high-risk patients. Because FIB-4 can be easily and repeatedly measured, they can be used as a real-time monitor of HCC risk after SVR.

There have been numerous reports assessing cancer risk and identifying high-risk groups at SVR [24–27]. It has been reported that liver fibrosis at SVR is associated with HCC development, and FIB-4, evaluating liver fibrosis, is also associated with HCC risk [15, 20]. However, the changes in liver fibrosis after SVR vary from patient to patient [28, 29], and the risk of HCC also changes over time [30]. We therefore conducted the current study, because it is necessary to reevaluate carcinogenic risk repeatedly, not only at the time of SVR but also at later follow-up points.

One new finding of this study was that the FIB-4 can be used to evaluate carcinogenic risk at any point in time. We also examined the risk of subsequent HCC development by measuring FIB-4 at SVR24 and at 1, 2, and 3 years after SVR24. The incidence of HCC development was significantly higher in the high-risk group (FIB-4 >3.25) at any given point. The adjusted HR for FIB-4 from SVR24 to 3 years after SVR24 ranged from 2.62 to 3.38, and these values were used to assess HCC risk at

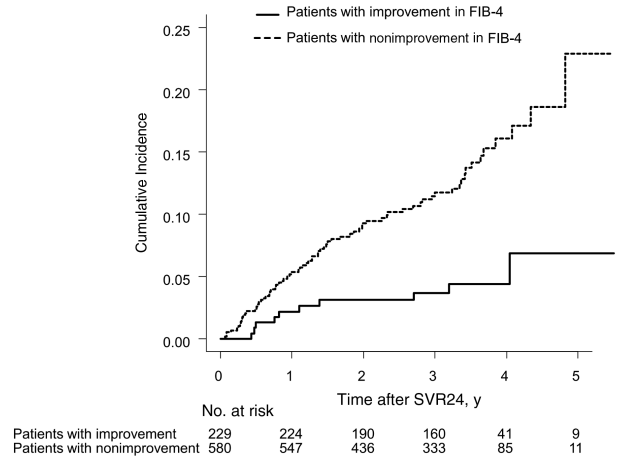

Figure 4. Cumulative incidence of hepatocellular carcinoma (HCC) development after sustained virological response (SVR) stratified by change in fibrosis 4 index (FIB-4). In patients with FIB-4 >3.25 at 24 weeks after achievement of SVR (SVR24), patients were categorized into 2 groups according to changes in FIB-4. Patients with FIB-4 ≤3.25 at last follow-up or at the time of HCC development were classified in the improvement group, and those with FIB-4 >3.25 at last follow-up or at the time of HCC development were classified in the nonimprovement group.

any point in time. The carcinogenic risk not only at SVR24 but at any given point in time can be evaluated by measuring FIB-4 repeatedly after SVR. FIB-4 can be easily and repeatedly measured, and the carcinogenic risk after SVR can be evaluated at any time. Therefore, FIB-4 can be used as a real-time monitor of carcinogenic risk.

Another finding of the current study was that the proportion of high-risk patients decreased over time after SVR. Previously, our group found that changes in FIB-4 were correlated with changes in histological fibrosis [18]. Therefore, it can be considered that the improvement in FIB-4 reflects improvement in liver fibrosis due to SVR. Similarly, in a study examining changes in FIB-4 after SVR achieved through interferon therapy, FIB-4 decreased over a 10-year period after SVR [16]. Our study also revealed that the HCC development risk decreases in patients whose FIB-4 improved from high risk (>3.25) to low risk (≤3.25). Similar results supporting our findings have been reported from a cohort of >18 000 veterans [15]. Therefore, it is useful to reevaluate the carcinogenic risk by repeatedly measuring FIB-4 and examining changes in these levels.

Table 2. Hepatocellular Carcinoma Development Risk Relative to Fibrosis 4 Index >3.25 by Time Point

FIB-4 by Time Point	Adjusted HR (95% CI)[a]	*P* Value
FIB-4 >3.25 at SVR24	3.38 (2.4–4.8)	< .001
FIB-4 >3.25 at 1 y after SVR24	2.95 (1.9–4.7)	< .001
FIB-4 >3.25 at 2 y after SVR24	2.62 (1.3–5.1)	.004
FIB-4 >3.25 at 3 y after SVR24	3.37 (1.4–9.8)	.009

Abbreviations: CI, confidence interval; FIB-4, fibrosis 4 index; HR, hazard risk; SVR24, 24 weeks after achievement of sustained virological response.

[a]Adjusted for sex, albumin, bilirubin, γ-glutamyltransferase, and α-fetoprotein levels, and FIB-4.

The major problem is that the lack of adequate HCC surveillance after SVR leads to HCC development and poor prognosis [31, 32]. High FIB-4 at the time of the achievement of SVR represents a risk of carcinogenesis, and it has been reported that the HCC risk remains even after several years [15]. Therefore, such high-risk patients require regular surveillance. However, long-term surveillance of all high-risk patients is difficult. Furthermore, regular screening of patients without cirrhosis is not cost-effective [33]. In this study, we found that the number of high-risk patients decreased over time, and the risk of carcinogenesis in patients with improvement in FIB-4 also decreased. About 30% of patients experienced a decrease in FIB-4 over 3 years, and such patients may reduce the regular HCC screening. However, about 70% of high-risk patients at SVR24 still had a high risk of HCC development after the follow-up period. The carcinogenic risk persisted in these patients, and this result supports the report that the carcinogenic risk persists for up to 4 years after SVR is achieved [15, 20]. These patients continue to require strict follow-up. Therefore, repeated assessments of FIB-4 to narrow down high-risk patients over time is an effective HCC screening strategy after the achievement of SVR.

The current study has some limitations. The observation period of 36 months was short. Further follow-up is needed to examine the usefulness of FIB-4 in long-term follow-up. HCC development was observed in patients in whom FIB-4 improved from >3.25 to ≤3.25. Furthermore, HCC also developed in patients at low risk at all time points. One important clinical issue is to identify patients who have no risk of HCC and need no further surveillance. In our study, these patients with no risk of HCC could not be identified; this was an important limitation, and further investigation of this issue is needed. In addition, some patients with low FIB-4 were lost to follow-up, and the HCC development rate may have been underestimated. All patients underwent HCC surveillance at the start of DAA treatment and every 3–6 months. Because contrast material–enhanced computed tomography or magnetic resonance imaging surveillance was not performed in all patients, patients with HCC at SVR24 might not be identified. Finally, because this was a study of a Japanese cohort with many elderly people at high risk of HCC, a validation study in other cohorts is necessary.

In conclusion, FIB-4 could be used to assess HCC development risk at any time point after SVR, and changes in FIB-4 were directly associated with changes in HCC risk. Repeated assessments of FIB-4 can be used as a real-time monitor of HCC development risk.

Notes

Author contributions. Study conception: N. T., M. K., and Y. Y. Data collection: N. T. M. Kurosaki, Y. Y., N. M., K. T., C. H., K. J., T. A., K. F.,

H. Kobashi, H. Kimura, H. Y., H. M., M. Kondo, Y. K., H. Y., Y. U., and N. I. Data analysis: N. T. and Y. Y. Manuscript drafting: N. T. Clinical revision: M. K., R. L., and N. I. Obtained funding: N. T., R. L., and N. I. Study supervision: M. K., R. L, and N. I. All authors read and approved the final version of the manuscript.

Financial support. This work was supported by the Japan Agency for Medical Research and Development (grant JP19fk0210025h0003 to N. I.), the National Institute of Environmental Health Sciences (grant 5P42ES010337 to R. L.), the National Center for Advancing Translational Sciences (grant (5UL1TR001442 to R. L.), the National Institute of Diabetes and Digestive and Kidney Diseases (grants R01DK106419, 1R01DK121378, R01 DK124318, and P30DK120515 to R. L.), the Department of Defense Peer Reviewed Cancer Research Program (grant CA170674P2 to R. L.), and the Uehara Memorial Foundation (N. T.).

Potential conflicts of interest. M. Kurosaki received lecture fees from Gilead Sciences and AbbVie. R. L. serves as a consultant or advisory board member for 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Celgene, Cirius, CohBar, DiCerna, Galmed, Gemphire, Gilead, Glympse Bio, Intercept, Ionis, Merck, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet and Viking Therapeutics, and his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, and Siemens. He is also cofounder of Liponexus. N. I. has received lecture fees from Gilead Sciences, and AbbVie. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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