A validation study of after direct-acting antivirals recommendation for surveillance score for the development of hepatocellular carcinoma in patients with hepatitis C virus infection who had received direct-acting antiviral therapy and achieved sustained virological response

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Abstract

Background and Aim: The pathogenic process underlying the development of hepatocellular carcinoma (HCC) is not yet clear in patients with hepatitis C virus (HCV) who have received direct-acting antiviral (DAA) therapy and achieved sustained virological response (SVR). This study validated a composite predictive model for HCC in these patients.

Methods: This study included 3058 patients in whom HCV was eradicated with DAA therapy. After DAAs recommendation for surveillance (ADRES) score, which is based on sex, FIB-4 index, and alpha-fetoprotein, was used as a composite predictive model for HCC development.

Results: The 1-, 3-, and 5-year cumulative incidence rates of HCC were 0.9, 4.5, and 15.2%, respectively. Multivariate analysis with Cox proportional hazards models showed that male sex (hazard ratio [HR], 2.646; 95% confidence interval [CI], 1.790–3.911), FIB-4 index >3.25 (HR, 2.891; 95% CI, 1.947–4.293), and alpha-fetoprotein >5 ng/mL (HR, 2.835; 95% CI, 1.914–4.200) are independently associated with HCC development. The incidence of HCC differed significantly by ADRES score (P < 0.001). Cox proportional hazards models showed that compared to the ADRES score 0 group, the HR for HCC development was 2.947 (95% CI, 1.367–6.354) in the ADRES score 1 group, 3.911 (95% CI, 4.339–19.380) in the ADRES score 2 group, and 20.630 (95% CI, 8.641–49.230) in the ADRES score 3 group. ADRES score had superior predictive power for HCC development compared with the FIB-4 index and alpha-fetoprotein according to time-dependent receiver operating characteristic analysis.

Conclusion: The ADRES score is useful for predicting HCC development after SVR.
Hepatocellular carcinoma risk score

Introduction

A recent study reported that hepatitis C virus (HCV) infection affects 71 million people worldwide. Chronic HCV infection may lead to cirrhosis, including decompensated cirrhosis with ascites, encephalopathy, or bleeding of varices in 10–20% of patients. In addition, chronic HCV infection may also cause hepatocellular carcinoma (HCC). In Japan, 1.0–1.5 million individuals have chronic HCV infection. In approximately 55% of patients, HCC is associated with HCV infection. 

Eradication of HCV with interferon-based antiviral therapy has been reported to decrease the severity of hepatic fibrosis and the incidence of liver-related events such as decompensated cirrhosis and HCC. A sustained virological response (SVR) to antiviral therapy is defined as eradication of HCV RNA. SVR leads to decreased liver inflammation, for example, normalization of alanine aminotransferase levels. Several studies have reported that patients who achieve SVR generally have a good clinical course and outcome. Although HCC is rare in this population, it sometimes occurs. Clinical risk factors for the development of HCC in patients after SVR include advanced age, male sex, high α-fetoprotein level, low albumin level, and advanced liver fibrosis. Direct-acting antivirals (DAAs) have recently been developed to treat patients with chronic HCV infection. These drugs have resulted in higher rates of SVR, shorter and simpler therapeutic regimens, and fewer treatment-related adverse events than with interferon-based antiviral therapy. Several studies have reported that patients who achieve SVR with DAA therapy also have a lower incidence of decompensated cirrhosis and HCC, respectively. However, there has been insufficient study of clinical risk factors for the development of HCC in patients with HCV who have achieved SVR with DAA therapy.

Several composite models such as aMAP score and GES score have been reported as predictors of HCC development in patients with HCV who have received DAA therapy and achieved SVR. The after DAAs recommendation for surveillance (ADRES) score was developed as a composite model for predicting HCC development in the short term among patients with HCV who have received DAA therapy and achieved SVR in Japan. However, this model has not been sufficiently validated in another HCV cohort that has achieved SVR with DAA therapy.

In this study, we validated the utility of the ADRES score for predicting the HCC development in patients who have received DAA therapy and achieved SVR. To compare the ability of the ADRES score, FIB-4 index, and α-fetoprotein in predicting HCC development, we generated time-dependent receiver operating characteristic (ROC) curves for censored data and evaluated the areas under the ROC curves (AUROCs).

Materials and methods

A nationwide multicenter registry cohort involving 15 institutions from the Japanese Red Cross Hospital Liver Study Group was registered as a derivation cohort. A total of 5863 patients with HCV received DAA-based therapy at our group’s institutions between September 2014 and March 2020. Of these, 3058 patients met the following eligibility criteria and were enrolled in this study: (i) achievement of SVR, (ii) no history of HCC, (iii) no evidence of HCC development for at least 6 months after SVR, and (iv) no missing clinical data.

The indications for DAA therapy and DAA regimens were based on the Japan Society of Hepatology guidelines for the management of HCV infection. SVR was defined as undetectable serum HCV RNA at 24 weeks after the end of treatment (SVR24). The date of SVR24 was defined as the start of follow-up. The end of follow-up was defined as the date of the final visit for patients who had not developed HCC, and as the date of HCC diagnosis for patients who developed HCC during follow-up.

Written informed consent was obtained from each patient before study enrollment. The study protocol conformed to the ethical guidelines in the Declaration of Helsinki. The study was approved by the institutional ethics review committee (approval number, 2022).

Clinical and laboratory data. Patient age and sex were recorded at entry into the study. Serum samples were collected at the time of SVR. The FIB-4 index was calculated according to the following formula: aspartate aminotransferase [IU/L] × age [years]/platelet count [10^9/L] × alanine aminotransferase [IU/L]^{1/2}.

HCC surveillance and diagnosis. Abdominal ultrasonography and blood tests, including tests for tumor markers, were carried out at the start of DAA treatment, SVR, and every 3–6 months thereafter for HCC surveillance. When tumor marker levels became higher than the reference range or ultrasonography suggested any lesions that were suspicious for HCC, contrast-enhanced computed tomography, magnetic resonance imaging, contrast-enhanced ultrasonography with perflubutane, angiography,
or any combination of these procedures were performed. HCC was diagnosed for tumors displaying vascular enhancement during the early phase and washout during a later phase based on the guidelines published 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.

**ADRES score.** The ADRES score was based on sex, FIB-4 index, and α-fetoprotein level upon achieving SVR, based on a previous report. One point is given for each parameter: male sex, FIB-4 index > 3.25, and α-fetoprotein > 5 ng/mL. The ADRES score was defined as the sum of the points.

**Statistical analysis.** Continuous variables are expressed as medians (interquartile range). The Kruskal–Wallis test was used for continuous variables. The chi-square test with Fisher’s exact test was used for categorical variables. Actuarial analysis of cumulative incidence of HCC was performed using the Kaplan–Meier method, and differences were tested using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) for the development of HCC. We performed multivariate analysis using the following covariates, which are factors in the ADRES score: sex, FIB-4 index, and α-fetoprotein. We used the same cut-off values for FIB-4 index and α-fetoprotein as in the definition of ADRES score. Time-dependent ROC curves for HCC development were obtained using the nearest neighbor estimation method (span, 0.05) using ADRES score, FIB-4 index, and α-fetoprotein. We calculated sensitivity and specificity at each survival time using the maximum Youden index (sensitivity + specificity - 1) as the cut-off level.

Statistical significance was defined as \( P < 0.05 \). Statistical analyses were performed with EZR, version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

**Results**

**Patient characteristics.** The characteristics of the 3058 patients are shown in Table 1. There were 1807 (59.1%) females

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**Table 1** Characteristics of study patients \( (n = 3058) \)

| Characteristic                  | 0 (n = 998) | 1 (n = 1409) | 2 (n = 567) | 3 (n = 84) | \( P \) value |
|--------------------------------|-------------|-------------|-------------|------------|--------------|
| Age (years) \(^\d\)           | 68.0 (59.4–76.0) | 68.5 (59.4–75.5) | 72.0 (64.0–78.0) | 71.0 (60.9–76.0) | <0.001 |
| Sex (female/male)              | 1807/1251   | 618/791     | 191/376     | 0/84       | <0.001 |
| Aspartate aminotransferase (IU/L) \(^\d\) | 23 (19–28) | 23 (19–27) | 27 (22–35) | 32 (26–43) | <0.001 |
| Alanine aminotransferase (IU/L) \(^\d\) | 15 (12–21) | 16 (12–22) | 18 (13–27) | 22 (16–31) | <0.001 |
| Total bilirubin (mg/dL) \(^\d\) | 0.7 (0.5–0.9) | 0.7 (0.5–0.9) | 0.8 (0.6–1.0) | 0.9 (0.7–1.2) | <0.001 |
| Platelet count \( (\times 10^{12}/\text{mm}^3) \) \(^\d\) | 16.5 (13.0–20.6) | 16.8 (13.3–20.4) | 12.1 (8.7–15.3) | 9.3 (7.2–12.8) | <0.001 |
| α-fetoprotein (ng/mL) \(^\d\) | 3.2 (2.2–4.9) | 3.5 (2.4–4.9) | 5.5 (3.0–7.3) | 7.9 (6.0–9.5) | <0.001 |
| HCV genotype (1/2/other or unknown) | 2203/838/17 | 2203/838/17 | 191/376/84 | 191/376/84 | <0.001 |
| FIB-4 index \(^\d\) | 2.41 (1.65–3.45) | 2.41 (1.65–3.45) | 2.41 (1.65–3.45) | 2.41 (1.65–3.45) | <0.001 |
| ADRES score (0/1/2/3) | 998/1409/567/84 | 998/1409/567/84 | 998/1409/567/84 | 998/1409/567/84 | <0.001 |
| Developed HCC                  | 8           | 36          | 49          | 14         | <0.001 |
| Follow-up duration (months) \(^\d\) | 2.4 (0.9–3.1) | 2.4 (1.0–3.1) | 2.5 (1.0–3.2) | 1.9 (0.8–3.1) | 0.008 |

\(^\d\)Values are expressed as medians (interquartile range).

ADRES, after direct-acting antivirals recommendation for surveillance; HCC, hepatocellular carcinoma.

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**Figure 1** Cumulative incidence of HCC. The 1-, 3-, and 5-year cumulative incidence rates for HCC were 0.9, 4.5, and 15.2%, respectively. HCC, hepatocellular carcinoma.
and 1251 (40.9%) males, with a median age of 68.0 (59.4–76.0) years. The median α-fetoprotein level and FIB-4 index were 3.2 (2.2–4.9) ng/mL and 2.41 (1.65–3.45), respectively. There were 998 (32.6%) patients with ADRES score 0; 1409 (46.1%) with ADRES score 1; 567 (18.5%) with ADRES score 2; and 84 (2.7%) with ADRES score 3. Median follow-up was 2.4 (0.9–3.1) years. During the follow-up period, 107 patients developed HCC.

Table 2 shows the characteristics of the study patients by ADRES score. There were significant differences in all clinical factors by ADRES score.

**Cumulative incidence of HCC.** Figure 1 shows the Kaplan–Meier curve for the cumulative incidence of HCC in all study patients. The 1-, 3-, and 5-year cumulative incidence rates for HCC were 0.9, 4.5, and 15.2%, respectively.

**Multivariate analysis.** Multivariate analysis with Cox proportional hazards modeling, including the covariates of sex, FIB-4 index, and α-fetoprotein showed that male sex (HR, 2.646; 95% confidence interval [CI], 1.790–3.911; \( P < 0.001 \)), FIB-4 index >3.25 (HR, 2.891; 95% CI, 1.947–4.293; \( P < 0.001 \)), and α-fetoprotein >5 ng/mL (HR, 2.835; 95% CI, 1.914–4.200; \( P < 0.001 \)) were independently associated with HCC development.

**Cumulative incidence of HCC based on the ADRES score.** Figure 2 shows the cumulative incidence of HCC for the study patients by ADRES score \(( P < 0.001 \), log-rank test). The incidence of HCC differed significantly between patients with ADRES score 0 versus 1 \(( P = 0.023 \)), ADRES score 0 versus 2 \(( P < 0.001 \)), ADRES score 0 versus 3 \(( P < 0.001 \)), ADRES score 1 versus 2 \(( P < 0.001 \)), ADRES score 1 versus 3 \(( P < 0.001 \)), and ADRES score 2 versus 3 \(( P = 0.042 \)), after Bonferroni correction. Univariate Cox proportional hazards models showed that compared with the ADRES score 0 group, the HR for HCC development was 2.947 (95% CI, 1.367–6.354) \(( P = 0.005 \)) for the ADRES score 1 group, 9.171 (95% CI, 4.339–19.380) \(( P < 0.001 \)) for the ADRES score 2 group, and 20.630 (95% CI, 8.641–49.230) \(( P < 0.001 \)) for the ADRES score 3 group.

In addition, we analyzed the cumulative incidence of HCC for the study patients by ADRES score who stratified with HCV genotype. Figures S1 and S2, Supporting information show the cumulative incidence of HCC for the study patients with HCV genotype 1 and 2 by ADRES score \(( P < 0.001 \) and <0.001, log-rank test).

**Time-dependent ROC analysis for development of HCC.** Figure 3a–e show the ROC curves (dotted lines) of
Figure 3  Time-dependent ROC curves of ADRES score, FIB-4 index, and α-fetoprotein at SVR24 for HCC development after the start of follow-up. (a) Year 1: The AUROCs of ADRES score (dotted line), FIB-4 index (solid line), and α-fetoprotein (dashed line) were 0.775, 0.624, and 0.700, respectively. (b) Year 2: The AUROCs of ADRES score (dotted line), FIB-4 index (solid line), and α-fetoprotein (dashed line) were 0.752, 0.628, and 0.672, respectively. (c) Year 3: The AUROCs of ADRES score (dotted line), FIB-4 index (solid line), and α-fetoprotein (dashed line) were 0.711, 0.623, and 0.637, respectively. (d) Year 4: The AUROCs of ADRES score (dotted line), FIB-4 index (solid line), and α-fetoprotein (dashed line) were 0.731, 0.590, and 0.630, respectively. (e) Year 5: The AUROCs of ADRES score (dotted line), FIB-4 index (solid line), and α-fetoprotein (dashed line) were 0.808, 0.699, and 0.678, respectively. ADRES, after direct-acting antivirals recommendation for surveillance; AUROC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; SVR, sustained virological response.
ADRES score for the development of HCC at years 1–5, respectively, after the start of follow-up using time-dependent ROC analysis. The AUCs at years 1, 2, 3, 4, and 5 were 0.775, 0.752, 0.711, 0.731, and 0.808, respectively. The sensitivity and specificity (optimal ADRES score cut-off level) for predicting the development of HCC were 65.4 and 79.1% (ADRES score 1) at year 1, 60.6 and 79.7% (ADRES score 1) at year 2, 52.8 and 80.2% (ADRES score 1) at year 3, 55.5 and 81.6% (ADRES score 1) at year 4, and 69.5 and 84.8% (ADRES score 1) at year 5, respectively. Table 3 shows the sensitivity and specificity for predicting the development of HCC by ADRES score at years 1–5, after the start of follow-up using time-dependent ROC analysis.

Figure 3a–e show the ROC curves (solid lines) of FIB-4 index for the development of HCC at years 1–5, respectively, after the start of follow-up using time-dependent ROC analysis. The AUROCs at years 1, 2, 3, 4, and 5 were 0.624, 0.628, 0.623, 0.590, and 0.699, respectively. The sensitivity and specificity (optimal FIB-4 index cut-off level) for predicting the development of HCC were 46.0 and 75.0% (FIB-4 index, 3.44) at year 1, 71.4 and 48.1% (FIB-4 index, 2.33) at year 2, 53.5 and 65.7% (FIB-4 index, 2.98) at year 3, 36.8 and 80.0% (FIB-4 index, 3.73) at year 4, and 67.4 and 71.9% (FIB-4 index, 3.09) at year 5.

Figure 3a–e show the ROC curves (dashed lines) of α-fetoprotein for the development of HCC at years 1–5, respectively, after the start of follow-up using time-dependent ROC analysis. The AUROCs at 1, 2, 3, 4, and 5 years were 0.700, 0.672, 0.637, 0.630, and 0.678, respectively. The sensitivity and specificity (optimal α-fetoprotein cut-off level) for predicting the development of HCC were 87.6 and 47.9% (α-fetoprotein, 3.0 ng/mL) at year 1, 88.1 and 39.3% (α-fetoprotein, 2.8 ng/mL) at year 2, 65.3 and 58.3% (α-fetoprotein, 3.6 ng/mL) at year 3, 77.2 and 49.5% (α-fetoprotein, 3.0 ng/mL) at year 4, and 80.6 and 50.2% (α-fetoprotein, 3.0 ng/mL) at year 5, respectively.

Figure 4 shows the AUROCs of ADRES score, FIB-4 index, and α-fetoprotein for the development of HCC by year for the start of follow-up. ADRES score (dotted line) had higher predictive power for the development of HCC than the FIB-4 index (solid line) and α-fetoprotein (dashed line) for all years. ADRES, after direct-acting antivirals recommendation for surveillance; AUROC, area under the receiver operating characteristic curve; HCC, hepatocellular carcinoma.

Table 3  Sensitivity and specificity for predicting HCC development by ADRES score at years 1–5 according to time-dependent ROC analysis

| Year | ADRES score | Sensitivity (%) | Specificity (%) |
|------|-------------|----------------|-----------------|
| 1    | 0           | 94.0           | 32.8            |
|      | 1           | 63.7           | 79.1            |
|      | 2           | 23.5           | 97.4            |
|      | 3           | 0.0            | 100.0           |
| 2    | 0           | 93.0           | 33.3            |
|      | 1           | 58.9           | 79.7            |
|      | 2           | 16.5           | 97.6            |
|      | 3           | 0.0            | 100.0           |
| 3    | 0           | 89.2           | 33.7            |
|      | 1           | 51.0           | 80.1            |
|      | 2           | 12.0           | 97.7            |
|      | 3           | 0.0            | 100.0           |
| 4    | 0           | 86.3           | 34.5            |
|      | 1           | 47.3           | 81.3            |
|      | 2           | 11.0           | 98.1            |
|      | 3           | 0.0            | 100.0           |
| 5    | 0           | 86.5           | 36.0            |
|      | 1           | 51.1           | 84.0            |
|      | 2           | 12.3           | 99.0            |
|      | 3           | 0.0            | 100.0           |

ADRES, after direct-acting antivirals recommendation for surveillance; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.
the first 5 years after the start of follow-up using time-dependent ROC analysis. ADRES score had higher predictive power for the development of HCC than the FIB-4 index and α-fetoprotein for all years.

Discussion

In this multicenter study with a large number of patients with HCV who had received DAA therapy and achieved SVR, Cox proportional hazards modeling that included sex, FIB-4 index, and α-fetoprotein as covariates showed that all of these factors are independently associated with the development of HCC after SVR. In addition, based on the time-dependent ROC analysis, we clarified that ADRES score has superior predictive power for the development of HCC after SVR than the FIB-4 index and α-fetoprotein. Therefore, the ADRES score, which is based on sex, FIB-4 index, and α-fetoprotein, was considered a reasonable model for predicting HCC development in patients with HCV who have received DAA therapy and achieved SVR.

Clinical factors such as age, sex, α-fetoprotein, albumin, total bilirubin, platelet count, and mac2 binding protein glycosylation isomer have been reported as predictors for HCC development in patients with HCV who have achieved SVR with DAA therapy.\(^\text{34-38}\) In addition, FIB-4 index, which is a simple composite index, has been validated to be associated with liver fibrosis in many studies of patients with HCV infection, hepatitis B virus infection, and nonalcoholic fatty liver disease. The FIB-4 index has been reported as a predictor for HCC development in patients with HCV who had achieved SVR with DAA therapy.\(^\text{36,37}\) Watanabe et al.\(^\text{36}\) investigated predictors for the development of HCC in 1174 patients with HCV who had achieved SVR with DAA therapy. The median follow-up was 1.5 years. They found that male sex (HR, 2.46; 95% CI, 1.01–6.03), post-treatment FIB-4 index (per 1 unit) (HR, 1.09; 95% CI, 1.02–1.18), and posttreatment α-fetoprotein (per 1 ng/mL) (HR, 1.11; 95% CI, 1.05–1.17) were independent factors that contribute to the development of HCC after DAA therapy in the multivariate analysis.\(^\text{36}\) Iio et al.\(^\text{37}\) investigated the predictors for HCC development in 1029 HCV patients who had achieved SVR with DAA therapy. The median follow-up was not available. They found that the tolloloid like 1 gene variant at rs17047200 AT/TT (HR, 2.80; 95% CI, 1.13–6.92), posttreatment FIB-4 index >2.67 (HR, 3.89; 95% CI, 1.10–13.82), and posttreatment α-fetoprotein >4.6 ng/mL (HR, 3.22 95% CI, 1.19–8.67) are independent factors that contribute to the development of HCC after DAA therapy in the multivariate analysis.\(^\text{37}\) In this study, we also found that male sex, high posttreatment FIB-4 index, and high posttreatment α-fetoprotein levels are independent risk factors associated with the development of HCC after DAA therapy. The advantage of this study was the inclusion of more patients than previous reports.\(^\text{36,37}\) Another advantage was the inclusion of patients with a longer follow-up period than in the study by Watanabe et al.\(^\text{36}\)

Hiraoka et al.\(^\text{28}\) reported developing the ADRES score as a composite model using clinical factors in 1069 patients with HCV who had received DAAAs and achieved SVR in Japan. The mean follow-up in their study was 1.4 years.\(^\text{28}\) They reported that the cumulative incidence of HCC at 1 and 2 years after SVR was 0.0 and 0.0% for patients with ADRES score 0, 0.5 and 1.6% for patients with ADRES score 1, 8.4 and 13.4% for patients with ADRES score 2, and 18.0 and 32.8% for patients with ADRES score 3, respectively \((P < 0.001)\).\(^\text{28}\) In this study, we found significant differences in the proportion of patients who developed HCC by ADRES score \((P < 0.001, \text{log-rank test})\). In addition, we found that the development of HCC differed significantly by ADRES score with Bonferroni correction for multiple comparisons. We validated the utility of this composite model for predicting the development of HCC in more patients with HCV and SVR with DAAs and longer follow-up than in the original study.\(^\text{28}\) Furthermore, we demonstrated that all the factors that make up the ADRES score (i.e., sex, FIB-4 index, and α-fetoprotein) are independently associated with the development of HCC in patients with HCV who had been treated with DAAs and achieved SVR.

ROC analysis is generally used to assess the discriminatory power of a continuous variable for a binary disease outcome (e.g., HCC development). However, clinical outcomes of many diseases have a time-dependent factor. Therefore, time-dependent ROC curve analysis has been introduced to assess the predictive power of diagnostic indicators for time-dependent disease outcomes. No previous studies have used time-dependent ROC analysis to assess a clinical composite model in terms of its association with HCC development in patients with HCV who had received DAA therapy and achieved SVR. In this study, we used time-dependent ROC analysis to show that ADRES score is superior to a single biomarker, FIB-4 index, or α-fetoprotein, in terms of predicting the development of HCC more than 5 years after SVR due to DAA therapy. In addition, we clarified the sensitivity and specificity of the ADRES score for HCC development at each year in the present cohort using time-dependent ROC analysis. We found that the optimal ADRES score cut-off level was 1 each year after SVR. Therefore, patients with ADRES score of 1 or higher are considered to need strict HCC surveillance after SVR.

The main limitations of this study include its hospital-based study population and retrospective nature. Although this study included a large number of patients from multiple liver disease centers across Japan, further prospective studies with community-based subjects are warranted. In addition, the median follow-up duration in this study was only approximately 2.5 years. Studies with longer-term follow-up should be performed in the future to validate the ADRES score. Finally, there were only six patients with follow-up period over 5 years in this study. Therefore, it was possible that the number of patients was too small to accurately analyze the time-dependent ROC for the development of HCC at year 5.

In conclusion, the ADRES score, which is a composite model of simple clinical parameters, was useful for predicting HCC development in patients with HCV who had received DAA therapy and achieved SVR. In addition, this score had better predictive ability for HCC development than the FIB-4 index or α-fetoprotein in patients who had achieved SVR with DAA therapy. Further studies should be conducted to confirm these findings in other populations.

References

1. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol. Hepatol. 2017; 2: 161–76.
2 Westbrook RH, Dusheiko G. Natural history of hepatitis C. J. Hepatol. 2014; 61: 558–68.

3 Tateishi R, Uchino K, Fujihara N et al. A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011–2015 update. J. Gastroenterol. 2019; 54: 367–76.

4 Marcellin P, Boyer N, Gervais A et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann. Intern. Med. 1997; 127: 875–81.

5 Ikeda K, Saitoh S, Arase Y et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology. 1999; 29: 1124–30.

6 Okanoue T, Itoh Y, Minami M et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. J. Hepatol. 1999; 30: 653–9.

7 Cardoso AC, Moucari R, Figueiredo-Mendes C et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J. Hepatol. 2010; 52: 652–7.

8 Iwasaki Y, Takaguchi K, Ikeda H et al. Risk factors for hepatocellular carcinoma in Hepatitis C patients with sustained virologic response to interferon therapy. Liver Int. 2004; 24: 603–10.

9 Tokita H, Fukui H, Tanaka A et al. Risk factors for the development of hepatocellular carcinoma among patients with chronic hepatitis C who achieved a sustained virological response to interferon therapy. J. Gastroenterol. Hepatol. 2005; 20: 752–8.

10 Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann. Intern. Med. 2013; 158: 329–37.

11 Asahina Y, Tsuchiya K, Nishimura T et al. α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology. 2013; 58: 1253–62.

12 Akahane T, Kurosaki M, Itakura J et al. Real-world efficacy and safety of sofosbuvir + ribavirin for hepatitis C genotype 2: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. Hepatol. Res. 2019; 49: 264–70.

13 Mashiba T, Joko K, Kurosaki M et al. Real-world efficacy of elbasvir and grazoprevir for hepatitis C virus (genotype 1): a nationwide, multicenter study by the Japanese Red Cross Hospital Liver Study Group. Hepatol. Res. 2019; 49: 1114–20.

14 Tahata Y, Sakamori R, Urabe A et al. Clinical outcomes of direct-acting antiviral treatments for patients with hepatitis C after hepatocellular carcinoma are equivalent to interferon treatment. Hepatol. Res. 2020; 50: 1118–27.

15 European Association for the Study of the Liver, Clinical Practice Guidelines Panel: Chair, EASL Governing Board representative, Panel members. EASL recommendations on treatment of hepatitis C: final update of the series. J. Hepatol. 2020; 73: 1170–218.

16 Kanwal F, Kramer J, Ash SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology. 2017; 153: 996–1005.

17 Nahon P, Layeze R, Bourcier V et al. Incidence of hepatocellular carcinoma after direct antiviral therapy for HCV in patients with cirrhosis included in surveillance programs. Gastroenterology. 2018; 155: 1436–50.

18 Janjua NZ, Wong S, Darvishian M et al. The impact of SVR from direct-acting antiviral- and interferon-based treatments for HCV on hepatocellular carcinoma risk. J. Viral Hepat. 2020; 27: 781–93.

19 Seko Y, Moriguchi M, Hara T et al. Presence of varices in patients after hepatitis C virus eradication predicts deterioration in the FIB-4 index. Hepatol. Res. 2019; 49: 473–8.

20 Inoue-Shinomiya E, Murakawa M, Asahina Y et al. Association of serum interferon-λ3 levels with hepatocarcinogenesis in chronic hepatitis C patients treated with direct-acting antiviral agents. Hepatol. Res. 2019; 49: 500–11.

21 Asahina Y, Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. JSH guidelines for the management of hepatitis C virus infection, 2019 update; protective effect of antiviral therapy against hepatocarcinogenesis. Hepatol. Res. 2020; 50: 775–90.

22 Nagaoki Y, Imamura M, Teraoka Y et al. Impact of viral eradication by direct-acting antivirals on the risk of hepatocellular carcinoma development, prognosis, and portal hypertension in hepatitis C virus-related compensated cirrhosis patients. Hepatol. Res. 2020; 50: 1222–33.

23 Yoshiji H, Nagoshi S, Akahane T et al. Evidence-based clinical practice guidelines for liver cirrhosis 2020. Hepatol. Res. 2021; 51: 725–49.

24 Yamashita Y, Joshta S, Sugiuara A et al. aMAP score prediction of hepatocellular carcinoma occurrence and incidence-free rate after a sustained virologic response in chronic hepatitis C. Hepatol. Res. 2021; 51: 933–42.

25 Shiga G, Waked I, Soliman R et al. GES: a validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals. Liver Int. 2020; 40: 2828–33.

26 Hiraoka A, Kumada T, Ogawa C et al. Proposed a simple score for recommendation of scheduled ultrasonography surveillance for hepatocellular carcinoma after direct acting antivirals: multicenter analysis. J. Gastroenterol. Hepatol. 2019; 34: 436–41.

27 Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics. 2005; 61: 92–105.

28 Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update. Hepatol. Res. 2020; 50: 791–816.

29 Sterling RK, Lissen E, Clumeck N et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatol. 2006; 43: 1317–25.

30 Heimbach JK, Kulik LM, Finn RS et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67: 358–80.

31 Kokudo N, Takemura N, Hasegawa K et al. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol. Res. 2019; 49: 1109–13.

32 Youden WJ. Index for rating diagnostic tests. Cancer. 1950; 3: 32–5.

33 Kanda Y. Investigation of the freely available easy-to-use software ‘EZIR’ for medical statistics. Bone Marrow Transplant. 2013; 48: 452–8.

34 Yasui Y, Kurosaki M, Komiyama Y et al. Wisteria floribunda agglutinin-positive Mac-2 binding protein predicts early occurrence of hepatocellular carcinoma after sustained virologic response by direct-acting antivirals for hepatitis C virus. Hepatol. Res. 2018; 48: 1131–9.

35 Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. J. Hepatol. 2018; 69: 1088–98.
Supporting information

Additional supporting information may be found in the online version of this article at the publisher’s website:

**Figure S1.** Cumulative incidence of HCC by ADRES score in patients with HCV genotype 1.

**Figure S2.** Cumulative incidence of HCC by ADRES score in patients with HCV genotype 2.