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Prediction of the Risk of Hepatocellular Carcinoma in Chronic Hepatitis C Patients after Sustained Virological Response by Aspartate Aminotransferase to Platelet Ratio Index

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Background/Aims: Following sustained virological response (SVR) for chronic hepatitis C (CHC) infection, patients with advanced fibrosis require regular monitoring for hepatocellular carcinoma (HCC). The aspartate aminotransferase to platelet ratio index (APRI) is a simple noninvasive surrogate marker known to reflect fibrosis. **Methods:** We retrospectively analyzed 598 patients who achieved SVR with interferon-based therapy for CHC. **Results:** Over a median of 5.1 years of follow-up, there were eight patients diagnosed with HCC and a 5-year cumulative incidence rate of 1.3%. The median pretreatment APRI was 0.83, which decreased to 0.29 after achieving SVR (p<0.001). Both the pre- and posttreatment indices were associated with HCC development. The 5-year cumulative HCC incidence rates were 0% and 2.8% for patients with pretreatment APRI <1.0 and ≥1.0, respectively (p=0.001) and 0.8% and 12.8% for patients with posttreatment APRI <1.0 and ≥1.0, respectively (p<0.001). Pretreatment APRI at a cutoff of 1.0 had a 100% negative predictive value until 10 years after SVR. **Conclusions:** HCC development was observed among CHC patients who achieved SVR. The pre- and post-treatment APRI could stratify HCC risk, indicating that the APRI could be a useful marker to classify HCC risk in CHC patients who achieved SVR. However, given the small number of HCC patients, this finding warrants further validation. **(Gut Liver 2016;10:796-802)**

Key Words: Carcinoma, hepatocellular; Aspartate aminotransferase to platelet ratio index; Hepatitis C, chronic; Sustained virological response

INTRODUCTION

Hepatitis C virus (HCV) infection is a worldwide health problem that affects more than 170 million people,[1] and is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC).[2] There has been significant improvement in the therapy for HCV. Interferon (IFN)-based therapy provides complete viral eradication in over one-half of patients with chronic hepatitis C (CHC),[3-5] and with a newer, oral direct antiviral agent, complete viral eradication can be expected for most patients today.[6] Consequently, there are growing numbers of patients with sustained virological response (SVR).

Virological relapse is very rare after achieving SVR, and thus, SVR is considered a complete viral eradication.[6] Since SVR typically aborts progression of liver injury,[7] the American Association for the Study of the Liver Disease/Infectious Disease Society of America/International Antiviral Society-USA (AASLD/ISDA/IAS) states that follow-up in patients without advanced liver fibrosis who achieved SVR is the same as if they were never infected with HCV.[8] In contrast, for patients with advanced fibrosis, SVR ameliorates progression to cirrhosis and the development of HCC,[9-13] but the risk for HCC does not completely disappear,[14-16] and regular surveillance for HCC is still recommended.[8,17]

The gold standard for assessing liver fibrosis is the liver biopsy, but it is an invasive procedure with potential complications.[18] Furthermore, currently a liver biopsy is not routinely

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recommended before HCV treatment.[6] For patients who do not have histological information, identifying patients who need regular HCC surveillance after achieving SVR is an open question. Instead of liver biopsy, a variety of noninvasive markers have been proposed for predicting liver fibrosis, i.e., aspartate aminotransferase (AST) to platelet ratio index (APRI), FIB-R, Forns index, Fibro index, FibroTest™, Enhanced liver fibrosis, Fibrometer, FIBROSpect II, Hepascore, transient elastography (Fibroscan®), and acoustic radiation force impulse imaging (ARFI).[19] Among them, APRI is the simplest biochemical marker for liver fibrosis and cirrhosis and is well-studied in chronic hepatitis C patients.[20,21] APRI has great advantages of simplicity, cost-effectiveness, and wide availability compared to all other measures. However, whether APRI can be used to risk stratify patients who achieved SVR has not been thoroughly evaluated.

Thus, the present study investigated the incidence of HCC in CHC patients who achieved SVR and assessed whether pre- or posttreatment APRI could stratify the risk for HCC and identify patients who need regular HCC surveillance.

MATERIALS AND METHODS

1. Study design and population

This is a retrospective study reviewing the database of Samsung Medical Center between January 1, 1998 and December 31, 2010. We screened adult patients (18 years and older) who met the following inclusion criteria: (1) CHC, based on continuously positive HCV antibody and HCV RNA detection tests (Amplicor HCV v2.0; Roche Molecular Systems, Pleasanton, CA, USA) for more than 6 months before treatment; (2) treated with IFN-based regimen, which comprised either IFN or pegylated-IFN with or without ribavirin; (3) achieved SVR. A total of 638 patients met inclusion criteria and were enrolled. Among them, 40 patients who met any of the following exclusion criteria were excluded: (1) seropositive of hepatitis B surface antigen; (2) other liver diseases including autoimmune hepatitis and primary biliary cirrhosis; (3) HCC that was diagnosed before treatment for HCV or developed within 6 months after the beginning of SVR. Thus, 598 patients were analyzed. The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center (IRB number: 201411076). Because the study is based on the retrospective analysis of existing administrative and clinical data, the requirement of obtaining informed patient consent was waived. All patients' records and clinical information were anonymized and de-identified prior to analysis.

2. Measurements and end-points

The duration of follow-up for each patient was counted from the date of SVR to HCC development or the last medical attendance. The reference date was June 30, 2014. Patients received regular HCC surveillance using ultrasonography and serum α-fetoprotein (AFP) at 6 to 12 months interval, at respective physician's direction. HCC was diagnosed either histologically or clinically according to the guideline for the diagnosis of HCC suggested by the Korean Association for the Study of the Liver.[22] We collected demographic data and biochemical data at the time of IFN-based therapy and at the time of SVR. Age, blood cell counts, serum AST, alanine transaminase (ALT), and AFP were measured using commercially available assays. Diabetes mellitus was diagnosed based on fasting serum glucose levels that exceeded 126 mg/dL, abnormal results for a 75-g oral glucose tolerant test, or the need for insulin or an oral antihyperglycemic drug to control glucose levels. The APRI was calculated by this calculation formula [(AST/normal upper limit AST)/platelet count]×100, as described originally.[23] The high and low APRI cutoff was chosen at 1.0, according to the meta-analysis.[24] An APRI threshold of 1.0 was reported to be 61% sensitive and 65% specific compared to histology for severe fibrosis, and 76% sensitive and 72% specific for cirrhosis.[24] Ultrasonographic finding was reviewed at the nearest time of SVR, and information for the presence of cirrhotic configuration was collected.

3. Statistical analysis

The cumulative incidence of HCC development was assessed by using the Kaplan-Meier method. The Cox proportional-hazards model was used to evaluate the association between APRI and HCC development. Differences of the incidence rate between groups were assessed and plotted by using the Kaplan-Meier method. Time dependent ROC curve analysis was performed to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at each time point according to the risk factors. All tests of significance were two-tailed and a p-value of less than 0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

A total 598 patient with SVR were enrolled for analysis. Median age was 52 years (range, 18 to 75 years) and median observational period was 5.1 years (range, 0.1 to 14.3 years) after achieving SVR. Laboratory data were presented at two time point: before treatment and at SVR. Overall the median values of platelet count (183 to 188), AST (56 to 22), ALT (75 to 18), AFP levels (4.5 to 3.0) were significantly improved at SVR ($p<0.001$ for all). Pretreatment APRI value also significantly decreased at the time of SVR (0.83 to 0.29, $p<0.001$). Pretreatment APRI was <1.0 in 346 patients and was ≥1.0 in 252 patients. Baseline characteristics were significantly different between two groups (Table 1). Those with high pretreatment APRI were older, had more patients with diabetes, higher BMI, more patients with cirrhotic configuration on USG. Laboratory variables before treatment and at SVR was also significantly different, yet, the median observation period were similar (4.8 vs 4.6 years,

Table 1. Comparison of Characteristics according to the Baseline APRI Value

Characteristic	Before treatment APRI ≥1.0 (n=252)	Before treatment APRI <1.0 (n=346)	p-value
Age, yr	56 (49–61)	50 (43–57)	<0.001
Male sex	138 (54.8)	188 (54.3)	0.91
Observation period, yr	4.8 (3.1–7.3)	4.6 (2.6–6.8)	0.14
Diabetes	38 (15.1)	31 (9)	0.021
Genotype			0.65
Genotype 1	74 (31.8)	139 (43.7)	
Genotype 2	150 (64.4)	172 (54.1)	
Others/undetermined	9 (3.8)	7 (2.2)	
BMI, kg/m^2	24.2 (22.5–26.2)	23.4 (21.9–25.8)	0.021
Cirrhotic configuration on USG	28 (11.1)	6 (1.7)	<0.001
Before treatment			
Platelet, ×10^3/L	150 (121–182)	196 (164–236)	<0.001
AST, IU/L	105 (76–146)	38 (28–78)	<0.001
ALT, IU/L	154 (80–210)	16 (13–23)	<0.001
APRI	1.59 (1.26–2.61)	0.48 (0.33–0.69)	<0.001
AFP, ng/mL	7.1 (4.3–13)	3.5 (2.5–5)	<0.001
At SVR			
Platelet, ×10^3/L	160 (129–198)	206 (174–241)	<0.001
AST, IU/L	24 (20–31)	20 (17–24)	<0.001
ALT, IU/L	20 (15–29)	16 (13–23)	<0.001
APRI	0.38 (0.27–0.58)	0.24 (0.19–0.33)	<0.001
AFP, ng/mL	3.4 (2.3–4.7)	2.8 (2–3.9)	<0.001

Data are presented as median (quartile range) or number (%).
APRI, aspartate aminotransferase to platelet ratio index; BMI, body mass index; USG, ultrasonography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; SVR, sustained virological response.

p=0.14).

2. Cumulative incidence of HCC development

During the follow-up period, HCC developed in eight patients. The cumulative incidence rates of HCC development were 0.2%, 1.3%, and 4.7% at 3 years, 5 years, and 10 years after achieving SVR, respectively. The median time to development of HCC was 3.8 years after achieving SVR, and three of eight patients (38%) developed HCC after 5 years. Seven factors were associated with HCC development: pretreatment platelet levels, pretreatment APRI, posttreatment platelet levels, posttreatment AFP, posttreatment APRI, cirrhotic configuration on radiologic evaluation and diabetes mellitus (Table 2).

3. APRI as a predictor for HCC

The median value of pretreatment APRI was 0.83 and 252 patients (42.1%) showed APRI ≥1.0. The 5-year cumulative HCC incidence rate was 0% and 2.8% for patients with pretreatment APRI <1.0 and ≥1.0 (p=0.001), respectively (Fig. 1A). Among the 252 patients with high pretreatment APRI, posttreatment APRI was decreased to <1.0 in 234 patients (92.9%), and remained

Table 2. Factors Associated with the Development of Hepatocellular Carcinoma

Variable	HR (95% CI)	p-value
Age, yr	1.08 (0.99–1.16)	0.06
Male sex	2.05 (0.41–10.2)	0.37
Body mass index, kg/m^2	1.02 (0.81–1.28)	0.88
Diabetes mellitus	5.54 (1.36–22.5)	<0.01
Pretreatment platelet, ×10^3/L	0.96 (0.94–0.98)	<0.001
Pretreatment ALT, IU/L	1.00 (0.99–1.01)	0.97
Pretreatment AFP, ng/mL	1.08 (0.99–1.02)	0.20
Pretreatment APRI	1.44 (1.16–1.80)	0.001
Posttreatment platelet, ×10^3/L*	0.96 (0.94–0.98)	<0.0001
Posttreatment ALT, IU/L*	1.01 (1.00–1.02)	0.21
Posttreatment AFP, ng/mL*	1.25 (1.11–1.42)	<0.001
Posttreatment APRI*	7.39 (3.17–17.11)	<0.0001
Cirrhotic configuration on ultrasonography	24.25 (5.73–102)	<0.0001

HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; AFP, α-fetoprotein; APRI, aspartate aminotransferase to platelet ratio index.
*Posttreatment value was accessed at the moment of sustained virological response.

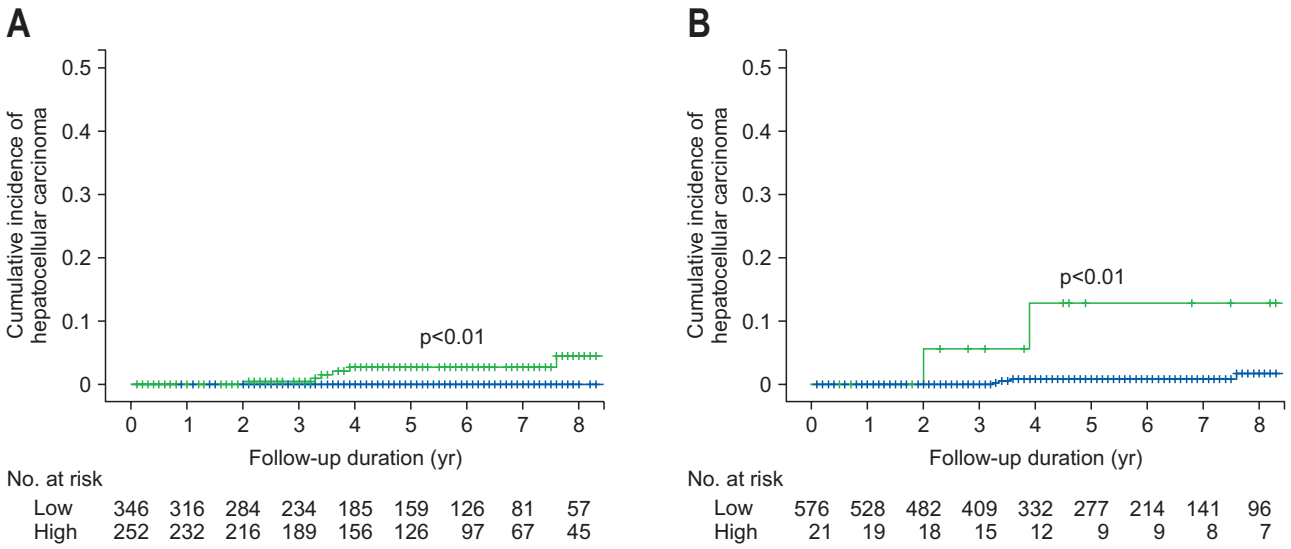

Fig. 1. Cumulative incidence of hepatocellular carcinoma according to the aminotransferase to platelet ratio index (APRI). Incidence rate of hepatocellular carcinoma was higher in patients with high APRI value (≥1.0) (p<0.01). (A) and (B) for pretreatment APRI and posttreatment APRI, respectively. Blue and green represent low and high APRI, respectively.

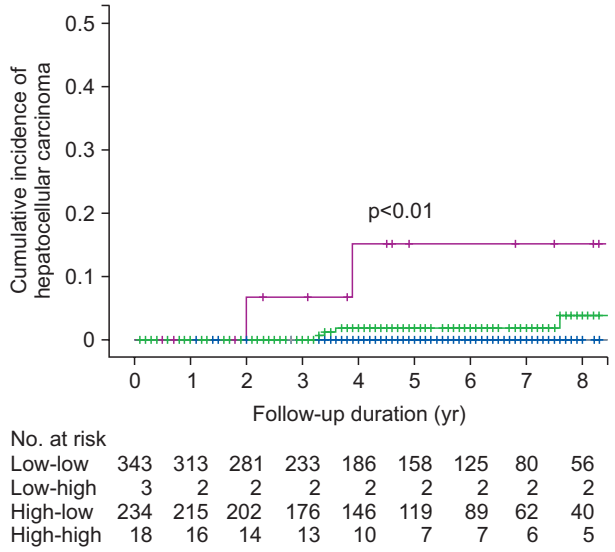

Fig. 2. The cumulative incidence of hepatocellular carcinoma (HCC) according to the pre- and posttreatment aminotransferase to platelet ratio index (APRI). Patients with high pretreatment/high posttreatment APRI (≥1.0) showed the highest cumulative incidence of HCC, which was 15.2% at 5 years, whereas there was no case of HCC in patients with low pretreatment/low posttreatment APRI (<1.0) (p<0.01). Blue, gray, green and purple represent low pretreatment/low posttreatment APRI, low pretreatment/high posttreatment APRI, high pretreatment/low posttreatment APRI and high pretreatment/high posttreatment APRI, respectively.

high in 18 patients (7.1%). Among 346 patients with low pretreatment APRI (<1.0), 343 patients remained in low posttreatment APRI, and three patients showed high posttreatment APRI (≥1.0). Thus at SVR, APRI ≥1.0 was seen in 21 patients while most of patients (577 patients, 96.5%) showed APRI <1.0. The 5-year cumulative HCC incidence rate was 0.8% and 12.8% for patients with posttreatment APRI <1.0 and ≥ 1.0 (p<0.001), respectively (Fig. 1B).

When the cumulative incidence rate of HCC was calculated according to the pretreatment and posttreatment APRI, patients with low pre-/low posttreatment APRI (<1.0, n=343) did not develop HCC during the entire follow-up period. Three patients who had low pre-/high posttreatment APRI also did not develop HCC. Among 234 patients who had high pre-/low posttreatment APRI, there were four cases of HCC, and the cumulative HCC incidence rate was 1.8% at 5 years. Among 18 patients with high pre-/high posttreatment APRI, the cumulative HCC incidence rate was 15.2% at 5 years (Fig. 2).

4. Comparison to other noninvasive risk factors

All the seven factors associated with HCC development showed high NPV (Table 3). Sensitivity, specificity, PPV and NPV at 5- and 10-years are shown in Table 3. Among them, pretreatment APRI showed NPV of 100% till 10 years after SVR. PPV was generally low, and was highest for cirrhotic configuration followed by posttreatment APRI. Pretreatment APRI showed higher NPV for HCC than pretreatment platelet, while posttreatment APRI showed higher PPV for HCC than posttreatment platelet.

DISCUSSION

In this study, the HCC incidence rate for CHC patients who achieved SVR was low (1.3% at 5 years), with the estimated mean annual incidence rate of 0.3%. However, CHC patients with SVR were not free from developing HCC. Of note, HCC developed even after 5 years from the time of SVR in this study. Several papers reported similar findings. HCC developed

Table 3. Comparison among Noninvasive Markers

Variable	HCC/ no. at risk	At 5 years, %					At 10 years, %				
		Incidence rate*	Sen.	Spe.	PPV	NPV	Incidence rate*	Sen.	Spe.	PPV	NPV
High pretreatment APRI			100	55.7	2.8	100		100	61.5	11.1	100
Yes	8/252	2.8					10.1				
No	0/346	0					0				
High posttreatment APRI			38.6	96.8	13.2	99.2		65.2	96.2	44.8	98.3
Yes	4/21	12.8					53.5				
No	4/577	0.8					1.7				
Low pretreatment platelet			79.6	68.6	3.1	99.6		76.4	73.1	12.0	98.5
Yes	6/164	3.4					11.5				
No	2/434	0.4					1.7				
Low posttreatment platelet			100	75.4	4.9	100		82.0	75.0	13.6	98.9
Yes	7/136	5.2					15.1				
No	1/462	0					1.2				
High posttreatment AFP			58.5	83.2	4.2	99.4		44.6	82.7	11.0	96.9
Yes	4/101	4.5					11.3				
No	4/497	0.6					3.1				
Diabetes			58.4	85.4	4.8	99.4		42.1	82.6	10.4	96.7
Yes	4/69	5.3					13.9				
No	4/529	0.6					3.1				
Cirrhotic configuration			78.8	96.1	20.3	99.7		47.6	98.0	54.2	97.5
Yes	5/34	19.6					46.4				
No	3/564	0.3%					2.5				

HCC, hepatocellular carcinoma; Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; APRI, aspartate aminotransferase to platelet ratio index; AFP, α-fetoprotein.
*Incidence rate was cases/100 person-years. The cutoff points for APRI, platelet and AFP were 1.0, 150×10^3/L, and 5 ng/mL, respectively.

in patients who achieved SVR,[25] and sometimes, it developed even after 10 years from SVR.[26,27] These findings indicate that long-term HCC surveillance is required for CHC patients who achieved SVR. HCC surveillance is recommended for those with increased risk of HCC.[28] However, as actual HCC risk is low in this population, stratifying patients according to the HCC risk are important in planning follow-up strategy for patients who achieved SVR.

The AASLD/ISDA/IAS recommends stratifying patients according to fibrosis stage based on histology.[8] The European Association for the Study of the Liver[17] also recommends regular monitoring for cirrhotic patients who achieved SVR. However, currently a liver biopsy is not routinely recommended before HCV treatment,[6] so many patients do not have histological information. Furthermore, since SVR is often accompanied by regression of fibrosis,[29] risk stratification according to the baseline fibrosis stage might not be the best approach. Besides, repeated histologic evaluation is not always available, and the clinical benefit of liver biopsy to stage fibrosis at the time of SVR is unknown.[8] In this study, we found that both pre- and posttreatment APRI were associated with the risk of HCC development. We also noticed that stratification of patients according to both pre- and posttreatment APRI are helpful in estimating future HCC risk. When pre- and posttreatment APRI were combined, patients with high pre-/high posttreatment APRI were at high risk for HCC (15.2% at 5 years), while those with low pre-/low posttreatment APRI had null risk for HCC. The incidence of HCC of those with high pre-/low posttreatment APRI was low (1.8% at 5 years). These findings suggest that APRI could be a useful indicator to determine the follow-up strategy in CHC patients who achieved SVR, and indicate that those with high pre-/high post-APRI, as well as those with high pre-/low post-APRI, need regular surveillance for HCC even after achieving SVR.

In this study, we also noticed some other noninvasive markers that were associated with HCC development; pre- and posttreatment platelet, posttreatment AFP, cirrhotic configuration on radiological exam and presence of diabetes. As APRI is a value made from AST and platelet, APRI has high correlation with platelet count. Cirrhotic configuration on radiological exam also correlated with APRI that those with cirrhotic configuration showed higher pretreatment APRI (median, 1.79 vs 0.41; $p<0.001$) and higher posttreatment APRI (median, 0.62 vs 0.27;

p<0.001). AFP level was higher in patients with higher APRI, and diabetes was also more frequently observed in patients with higher APRI (Table 1). Therefore, multivariate analysis is needed to find out independent factor for HCC, yet, this was not performed considering type 2 error, as number of HCC was small (n=8) in this study. Further studies with larger HCC number are needed. Nevertheless, all these noninvasive markers showed high NPV (over 95%), indicating that these markers can be helpful in risk-stratifying patients risk. Among them, cirrhotic configuration showed highest PPV (20.3% at 5 year), followed by posttreatment APRI (13.2% at 5 year). In terms of cancer screening, NPV can be more important than PPV. Among noninvasive markers, pretreatment APRI and posttreatment platelet showed 100% NPV at 5 year, and only pretreatment APRI showed 100% NPV at 10 years. Looking into individual HCC cases (Supplementary Table 1), it showed that age at SVR was under 50 in three patients, no-diabetes in four patients, no cirrhotic configuration in three patients, posttreatment APRI <1.0 in four patients. In contrast, no patients who developed HCC after achieving SVR had pretreatment APRI <1.0. These findings suggest that APRI may be most useful marker in terms of NPV, while cirrhotic configuration may be most useful marker in terms of PPV. However, this needs further validation with larger size studies.

There are some other limitations in this study. This is a retrospective cohort study with small number of HCC cases. Histological data are lacking in most of the patients, thus, comparison of fibrosis stage by histology versus APRI was not done. South Korea is an endemic area for hepatitis B virus infection,[30] and occult hepatitis B virus infection might be associated with HCC development in patients who cleared HCV by IFN treatment.[31] Therefore, our findings need to be interpreted with caution in non HBV-endemic area. APRI is a simple and noninvasive biochemical marker of liver fibrosis and cirrhosis, but performance of APRI in diagnosing significant fibrosis is lower than Fibroscan®, Fibrotest™, and so forth.[32] Although cost-effectiveness should be demonstrated, performance of these noninvasive tools in CHC patients who achieved SVR is of interest, and needs further clarification. However, strength of this study is that this cohort involved relatively large number of patients (n=598) with long-term follow-up period (median, 5.1 years).

In conclusion, our data demonstrates that the risk of HCC is low, but still present, in patients who cleared HCV by IFN-based treatment. HCC could develop even after many years from SVR, indicating long-term HCC surveillance is required in some patients. Thus, identifying at risk patients is of clinical importance. APRI, a simple, noninvasive surrogate marker for fibrosis, was able to stratify patients risk for HCC, and may help select patients who will likely benefit from regular HCC surveillance.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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