

# Simple score to predict risk of hepatocellular carcinoma in chronic hepatitis C patients with advanced fibrosis after pegylated interferon and ribavirin therapy

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**Purpose:** Eradication of chronic hepatitis C virus (HCV) after interferon-based therapy and its association with the reduction of risk of hepatocellular carcinoma (HCC) in HCV-infected patients with advanced fibrosis is controversial. The study is aimed to develop a simple scoring model for HCC prediction among advanced fibrotic chronic hepatitis C (CHC) patients after pegylated interferon (pegIFN) and ribavirin (RBV) therapy.

**Patients and methods:** We enrolled 271 biopsy-proven CHC patients with advanced fibrosis between 2003 and 2016, and divided them into non-HCC (n=211) and HCC (n=60) groups. The median observation duration was 6.0 years (range: 0.9–12.6 years).

**Results:** The HCC prevalence after pegIFN and RBV therapy in CHC patients with sustained virologic response (SVR) and without SVR was 14.7% and 32.2%, respectively. Multivariate Cox regression showed age  $\geq 59.5$  years old at initiation of therapy (HR: 2.542, 95% CI: 1.390–4.650,  $P=0.002$ ), pretreatment total bilirubin  $\geq 1.1$  mg/dL (HR: 2.630, 95% CI: 1.420–4.871,  $P=0.002$ ), pretreatment platelet counts  $< 146.5 \times 10^3/\mu\text{L}$  (HR: 2.751, 95% CI: 1.373–5.511,  $P=0.004$ ), no achievement of SVR (HR: 2.331, 95% CI: 1.277–4.253,  $P=0.006$ ), and no diabetes at treatment initiation (HR: 3.085, 95% CI: 1.283–7.418,  $P=0.012$ ) were significant predictors of HCC development. The scoring model consisted of the five categorical predictors and had an optimal cutoff point of 2.5. The area under receiver operating characteristic (AUROC) of the scoring model was  $0.774 \pm 0.035$  ( $P < 0.001$ ). The sensitivity and specificity of the cutoff value to detect HCC were 81.3% and 57.5%. The 5-year and 10-year cumulative incidence of HCC was 4.9% and 10.0% in patients with simple score  $\leq 2$ ; and 25.9% and 44.6% in patients with simple score  $\geq 3$  ( $P < 0.001$ ).

**Conclusion:** The simple clinical-guided score has high discriminatory power for HCC prediction in advanced fibrotic CHC patients after pegIFN and RBV therapy.

**Keywords:** HCC, HCV, advanced fibrosis, SVR, score, cumulative incidence

## Introduction

Chronic hepatitis C infection is a major global health problem and an important cause of morbidity and mortality from sequelae such as liver cirrhosis and HCC.<sup>1–4</sup> It has been estimated that, globally, 27% of cirrhosis and 25% of HCC cases develop in HCV-infected people.<sup>5</sup> In patients with HCV-related cirrhosis, the annual incidence rates of developing hepatic decompensation and HCC are 3.9% and 1.4%–8%, respectively.<sup>4,6,7</sup> The main goals of therapy in patients with HCV-related cirrhosis are to eradicate HCV, improve liver histologic activity, and reduce fibrosis. In addition, several

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studies have shown that chronic HCV infected patients with advanced fibrosis achieving SVR after IFN-based therapy have reduced risks of developing liver decompensation, HCC, and liver-related mortality.<sup>8–13</sup> Therefore, although these patients are considered to be a difficult-to-treat population with less tolerability and poor therapeutic responses to pegIFN and RBV therapy, they could still benefit from the treatment with a lower risk of HCC, liver disease progression and liver-related complications.<sup>14,15</sup> There are several risk factors associated with HCC development in CHC patients with advanced fibrosis, including male gender, older age at treatment initiation, HCV genotype 1b, low serum albumin and high serum total bilirubin levels, low platelet counts, and presence of esophageal varices.<sup>2,11,16–18</sup> However, another report demonstrated a controversial result that achievement of SVR after IFN-based therapy did not influence the rate of HCC development.<sup>19</sup>

Combination therapy with pegIFN plus RBV has greatly improved the rate of SVR compared to conventional IFN with and without RBV and is the standard treatment strategy for chronic HCV infection before the introduction of DAAs.<sup>20–22</sup> However, only a few studies have been focused on the influence of the pegIFN and RBV therapy on HCC development in CHC patients with advanced fibrosis.<sup>11,18,19</sup> Besides, there was no report regarding the assessment of HCC risk score of those advanced fibrotic CHC patients after pegIFN and RBV therapy. We therefore conducted this study to evaluate the predictors on HCC development and to develop a simple risk score model for HCC prediction in advanced fibrotic chronic hepatitis C patients after pegIFN and RBV therapy.

## Patients and methods

### Patients

This study was conducted at our institute between October 2003 and November 2016. There were in total 271 patients with biopsy proven chronic HCV infection with advanced fibrosis enrolled into the study (Figure 1). Chronic hepatitis C infection was defined as seropositive for anti-HCV and HCV RNA for more than 6 months. Clinical and demographic data were recorded within three months before the initiation of therapy. The degree of hepatic inflammation and fibrosis was graded using an Ishak modified scores and read by a single pathologist. Advanced fibrosis and cirrhosis were defined as a fibrosis score  $\geq 4$  and  $\geq 5$  on the Ishak modification of histologic activity index. The diagnosis of type 2 diabetes was based on a value of fasting glucose  $\geq 126$  mg/dL on at least two occasions or ongoing hypoglycemic agent treatment.<sup>23</sup>

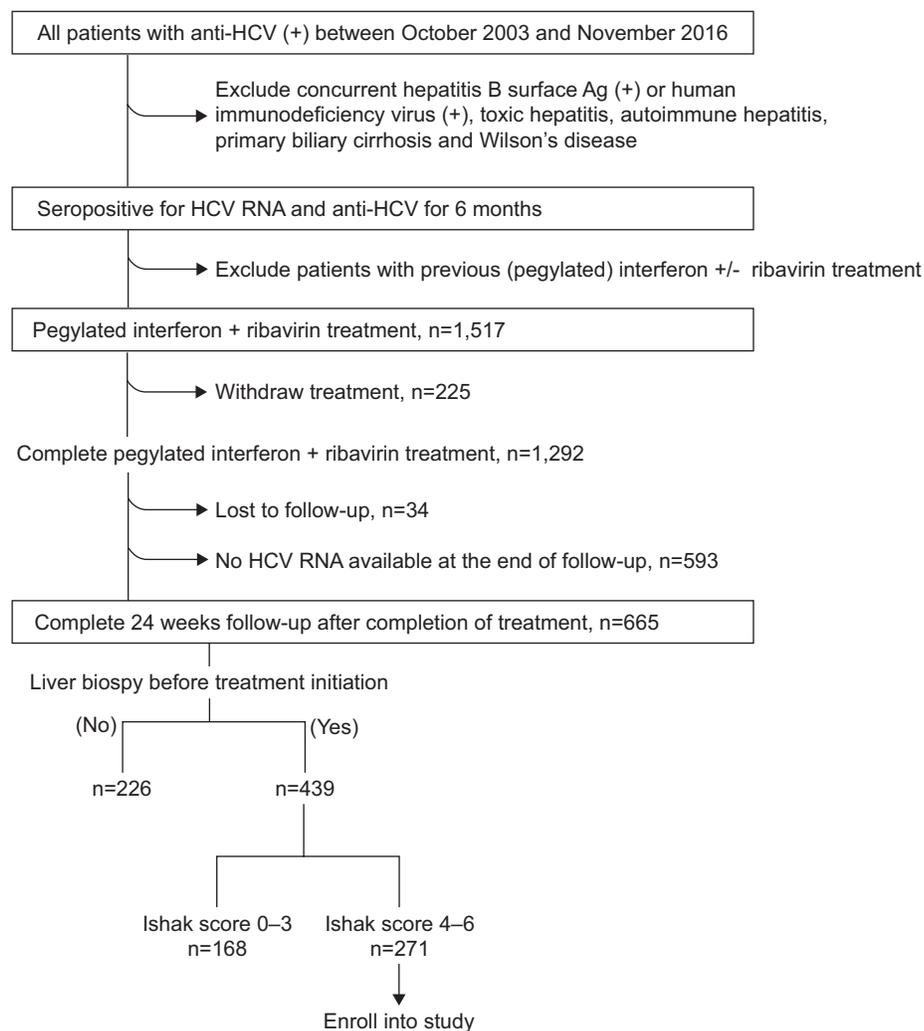
All patients received and completed the pegIFN plus RBV therapy for 24 or 48 weeks according to the reimbursement policy of the National Health Insurance in Taiwan. The prescribed types of pegIFNs were pegIFN- $\alpha$ -2a (180  $\mu$ g) or weight-based pegIFN- $\alpha$ -2b (1.5  $\mu$ g/kg). For genotype-1b-HCV-infected patients with body weight  $< 75$  kg, the oral RBV dose was 1,000 mg per day and for those with body weight  $\geq 75$  kg, 1,200 mg per day. For genotype non-1b-HCV-infected patients, the RBV dose was 800 mg per day. All patients were followed up for 24 weeks after the completion of treatment. RVR was defined as undetectable serum HCV RNA by using PCR at the end of week 4 of therapy. SVR was defined as achievement of undetectable serum HCV RNA by using PCR at the end of treatment that was sustained after the end of six-month follow-up. A non-responder had terminated the treatment course before week 16, and was excluded from our study. We also excluded patients with HCC diagnosed before treatment initiation or within 6 months after the end of therapy, concurrent hepatitis B virus or human immunodeficiency virus infection, toxic hepatitis, autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, or hemoglobinopathies. Written informed consent was obtained from all patients enrolled in this study. The study was performed in accordance with the ethical guidelines of the International Conference on Harmonization for Good Clinical Practice and has been approved by the Institutional Review Board of Chang Gung Memorial Hospital (No 201600519B0).

### Laboratory test

Anti-HCV tests were conducted using a third-generation enzyme immunoassay kit (AxSYM<sup>®</sup> HCV Version 3.0; Abbott Laboratories, Abbott Park, IL, USA). Serum HCV RNA was quantified using a real-time polymerase chain reaction (PCR) assay (COBAS<sup>®</sup> AmpliPrep Instrument and COBAS TaqMan<sup>®</sup> 48; Hoffman-La Roche Ltd, Basel, Switzerland), with a detection limit of 15 IU/mL. HCV genotyping was determined using a linear probe assay (VERSANTTM HCV Genotype Assay [LiPA]; Bayer AG, Leverkusen, Germany).

### Follow-up and assessment of HCC development

The observation duration was started from the date of the end of six-month follow-up after the pegIFN and RBV therapy to the date of HCC diagnosis, last-visit or death of the patient. During the observation period, patients with and without liver cirrhosis returned to the clinic every three and six months



**Figure 1** Diagram of the study design and diagnosis.

**Abbreviation:** HCV, hepatitis C virus.

for liver biochemistry and liver ultrasonography study. If a liver tumor was suspected by ultrasonography study, further examination was arranged for HCC confirmation. The HCC was diagnosed based on histopathology or two image studies, such as dynamic liver computed tomography or magnetic resonance imaging with typical arterial enhancement, or one image study plus elevated serum AFP level of more than 400 ng/mL.<sup>24</sup>

## Statistical analysis

Continuous variables were expressed as mean±standard deviation. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. The Student's *t*-test was used to compare the means of continuous variables and normally distributed data, otherwise the Mann–Whitney *U* test was used. Categorical data were tested using the chi-square test.

Finally, risk factors were assessed by univariate Cox regression analysis, and variables that were statistically significant ( $P<0.05$ ) were included in multivariate analysis by applying a multivariate Cox regression based on forward elimination of data. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test to compare the number of observed and predicted events in risk groups for the entire range of HCC probabilities. Discrimination was assessed by AUROC. The AUROCs were compared using a nonparametric approach. AUROC analyses were also used to calculate cutoff values, sensitivity, specificity, and overall correctness. Finally, cutoff points were calculated by acquiring the best Youden index (sensitivity + specificity – 1). Cumulative survival curves as a function of time were generated using the Kaplan–Meier approach and compared by log-rank test. All statistical tests were two-tailed, with  $P$ -values  $<0.05$  being considered as

statistically significant. Data were analyzed using SPSS 12.0 software for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

### Subject characteristics

Baseline demographic and clinical characteristics of non-HCC and HCC patients are shown in Table 1. Total 271 patients receiving pegIFN and RBV therapy were enrolled into this study. The median observation duration was 6.0 years (range: 0.9–12.6 years). SVR developed in 57.6% of patients. The overall HCC prevalence of the entire population after pegIFN and RBV therapy was 22.1% (60/271). The mean age of the patients at initiation of therapy was 57.5±10.3 years, with 128 (47.2%) being men. Patients with HCC development after pegIFN and RBV treatment were significantly older at initiation of therapy, had higher pretreatment serum aspartate aminotransferase to alanine aminotransferase ratio, total bilirubin, AFP levels, and higher frequency of liver cirrhosis. Those patients with HCC also had lower pretreatment serum albumin levels, platelet counts, and lower frequency of SVR. Fewer patients with fatty liver and diabetes at initiation of therapy developed HCC after completion of pegIFN and RBV treatment. The mean pretreatment aspartate and alanine aminotransferase level, HCV RNA viral load, and percentage of

HCV genotype 1b and male gender, treatment duration, and types of pegIFN (2a vs 2b) prescribed were similar between the non-HCC and HCC patients.

### Predictors of HCC

In univariate Cox regression analysis, several clinical factors, including age, serum albumin, aspartate aminotransferase to alanine aminotransferase ratio, total bilirubin, platelet count, AFP, SVR, cirrhosis, fatty liver and diabetes were identified to be significantly associated with HCC development (Table 2). ROC curve analysis showed that 59.5 years at initiation of therapy was the best cutoff point to discriminate among HCC and non-HCC occurrence (AUROC: 0.663±0.038,  $P<0.001$ ). The cutoff points of pretreatment total bilirubin level and platelet count to predict HCC development were 1.1 mg/dL (AUROC: 0.659±0.043,  $P=0.001$ ) and  $146.5 \times 10^3/\mu\text{L}$  (AUROC: 0.652±0.043,  $P=0.001$ ). Then we divided the age at initiation of therapy, pretreatment total bilirubin levels and platelet counts into two separate groups according to the cutoff points determined by the ROC curves. In multivariate analysis, the three categorical factors and the rest of the significant factors in univariate analysis were entered in the final stepwise regression analysis. Multivariate Cox regression showed age  $\geq 59.5$  years old

**Table 1** Baseline clinical and virologic characteristics of advanced fibrotic chronic hepatitis C patients with and without HCC

Parameter	All (n=271)	Non-HCC (n=211)	HCC (n=60)	P-value
Age (years) <sup>a</sup>	57.5±10.3	56.2±10.4	62.0±8.5	<0.001***
Gender (male) <sup>b</sup>	128 (47.2)	97 (46.0)	31 (51.7)	0.436
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	25.6±3.5	25.5±3.6	26.1±3.1	0.263
Albumin (g/dL) <sup>a</sup>	4.1±0.3	4.2±0.3	4.0±0.4	0.001**
AST (U/L) <sup>a</sup>	93.0±51.1	90.1±50.4	105.4±52.8	0.068
ALT (U/L) <sup>a</sup>	124.0±87.5	124.8±91.4	121.0±70.8	0.788
AST/ALT ratio <sup>a</sup>	0.83±0.28	0.81±0.28	0.92±0.27	0.016*
Total bilirubin (mg/dL) <sup>a</sup>	1.0±0.36	1.0±0.3	1.2±0.4	0.001**
White blood cells ( $\times 10^3/\mu\text{L}$ ) <sup>a</sup>	5.6±1.8	5.7±1.8	5.4±1.7	0.227
Hemoglobin level (g/dL) <sup>a</sup>	14.1±1.7	14.1±1.7	14.1±1.7	0.891
Platelet count ( $\times 10^3/\mu\text{L}$ ) <sup>a</sup>	144.0±54.3	149.3±54.4	122.7±49.0	0.002**
AFP (ng/mL) <sup>a</sup>	39.6±251.3	18.2±30.7	120.4±541.4	0.007**
HCV RNA ( $\times 10^6$ IU/mL) <sup>a</sup>	7.38±12.86	7.44±12.00	7.16±15.63	0.890
HCV Genotype 1b <sup>b</sup>	158/260 (60.8)	123/203 (60.6)	35/57 (59.9)	0.912
RVR <sup>b</sup>	108/200 (54.0)	87/157 (55.4)	21/73 (48.8)	0.443
SVR <sup>b</sup>	156 (57.6)	133 (63.0)	23 (38.3)	0.001**
PegIFN 2a <sup>b</sup>	178 (65.7)	143 (68.7)	35 (58.3)	0.174
PegIFN (48 weeks) <sup>b</sup>	40 (14.8)	34 (16.1)	6 (10.0)	0.239
Cirrhosis <sup>b</sup>	189 (69.7)	138 (65.4)	51 (85.0)	0.004**
Fatty liver <sup>b</sup>	80 (29.5)	71 (33.6)	9 (15.0)	0.005**
DM <sup>b</sup>	62 (22.9)	54 (25.6)	8 (13.3)	0.046*

**Notes:** \* $P<0.05$ ; \*\* $P<0.01$ ; \*\*\* $P<0.001$ ; <sup>a</sup>mean±standard deviation; <sup>b</sup>no (%)

**Abbreviations:** AFP,  $\alpha$ -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; pegIFN, pegylated interferon; RVR, rapid virologic response; SVR, sustained virologic response.

**Table 2** Analysis of predictors of HCC using univariate and multivariate Cox regression models

	B	SE	HR (95% CI)	P-value
<b>Univariate</b>				
Age (years)	0.051	0.14	1.025 (1.023–1.082)	<0.001***
Gender (M vs F)	0.297	0.258	1.346 (0.811–2.235)	0.250
Body mass index (kg/m <sup>2</sup> )	0.030	0.038	1.031 (0.957–1.110)	0.421
Albumin (g/dL)	-1.154	0.347	0.315 (0.160–0.623)	0.001**
AST (U/L)	0.004	0.002	1.004 (1.000–1.009)	0.078
ALT (U/L)	-0.001	0.002	0.999 (0.996–1.003)	0.688
AST/ALT ratio	0.985	0.383	2.446 (1.156–5.179)	0.019
Total bilirubin (mg/dL)	0.855	0.294	2.351 (1.321–4.185)	0.004**
White blood cells (×10 <sup>3</sup> /μL)	-0.095	0.084	0.909 (0.770–1.073)	0.259
Hemoglobin level (g/dL)	0.011	0.085	1.011 (0.856–1.194)	0.900
Platelet count (×10 <sup>3</sup> /μL)	-0.010	0.003	0.990 (0.984–0.996)	0.001**
AFP (ng/mL)	0.001	0.000	1.001 (1.000–1.001)	0.003**
HCV RNA (IU/mL)	0.015	0.011	1.015 (0.993–1.038)	0.180
Genotype (1b vs non-1b)	0.033	0.272	1.033 (0.606–1.762)	0.904
nRVR (yes vs no)	0.426	0.307	1.530 (0.838–2.794)	0.166
nSVR (yes vs no)	0.901	0.267	2.461 (1.459–4.151)	0.001**
pegIFN (2a vs 2b)	-0.404	0.263	0.667 (0.399–1.117)	0.124
pegIFN (48 vs 24 wk)	0.287	0.443	1.333 (0.560–3.174)	0.516
Cirrhosis (yes vs no)	1.316	0.364	3.728 (1.828–7.605)	<0.001***
Fatty liver (yes vs no)	-1.106	0.362	0.331 (0.163–0.673)	0.002**
DM (no vs yes)	0.861	0.380	2.365 (1.123–4.983)	0.024*
<b>Multivariate</b>				
Age ≥59.5 vs <59.5 (years)	0.933	0.308	2.542 (1.390–4.650)	0.002**
Total bilirubin ≥1.1 vs <1.1 (mg/dL)	0.967	0.314	2.630 (1.420–4.871)	0.002**
nSVR (yes vs no)	0.846	0.307	2.331 (1.277–4.253)	0.006**
Platelet count <146.5 vs ≥146.5 (×10 <sup>3</sup> /μL)	1.012	0.355	2.751 (1.373–5.511)	0.004**
DM (no vs yes)	1.127	0.448	3.085 (1.283–7.418)	0.012*

Notes: \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

Abbreviations: AFP,  $\alpha$ -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; nSVR, no sustained virologic response; nRVR, no rapid virologic response; pegIFN, pegylated interferon; wk, week.

at initiation of therapy (HR: 2.542, 95% CI: 1.390–4.650,  $P=0.002$ ), pretreatment total bilirubin  $\geq 1.1$  mg/dL (HR: 2.630, 95% CI: 1.420–4.871,  $P=0.002$ ), pretreatment platelet count  $< 146.5 \times 10^3/\mu\text{L}$  (HR: 2.751, 95% CI: 1.373–5.511,  $P=0.004$ ), no achievement of SVR (HR: 2.331, 95% CI: 1.277–4.253,  $P=0.006$ ), and no diabetes at baseline (HR: 3.085, 95% CI: 1.283–7.418,  $P=0.012$ ) were significant predictors of HCC development.

### Simple score to predict HCC

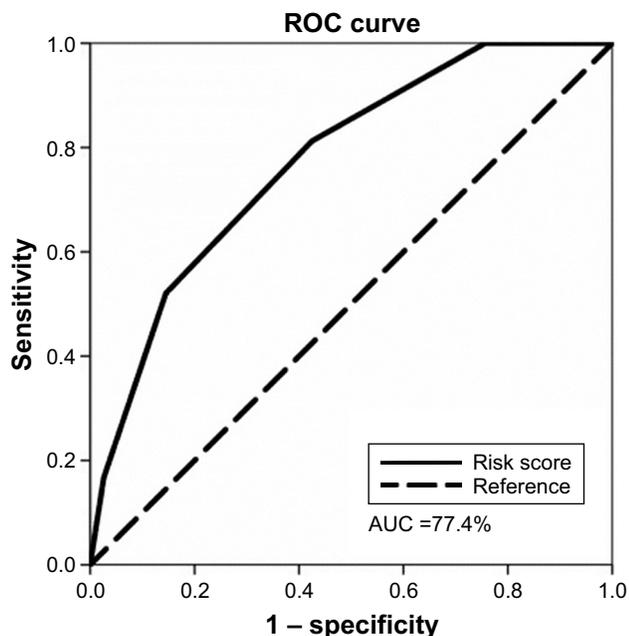
Then we used the five significant independent categorical predictors in multivariate Cox regression to form a new simple score for HCC prediction. We assigned patients with age  $< 59.5$  years old at initiation of therapy 0 point and age  $\geq 59.5$  years old at initiation of therapy 1 point; pretreatment total bilirubin  $< 1.1$  mg/dL 0 point and total bilirubin  $\geq 1.1$  mg/dL 1 point; pretreatment platelet count  $\geq 146.5 \times 10^3/\mu\text{L}$  0 point and platelet count  $< 146.5 \times 10^3/\mu\text{L}$  1 point; presence of diabetes at treatment initiation

0 point and no diabetes at treatment initiation 1 point; and post-treatment SVR 0 point and post-treatment non-SVR 1 point. The simple score equaled the sum of points of these five variables.

The simple score had a cutoff point of 2.5 by the ROC curve to predict HCC (Table 3). The sensitivity, specificity and overall correctness were 78.5%, 57.5% and 62.2%, respectively. The AUROC of the simple score was  $0.774 \pm 0.035$  ( $P < 0.001$ ) (Figure 2). Cumulative HCC incidence differed significantly ( $P < 0.001$ ) in advanced fibrotic CHC patients with simple scores  $\leq 2$  versus simple scores  $\geq 3$  (Figure 3). The 5-year and 10-year cumulative incidence of

**Table 3** Prediction of hepatocellular carcinoma using the new score

Predictive factor	Cutoff point	Youden index	Sensitivity %	Specificity %	Overall correctness %
New score	2.5	0.388	81.3	57.5	62.2



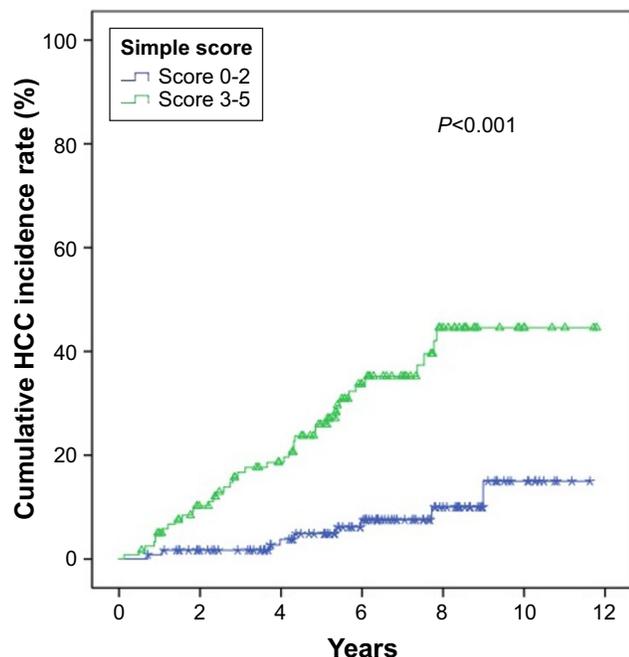
**Figure 2** Area under receiver operating curve (AUROC) analysis of the simple score to predict the occurrence of hepatocellular carcinoma.

**Abbreviation:** AUC, area under curve.

HCC development were 4.9% and 10.0% in patients with simple score  $\leq 2$ ; and 25.9% and 44.6% in patients with simple score  $\geq 3$ .

## Discussion

In this study, we developed a simple scoring system using commonly available clinical and laboratory parameters to



**Figure 3** Cumulative incidence rate of hepatocellular carcinoma.

**Abbreviation:** HCC, hepatocellular carcinoma.

predict the risk of HCC development after pegIFN and RBV therapy in previous non-HCC CHC patients with advanced fibrosis. The simple scoring system only included 5 clinical factors, including pretreatment age, serum bilirubin levels, platelet counts, presence of diabetes at treatment initiation and achievement of SVR, which was easier to use in the clinical setting. Patients with a score  $\geq 3$  had significant higher risk of HCC development. The 10-year cumulative incidence of HCC was 44.6%. In contrast, only 10.0% of patients with a score  $\leq 2$  developed HCC at 10 years. A surveillance program in advanced fibrotic CHC patients after pegIFN and RBV therapy could be scheduled respectively according to high or low risk scoring.

Advanced fibrosis has been considered a strong negative predictor for SVR in pegIFN and RBV combination treatment. There has been a lot of debate on the use of this combination therapy to treat CHC patients with advanced fibrosis, because of a high frequency of adverse effects, a high rate of treatment discontinuation, and decreased SVR. Previous reports have shown that an overall SVR rate for patients with advanced fibrosis is 24%–52%.<sup>21,22,25</sup> There were also several clinical adverse effects that developed during therapy, including pruritus (40%), malaise (36%), anemia (31%), insomnia (29%), anorexia (28%), dizziness (27%), thrombocytopenia (26%), fever (23%), dyspnea (23%), and myalgia (23%) in our study. However, several studies have demonstrated that CHC patients with advanced fibrosis achieving SVR after IFN-based therapy have reduced risks of developing liver decompensation, HCC, and liver-related mortality.<sup>8–11</sup> Moreover, a large proportion of patients in those studies received conventional IFN rather than pegIFN. Our study enrolled only pegIFN and RBV treated CHC patients with advanced fibrosis and showed that the combination therapy decreased the risk of HCC occurrence significantly. In our present study, SVR developed in 57.6% of patients. However, in those sustained responders, the risk of HCC could not be fully eliminated after pegIFN and RBV therapy. There were 23 (14.7%) patients with SVR who developed HCC during follow-up. The sensitivity and specificity of non-SVR to predict HCC were 61.7% and 63.0% with an AUROC: 0.623 ( $P=0.004$ ), which were lower than the simple score with cutoff point: 2.5 (AUROC: 0.774;  $P < 0.001$ , sensitivity: 81.3%, specificity: 57.5%). Therefore, the simple score  $\geq 3$  was a much better predictor to predict HCC development after pegIFN and RBV therapy and those patients with simple score  $\geq 3$  should be closely followed for HCC surveillance.

Liver cirrhosis at treatment initiation has been shown to be a significant predictor for HCC occurrence in CHC patients treated with IFN-based therapy or DAAs.<sup>26,27</sup>

Our study also showed that more HCC patients had cirrhosis at treatment initiation. However, the discrimination between severe bridging fibrosis (Ishak modified fibrosis score 4) and cirrhosis (Ishak modified fibrosis score 5–6) disappeared after adjustment for other risk factors in the multivariate Cox regression analysis.

Serum AFP measurement was frequently used for HCC surveys because it is inexpensive, simple to perform, and commonly available. Our report as well as previous studies have also shown that an elevated serum AFP level was a significant predictor of HCC development in CHC patients.<sup>2,16,28</sup> Although the patients with HCC had higher pretreatment serum AFP levels than those without HCC in the present study, we found the serum AFP level was not a predictor for HCC development in advanced fibrotic CHC patients. In addition, AFP alone was not recommended for HCC survey because of its low sensitivity and specificity for detecting HCC. At a serum cutoff level of 20 ng/mL, AFP has low sensitivity ranging from 25% to 65% for detecting HCC.<sup>29</sup> Moreover, only one third of patients with HCC had elevated serum AFP levels higher than 100 ng/mL.<sup>30</sup> Hu et al showed an association between serum AFP levels and liver disease activity, suggesting that AFP production was increased during liver necroinflammation.<sup>31</sup> AFP elevation was also noted in patients with advanced chronic hepatitis C without evidence of HCC.<sup>31–34</sup> Our advanced fibrotic patients with HCC had higher AST to ALT ratio, representing a more prominent liver necroinflammation, and may thus have resulted in more elevated serum AFP levels.

Diabetes has been shown to impair the treatment response to IFN-based therapy and increase the HCC risk in non-cirrhotic CHC patients treated with IFN-based therapy.<sup>35–38</sup> In contrast to those reports, our study found that presence of diabetes at treatment initiation was a predictor of reduced HCC risk in advanced fibrotic CHC patients. The possible explanation for this conflicting result was that in the study of Hung et al,<sup>38</sup> the diabetic patients were significantly older in age, and had higher fibrosis scores, and lower platelet counts and SVR rates than those of the non-diabetic patients. These factors may mask the protective influence of diabetes. Conversely, the baseline clinical factors and achievements of SVR rate between the diabetic and non-diabetic patients were similar in our present study (62.9% vs 56.0%;  $P=0.333$ ). An increase of SVR rate in diabetic patients may provide an increased benefit in HCC prevention. Interestingly, 82% (51/62) of the diabetes patients had been treated with metformin. Previous studies have shown the use of metformin was associated with a significant reduction of HCC risk compared with the use of other hypoglycemia agents.<sup>39,40</sup>

The use of metformin may be associated with reduced risk of HCC in our present study. The conflicting data might also be associated with different patient data collection and more careful diet control, resulting in less hepatotoxin exposure in diabetic patients.

Previous reports have shown the HCV genotype 1b was associated with higher risk of HCC.<sup>17,41</sup> In the present study we did not find a significant difference of HCC risk between advanced fibrotic CHC patients with HCV genotype 1b and non-1b. IFN has also been considered to have anticarcinogenic activity in addition to its antiviral effect to decrease the risk of HCC.<sup>42</sup> However, the treatment duration (48 weeks vs 24 weeks) or types of pegIFN prescribed in our study did not influence the rate of HCC development. From previous studies, the contribution of gender to the risk of HCC development is controversial.<sup>17,38,41,43</sup> Our study found that gender was not a risk factor for HCC occurrence in CHC patients with advanced fibrosis.

## Conclusion

The simple score has a better discriminatory power for HCC prediction in CHC patients with advanced fibrosis. SVR after pegIFN and RBV therapy could reduce the risk of HCC in those patients. However, the risks of HCC still remained after achieving SVR, especially in those with a score  $\geq 3$ , who should be intensively followed for HCC surveillance. For high-risk patients who failed the pegIFN and RBV therapy, more aggressive treatment with DAAs to eradicate the virus should be considered in order to reduce the risk of HCC.

## Abbreviations

AFP,  $\alpha$ -fetoprotein; AUROC, area under receiver operating characteristic; CHC, chronic hepatitis C; DAA, direct-acting antiviral agents; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; ROC, receiver operating characteristic; RVR, rapid virologic response; SVR, sustained virologic response.

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## Author contributions

Ching-Chih Hu, Cheng-Hao Weng, and Rong-Nan Chien conceived the study. Ching-Chih Hu, Cheng-Hao Weng and Ching-Fang Hu analyzed the data. Yen-Ting Chen, Man-Chin Hua and Li-Wei Chen contributed to data collection.

Ching-Chih Hu and Cheng-Hao Weng contribute to manuscript writing, and Rong-Nan Chien contributed to reviewing and revising the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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